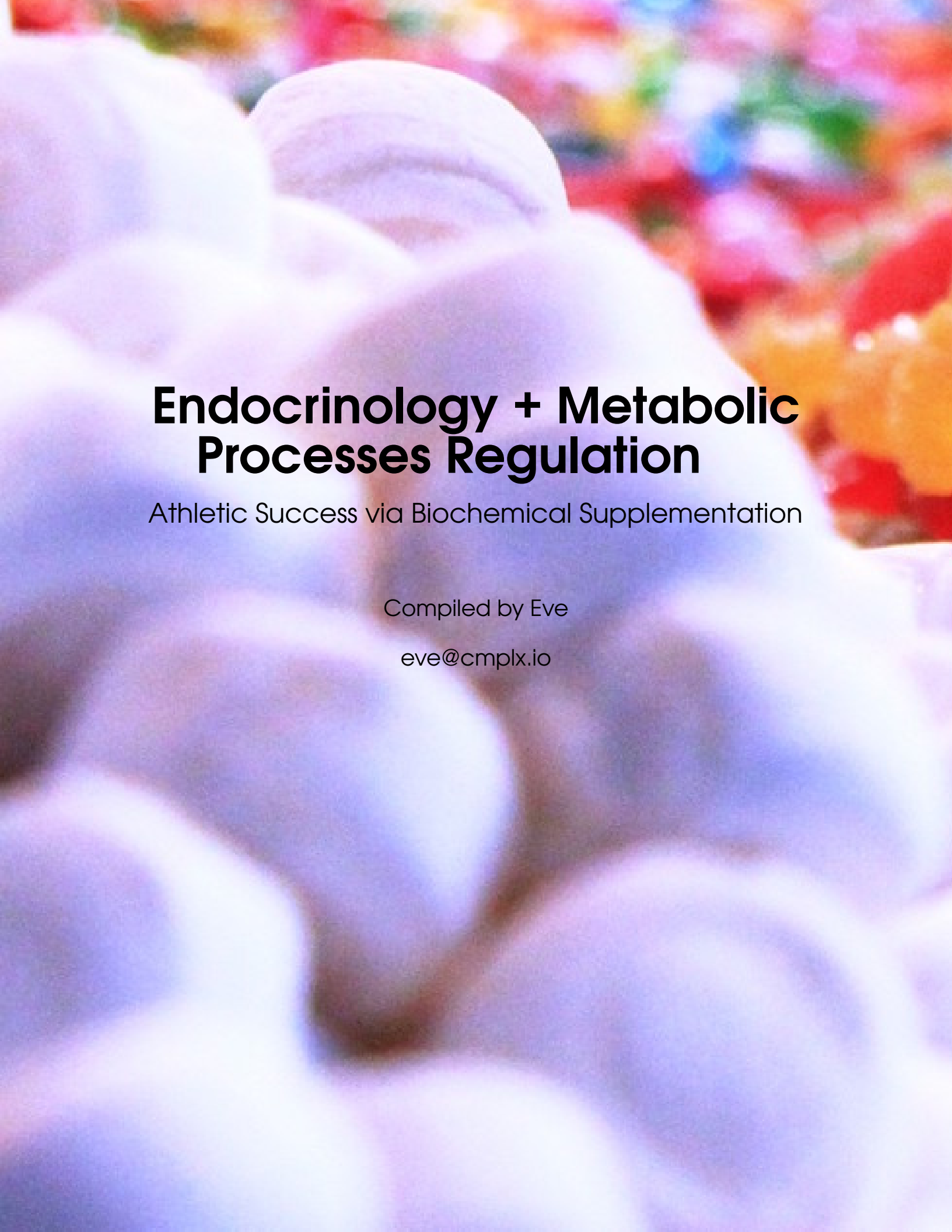

Endocrinology + Metabolic Processes Regulation

Athletic Success via Biochemical Supplementation

Compiled by Eve

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AN ONGOING ANALYSIS VIA INTELLECTUAL ABSORPTION.
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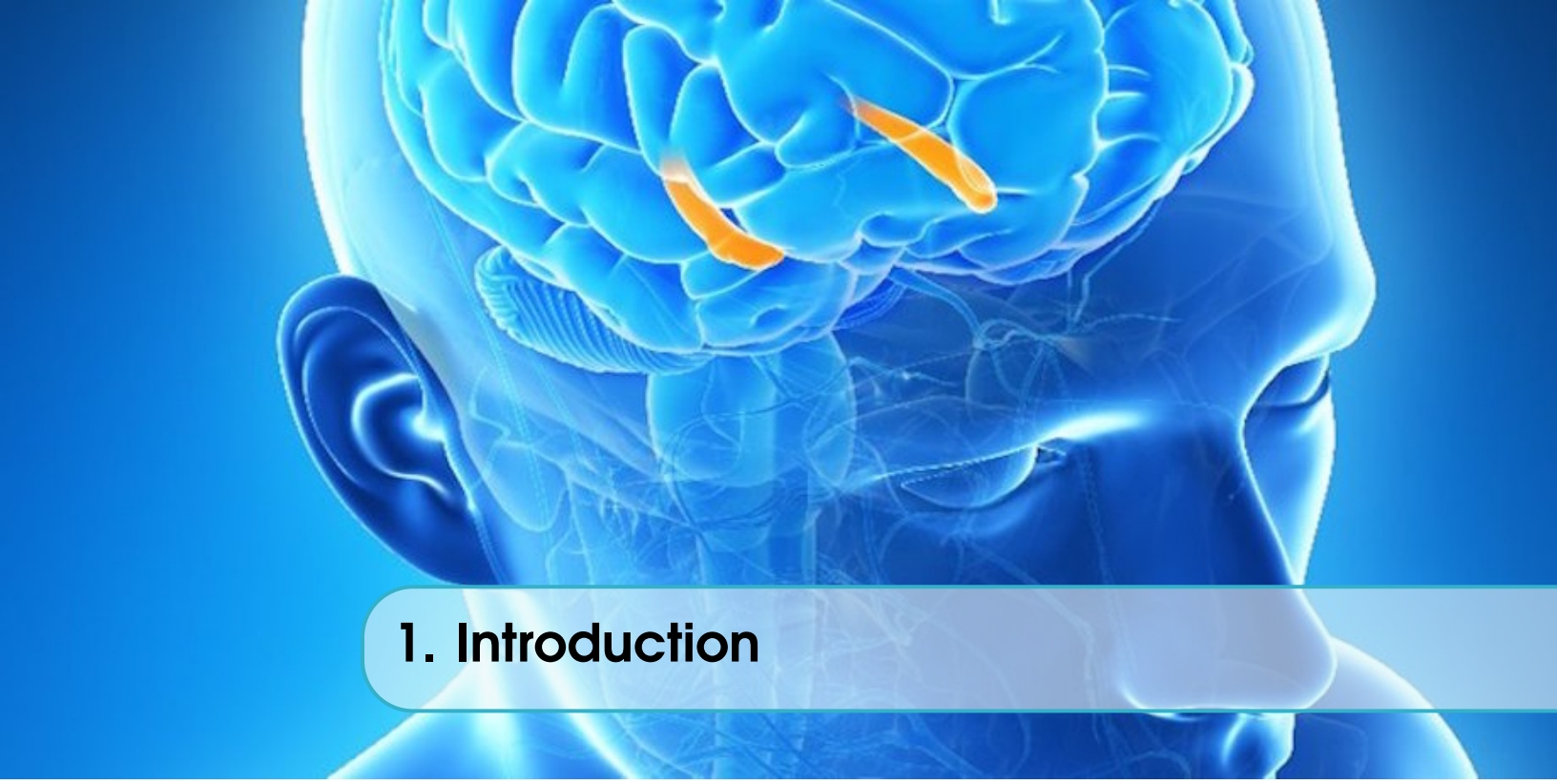
Note to the reader: This is an ongoing work in progress. Some content is compiled directly from the source material listed in the bibliography. Some writing is from the author's contextual knowledge with medications/supplementation and statistical analysis based on blood tests and consultation with endocrinologists and other members of various medical organizations. This document is not published for profit. It is a compendium of information on the topic meant for general knowledge, research, and education. The author cannot be held liable for any use or misuse of information contained here-in. The author is not a medical professional and does not offer this material on which to base clinical treatment. It is not meant as a substitute for medical care by an HRT doctor/endocrinologist. The medications discussed in this document have potentially dangerous side effects; as such this document does not condone or recommend DIY medication/hormone administration. User assumes all risk.

Contents



1. Introduction

1.1 Fundamental Terms

There are several background fundamentals that the reader should be familiar with. These terms, concepts, and cycles are essential to understanding how one's metabolism and hormonal balances are controlled by diet, which in turn defines our physical capabilities in performance, growth, repair, aging, and overall potential for change. The following terms will come up occasionally throughout this document and, as such, one would benefit from knowing the context around them prior to continuing.

1.1.1 Endogenous

Originating from within an organism, not attributable to any external or environmental factor. eg: biologically produced estrogen created by the ovaries.

1.1.2 Exogenous

Originating from outside an organism, caused by an agent or organism outside the body. eg: hormone replacement medication taken by injection.

1.1.3 MacroNutrients

The combined requirements of base nutrition required to sustain healthy human existence. There are three primary macronutrients: protein, fat, and carbohydrate. Macronutrients are defined as a class of chemical compounds which humans consume in the largest quantities (must be above a threshold amount) and which provide humans with the bulk of energy. [30]

1.1.4 CNS, The Central Nervous System

The central nervous system is composed of the brain and spinal cord. Your brain and spinal cord serve as the main "processing center" for the entire nervous system, and control all the workings of your body.

1.1.5 PSN, The Peripheral Nervous System

The peripheral nervous system consists of the nerves that branch out from the brain and spinal cord. These nerves form the communication network between the CNS and the body parts. The peripheral nervous system is further subdivided into the somatic nervous system and the autonomic nervous system. The somatic nervous system consists of nerves that go to the skin and muscles and is involved in conscious activities. The autonomic nervous system consists of nerves that connect the CNS to the visceral organs such as the heart, stomach, and intestines. It mediates unconscious activities.

1.1.6 Endocrinology

A branch of biology and medicine dealing with the endocrine system, its diseases, and its specific secretions known as hormones. It is also concerned with the integration of developmental events proliferation, growth, and differentiation, and the psychological or behavioral activities of metabolism, growth and development, tissue function, sleep, digestion, respiration, excretion, mood, stress, lactation, movement, reproduction, and sensory perception caused by hormones.

1.1.7 Metabolism

The set of life-sustaining chemical transformations within the cells of living organisms. These enzyme-catalyzed reactions allow organisms to grow and reproduce, maintain their structures, and respond to their environments.

1.1.8 Glycogenesis

Glycogenesis is the formation of glycogen from glucose. Glycogen is synthesized depending on the demand for glucose and ATP (energy).

1.1.9 Glycogenolysis

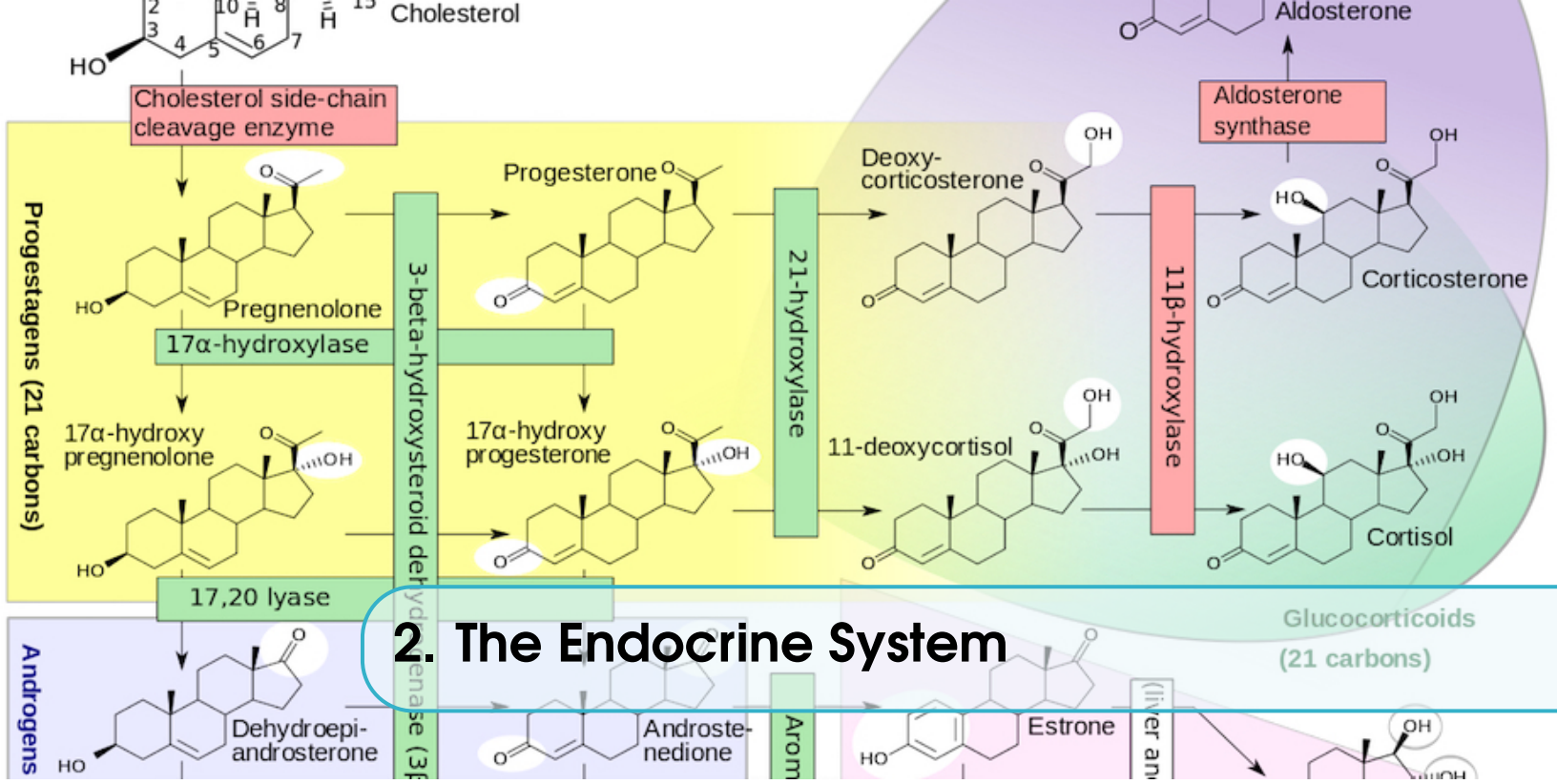
In glycogenolysis, glycogen stored in the liver and muscles, is converted first to glucose-1- phosphate and then into glucose-6-phosphate.

1.1.10 Gluconeogenesis

Gluconeogenesis is the process of synthesizing glucose from non-carbohydrate sources. [46]

1.1.11 Pharmacokinetics

Sometimes described as what the body does to a drug, refers to the movement of drug into, through, and out of the body - the time course of its absorption, bioavailability, tissue distribution, metabolism, and excretion. [51]



2. The Endocrine System

2.1 Introduction to Endocrinology

The endocrine system functions primarily as a signaling system that notifies cellular systems to express certain functions of their genetic markup. The endocrine system is a collection of glands that secrete hormones directly into the circulatory system to be carried towards distant target organs. The major endocrine glands include the pineal gland, pituitary gland, pancreas, ovaries, testes, thyroid, parathyroid, hypothalamus, gastrointestinal tract, and adrenal glands.

The endocrine system is in contrast to the exocrine system, which secretes its hormones to the outside of the body using ducts. The endocrine system is an information signal system like the nervous system, yet its effects and mechanism are classifiably different. The endocrine system's effects are slow to initiate, and prolonged in their response, lasting from a few hours up to weeks. The nervous system sends information very quickly, and responses are generally short lived. Changes induced to the endocrine system are not immediate, such as exogenous hormone administration, and the full changes to cellular expression may take months to obtain.

In addition to the specialized endocrine organs mentioned above, many other organs that are part of other body systems, such as bone, kidney, liver, heart and gonads, have secondary endocrine functions. For example, the kidney secretes endocrine hormones such as erythropoietin and renin. Hormones can consist of either amino acid complexes, steroids, eicosanoids, leukotrienes, or prostaglandins.

A number of glands that signal each other in sequence are usually referred to as an axis, for example, the hypothalamic-pituitary-adrenal axis (HPA-axis) and the hypothalamic-pituitary-gonadal (HPG-axis).

R `https://en.wikipedia.org/wiki/Endocrine_system`

2.2 The Role of Hormones

Hormones are the body's signaling molecules that are used to communicate between organs and tissues. They regulate physiological and behavioral activities, such as digestion, metabolism, respiration, tissue function, sensory perception, sleep, excretion, lactation, stress, growth and development, movement, reproduction, and mood. The particulars of each hormone are covered in the section titled "Neurotransmitters, Hormones, and Histamines".

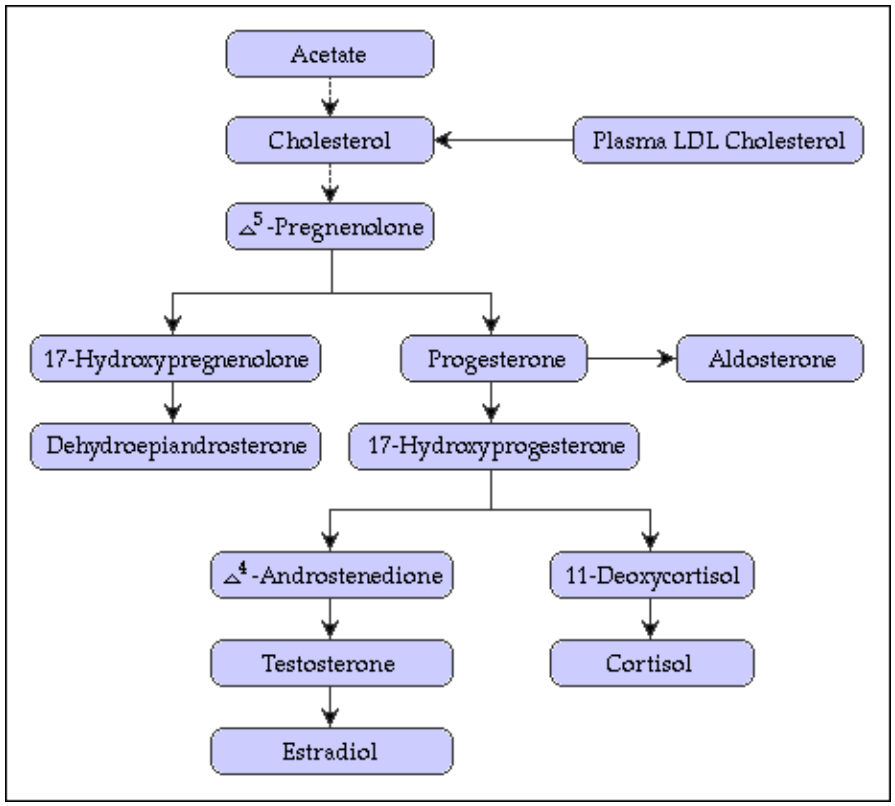


Figure 2.1: Overview of Hormonal Biosynthesis

2.3 Endocrine Glands and Axes

2.3.1 Adrenal

The adrenal glands are endocrine glands that produce a variety of hormones including adrenaline and the steroids aldosterone and cortisol. Each gland has an outer cortex which produces steroid hormones and an inner medulla. The adrenal cortex itself is divided into three zones: zona glomerulosa, the zona fasciculata and the zona reticularis.

The adrenal cortex produces three main types of steroid hormones: mineralocorticoids, glucocorticoids, and androgens. Mineralocorticoids (such as aldosterone) produced in the zona glomerulosa help in the regulation of blood pressure and electrolyte balance. The glucocorticoids cortisol and corticosterone are synthesized in the zona fasciculata; their functions include the regulation of metabolism and immune system suppression. The innermost layer of the cortex, the zona reticularis, produces androgens that are converted to fully functional sex hormones in the gonads and other target organs. The production of steroid hormones is called steroidogenesis, and involves a number of reactions and processes that take place in cortical cells. The medulla produces the catecholamines adrenaline and noradrenaline, which function to produce a rapid response throughout the body in stress situations.

2.3.2 Gonads

A gonad or sex gland or reproductive gland is an endocrine gland that produces the gametes (germ cells) of an organism. In the female of the species the reproductive cells are the egg cells, and in the male the reproductive cells are the sperm. The male gonad, the testicle, produces sperm in the form of spermatozoa. The female gonad, the ovary, produces egg cells. Both of these gametes, are haploid germ cells. The gonads are controlled by luteinizing hormone and follicle-stimulating hormone, produced and secreted by gonadotropes in the anterior pituitary gland. This secretion is regulated by gonadotropin-releasing hormone produced in the hypothalamus.

2.3.3 Hypothalamus

The hypothalamus is a portion of the brain that contains a number of small nuclei with a variety of functions. One of the most important functions of the hypothalamus is to link the nervous system to the endocrine system via the pituitary gland. The hypothalamus is responsible for certain metabolic processes and other activities of the autonomic nervous system. It synthesizes and secretes certain neurohormones, called releasing hormones or hypothalamic hormones, and these in turn stimulate or inhibit the secretion of pituitary hormones. The hypothalamus controls body temperature, hunger, important aspects of parenting and attachment behaviors, thirst, fatigue, sleep, and circadian rhythms.

2.3.4 Ovaries

The ovary is an ovum-producing reproductive organ, often found in pairs in the female as part of the vertebrate female reproductive system. Ovaries in female are analogous to testes in male, in that they are both gonads and endocrine glands. Ovaries secrete estrogen, testosterone and progesterone. In women, fifty percent of testosterone is produced by the ovaries and adrenal glands and released directly into the blood stream. Estrogen is responsible for the appearance of secondary sex characteristics for females at puberty and for the maturation and maintenance of the reproductive organs in their mature functional state. Progesterone prepares the uterus for pregnancy, and the

mammary glands for lactation. Progesterone functions with estrogen by promoting menstrual cycle changes in the endometrium.

2.3.5 Pancreas

The pancreas is a glandular organ in the digestive system and endocrine system. In humans, it is located in the abdominal cavity behind the stomach. It is an endocrine gland producing several important hormones, including insulin, glucagon, somatostatin, and pancreatic polypeptide which circulate in the blood. The pancreas is also a digestive organ, secreting pancreatic juice containing digestive enzymes that assist digestion and absorption of nutrients in the small intestine. These enzymes help to further break down the carbohydrates, proteins, and lipids in the chyme. The pancreas is involved in sugar control and metabolism within the body, and also in the secretion of substances which help digestion. Classically, these are divided into an "endocrine" role, relating to the secretion of insulin and other substances within pancreatic islets and helping control blood sugar levels and metabolism within the body, and an "exocrine" role, relating to the secretion of enzymes involved in digesting substances from outside of the body.

2.3.6 Parathyroid

The major function of the parathyroid glands is to maintain the body's calcium and phosphate levels within a very narrow range, so that the nervous and muscular systems can function properly. The parathyroid glands do this by secreting parathyroid hormone. Parathyroid hormone (PTH, also known as parathormone) is a small protein that takes part in the control of calcium and phosphate homeostasis, as well as bone physiology.

2.3.7 Pineal

The pineal gland is a small endocrine gland in the brain. It produces melatonin, a serotonin derived hormone, which affects the modulation of sleep patterns in both seasonal and circadian rhythms. Melatonin is N-acetyl-5-methoxy-tryptamine, a derivative of the amino acid tryptophan, which also has other functions in the central nervous system. The production of melatonin by the pineal gland is stimulated by darkness and inhibited by light.

2.3.8 Pituitary

The pituitary gland, or hypophysis, is an endocrine gland composed of three lobes: anterior, intermediate, and posterior. Hormones secreted from the pituitary gland help control: growth, blood pressure, certain functions of the sex organs, thyroid glands and metabolism as well as some aspects of pregnancy, childbirth, nursing, water/salt concentration and the kidneys, temperature regulation and pain relief.

2.3.9 Testes

The testicle, testes for plural, is the male gonad in animals. Like the ovaries to which they are homologous, testes are components of both the reproductive system and the endocrine system. The primary functions of the testes are to produce sperm (spermatogenesis) and to produce androgens, primarily testosterone.

Both functions of the testicle are influenced by gonadotropic hormones produced by the anterior pituitary. Luteinizing hormone (LH) results in testosterone release. The presence of both testosterone

and follicle-stimulating hormone (FSH) is needed to support spermatogenesis. It has also been shown in animal studies that if testes are exposed to either too high or too low levels of estrogens (such as estradiol; E2) spermatogenesis can be disrupted to such an extent that the animals become infertile.

2.3.10 Thyroid

The thyroid gland is one of the largest endocrine glands in the body, and consists of two connected lobes. The thyroid gland controls rate of use of energy sources, protein synthesis, and controls the body's sensitivity to other hormones. It participates in these processes by producing thyroid hormones, the principal ones being thyroxine (T4) and triiodothyronine (T3), which is more active. These hormones regulate the growth and rate of function of many other systems in the body. T3 and T4 are synthesized from iodine and tyrosine. The thyroid also produces calcitonin, which plays a role in calcium homeostasis. Hormonal output from the thyroid is regulated by thyroid-stimulating hormone (TSH) produced by the anterior pituitary, which itself is regulated by thyrotropin-releasing hormone (TRH) produced by the hypothalamus.

2.3.11 HPA Axis

The hypothalamic–pituitary–adrenal axis (HPA axis or HTPA axis) is a complex set of direct influences and feedback interactions among three endocrine glands: the hypothalamus, the pituitary gland (a pea-shaped structure located below the hypothalamus), and the adrenal (also called "suprarenal") glands (small, conical organs on top of the kidneys).

The interactions among these organs constitute the HPA axis, a major part of the neuroendocrine system that controls reactions to stress and regulates many body processes, including digestion, the immune system, mood and emotions, sexuality, and energy storage and expenditure. It is the common mechanism for interactions among glands, hormones, and parts of the midbrain that mediate the general adaptation syndrome (GAS).

The HPA axis has a central role in regulating many homeostatic systems in the body, including the metabolic system, cardiovascular system, immune system, reproductive system and central nervous system. The HPA axis integrates physical and psychosocial influences in order to allow an organism to adapt effectively to its environment, use resources, and optimize survival.

2.3.12 HPG Axis

The hypothalamic–pituitary–gonadal axis (also HPG axis) refers to the effects of the hypothalamus, pituitary gland, and gonads as if these individual endocrine glands were a single entity as a whole. Because these glands often behave in cooperation, physiologists and endocrinologists find it convenient and descriptive to speak of them as a single system.

The hypothalamic–pituitary–gonadal axis is a critical part in the development and regulation of a number of the body's systems, such as the reproductive and immune systems. Fluctuations in the hormones cause changes in the hormones produced by each gland and have various widespread and local effects on the body.

This axis controls development, reproduction, and aging in animals. Gonadotropin-releasing hormone

(GnRH) is secreted from the hypothalamus by GnRH-expressing neurons. The anterior portion of the pituitary gland produces luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and the gonads produce estrogen and testosterone.

2.3.13 HPT Axis

The hypothalamic–pituitary–thyroid axis (HPT axis for short, aka thyroid homeostasis or thyrotropic feedback control) is part of the neuroendocrine system responsible for the regulation of metabolism. As its name suggests, it depends upon the hypothalamus, the pituitary gland, and the thyroid gland.

The hypothalamus senses low circulating levels of thyroid hormone (Triiodothyronine (T3) and Thyroxine (T4)) and responds by releasing thyrotropin-releasing hormone (TRH). The TRH stimulates the pituitary to produce thyroid-stimulating hormone (TSH). The TSH, in turn, stimulates the thyroid to produce thyroid hormone until levels in the blood return to normal. Thyroid hormone exerts negative feedback control over the hypothalamus as well as anterior pituitary, thus controlling the release of both TRH from hypothalamus and TSH from anterior pituitary gland.

2.4 Overview of Receptors

In biochemistry and pharmacology, a receptor is a protein molecule usually found embedded within the plasma membrane surface of a cell that receives chemical signals from outside the cell. When such chemical signals bind to a receptor, they cause some form of cellular/tissue response, e.g. a change in the electrical activity of the cell. In this sense, a receptor is a protein molecule that recognizes and responds to endogenous chemical signals. [50]

2.4.1 Receptor: Adrenergic

The adrenergic receptors (or adrenoceptors) are a class of G protein-coupled receptors that are targets of the catecholamines, especially norepinephrine (noradrenaline) and epinephrine (adrenaline). [55]

2.4.2 Receptor: Androgen

The androgen receptor is a type of nucleus receptor that is activated by binding either of the androgenic hormones, testosterone, or dihydrotestosterone in the cytoplasm and then translocating into the nucleus. The androgen receptor is most closely related to the progesterone receptor, and progestins in higher dosages can block the androgen receptor. [28] The androgen receptor is also the primary target for all anabolic steroid hormones.

2.4.3 Receptor: Estrogen

Estrogen receptors are a group of proteins found inside cells. They are receptors that are activated by the hormone estrogen (17β-estradiol). [27]

2.4.4 Receptor: Progesterone

The progesterone receptor (PR, also known as NR3C3 or nuclear receptor subfamily 3, group C, member 3), is a protein found inside cells. It is activated by the steroid hormone progesterone.

2.4.5 Receptor: Histamine

The histamine receptors are a class of G protein–coupled receptors with histamine as their endogenous ligand. There are four receptors: H1, H2, H3, H4. See the Histamine section of this document for more details.

2.5 Steroids of the Endocrine System

Hormones that affect change in the body by binding to cellular receptors. Cells are capable of changing their fundamental expression based on the type and quantity of hormones are attached to their receptors.

2.5.1 Sex Steroids

These hormones influence sexual evolution of the human form and support reproduction; these include androgens, estrogens, and progestogens. These are the hormones that signal primary and secondary sexual characteristics of our exterior selves as well as internal expressions of cellular growth and change over time.

2.5.2 Corticosteroids

Responsible for regulation of many aspects of the metabolism and immune function that help maintain blood volume and control renal excretion of electrolytes.

2.5.3 Anabolic steroids

Natural and synthetic, Testosterone being the most common, these hormones interact with androgen receptors to increase muscle and bone synthesis. The anabolic profile of a hormone determines the "explosive/powerful" feeling that Testosterone brings, along with synthetic anabolic steroids that are covered later in this text. In popular social expression, use of the term "steroids" typically refers to anabolic steroids though the term is not always inclusive of pure Testosterone.

2.5.4 Androgenic steroids

Natural and synthetic, including Testosterone, Dihydrotestosterone (DHT) and Androstenedione, these sex steroids interact with androgen receptors and stimulate "masculine features": body hair growth, vocal chord changes, male pattern baldness, and various other changes. All anabolic steroids have an androgenic quality to them, some more than others. These are covered later in the text under "Hormone Supplementation". We all start in the womb as female, it is the androgenic sex hormones that change the fetus into male. Women also have these hormones, though to a much lesser extent by comparison to natal males.

2.6 Neurotransmitters

Neurotransmitters are the brain chemicals that communicate information throughout our brain and body. They relay signals between nerve cells, called "neurons." The brain uses neurotransmitters to tell your heart to beat, your lungs to breathe, and your stomach to digest. They can also affect mood, sleep, concentration, weight, and can cause adverse symptoms when they are out of balance.

There are two kinds of neurotransmitters – inhibitory and exitatory. Excitatory neurotransmitters are not necessarily exciting – they are what stimulate the brain. Those that calm the brain and help create balance are called inhibitory. Inhibitory neurotransmitters balance mood and are easily depleted when the excitatory neurotransmitters are overactive.

Neurotransmitters are endogenous chemicals that transmit signals across a synapse or junction from one neuron (nerve cell) to another "target" neuron, muscle cell or gland cell. Neurotransmitters are released from synaptic vesicles in synapses into the synaptic cleft, where they are received by receptors on other synapses. Many neurotransmitters are synthesized from simple and plentiful precursors such as amino acids, which are readily available from the diet and only require a small number of biosynthetic steps to convert them. Neurotransmitters play a major role in shaping everyday life and functions. [11]

https://www.neurogistics.com/TheScience/WhatareNeurotransmi09CE.asp

2.6.1 Dopamine

Dopamine is a special neurotransmitter because it is considered to be both excitatory and inhibitory. Dopamine helps with depression and it is our main focus neurotransmitter. When dopamine is either elevated or low – we can have focus issues such as not remembering where we put our keys, forgetting what a paragraph said when we just finished reading it or simply daydreaming and not being able to stay on task. Dopamine is also responsible for our drive or desire to get things done – or motivation. Stimulants such as medications for ADD/ADHD and caffeine cause dopamine to be pushed into the synapse so that focus is improved. Unfortunately, stimulating dopamine consistently can cause a depletion of dopamine over time.

- Commonly functions as a stimulation neurotransmitter.
- Naturally is released before we wake up and causes that get up and go feeling we should have when waking up.
- If you go to bed too late in the dark cycle it will not be released and you'll feel sluggish and drowsy.
- Operates the fight or flight response with the release of adrenaline.
- Causes involuntary movements like blinking, emotional drive and spontaneity.
- Reduces with age and can be burnt out faster by abusing drugs like marijuana, speed, crack and cocaine.
- Deficiency is known as Parkinson's disease.

2.6.2 Epinephrine

Epinephrine is an excitatory neurotransmitter that is reflective of stress. This neurotransmitter will often be elevated when ADHD like symptoms are present. Long term stress or insomnia can cause

epinephrine levels to be depleted (low). Epinephrine also regulates heart rate and blood pressure.

2.6.3 GABA

GABA (γ-aminobutyric acid) is the chief inhibitory neurotransmitter in the mammalian central nervous system. It plays the principal role in reducing neuronal excitability throughout the nervous system. In humans, GABA is also directly responsible for the regulation of muscle tone.

2.6.4 Histamines

Histamine is an organic nitrogenous compound involved in local immune responses as well as regulating physiological function in the gut and acting as a neurotransmitter. See the Histamine chapter for more detailed information.

2.6.5 Norepinepherine

Norepinepherine is an excitatory neurotransmitter that is responsible for stimulatory processes in the body. Norepinephrine helps to make epinephrine as well. This neurotransmitter can cause anxiety at elevated excretion levels as well as some mood dampening effects. Low levels of norepinephrine are associated with low energy, decreased focus ability and sleep cycle problems.

2.6.6 Serotonin

Serotonin is an inhibitory neurotransmitter – which means that it does not stimulate the brain. Adequate amounts of serotonin are necessary for a stable mood and to balance any excessive excitatory (stimulating) neurotransmitter firing in the brain. If you use stimulant medications or caffeine in your daily regimen – it can cause a depletion of serotonin over time. Serotonin also regulates many other processes such as carbohydrate cravings, sleep cycle, pain control and appropriate digestion. Low serotonin levels are also associated with decreased immune system function.

- A neurotransmitter that affects our cravings, obsessive behavior, appetite, tranquility, peace of mind, and comfort.
- Serotonin mitigates negative impulses and behaviors.
- Too much causes nausea and diarrhea, while too little causes a person to be anxious, restless, depressed, impulsive, and aggressive.
- Serotonin has to be balanced with melatonin (below), imbalances cause increases in stress, poor impulse control, depression, overeating and drinking.
- Serotonin is produced in the brain from the amino acid tryptophan.
- When levels of tryptophan rise and fall so do levels of serotonin.

2.7 Histamines in Detail

Histamine is an organic nitrogenous compound involved in local immune responses as well as regulating physiological function in the gut and acting as a neurotransmitter. Histamine is involved in the inflammatory response and have central role as a mediator of pruritus. As part of an immune response to foreign pathogens, histamine is produced by basophils and by mast cells found in nearby connective tissues. Histamine increases the permeability of the capillaries to white blood cells and some proteins, to allow them to engage pathogens in the infected tissues. [50]

2.7.1 CNS histamine reactions

Histamine neurotransmissions assist in regulation and management of many Central Nervous System functions.

- regulation of the sleep-wake cycle
- modulation of body temperature
- nociception; the ability to sense pain
- modulation of endocrine homeostasis
- appetite management
- mood and emotional balance
- learning + memory functions

2.7.2 PNS histamine reactions

Histamine neurotransmissions assist in regulation and management of many Peripheral Nervous System functions.

- Causes broncho-constriction; bronchial smooth muscle contraction
- Vasodilation regulation; alteration of blood flow capacity, resource transport, blood pressure.
- Separation of endothelial cells (responsible for hives) and pain and itching due to insect stings.
- Function as the primary receptors involved in allergic rhinitis symptoms and motion sickness

2.7.3 Medications: H1-receptor antagonists

Histamine H1 receptors are activated by endogenous histamine, which is released by neurons that have their cell bodies in the tuberomammillary nucleus of the hypothalamus. Antihistamines that target the histamine H1-receptor are used to treat allergic reactions in the nose (e.g., itching, runny nose, and sneezing) as well as for insomnia. They are sometimes also used to treat motion sickness or vertigo caused by problems with the inner ear. H1-antihistamines work by binding to histamine H1 receptors in mast cells, smooth muscle, and endothelium in the body as well as in the tuberomammillary nucleus in the brain.

Anti-histamines that antagonize the H1 receptors offer functional changes to CNS/PNS:

- Ileum contraction
- Modulate circadian cycle
- Control/reduce itching
- Systemic vasodilatation
- Bronchoconstriction (allergy-induced asthma or reduction of sympathomimetic dilation)

H1-receptor antagonist medications:

- Diphenhydramine

- Loratadine
- Cetirizine
- Fexofenadine
- Clemastine

2.7.4 Medications: H2-receptor antagonists

H2 antagonists, also called H2 blockers, are a class of medications that block the action of histamine at the histamine H2 receptors of the parietal cells in the stomach. This decreases the production of stomach acid. H2 antagonists can be used in the treatment of dyspepsia, but have been surpassed by the more effective proton pump inhibitors for that indication. They are also used to treat peptic ulcer disease and gastroesophageal reflux disease. Antihistamines that target the histamine H2-receptor are used to treat gastric acid conditions (e.g., peptic ulcers and acid reflux). H2-antihistamines bind to histamine H2 receptors in the upper gastrointestinal tract, primarily in the stomach.

Anti-histamines that antagonize the H2 receptors offer functional changes to CNS/PNS:

- Speed up sinus rhythm
- Stimulation of gastric acid secretion
- Smooth muscle relaxation
- Inhibit antibody synthesis, T-cell proliferation and cytokine production

H2-receptor antagonist medications:

- Ranitidine
- Cimetidine
- Famotidine
- Nizatidine

2.7.5 Medications: H3-receptor antagonists

The histamine H3 receptor is an inhibitory autoreceptor located on histaminergic nerve terminals, and is believed to be involved in modulating the release of histamine in the brain. Histamine has an excitatory effect in the brain via H1 receptors in the cerebral cortex, and so drugs such as ciproxifan which block the H3 receptor and consequently allow more histamine to be released have an alertness-promoting effect.

Anti-histamines that antagonize the H3 receptors offer functional changes to CNS/PNS:

- Decrease Acetylcholine, Serotonin and Norepinephrine Neurotransmitter release in CNS
- Presynaptic autoreceptors

H3-receptor antagonist medications:

- ABT-239
- Ciproxifan
- Clobenpropit
- Thioperamide

2.7.6 Medications: H4-receptor antagonists

The Histamine H4 receptor has been shown to be involved in mediating eosinophil shape change and mast cell chemotaxis. H4 is highly expressed in bone marrow and white blood cells and regulates neutrophil release from bone marrow.

Anti-histamines that antagonize the H4 receptors offer functional changes to CNS/PNS:

- Mediate mast cell chemotaxis.

H4-receptor antagonist medications:

- Thioperamide
- TJNJ 7777120

2.8 Hormones, In More Detail

As a follow up to generic data about "Steroids of the Endocrine System", this section itemizes the properties of the major hormones.

2.8.1 Testosterone

The “male hormone”. There are typically two levels tested: Total and Free. Total is the amount circulating in the body, Free is the amount that is *not* bound to SHBG and is available to muscle tissue, skeletal structures, the brain, and other androgen receptor sites.

Excess testosterone is converted into estradiol (estrogen/E2) by the aromatase enzyme process. Medications such as Amiridex can be used to prevent the aromatization process, which is typically used in some forms of breast cancer treatment or by male body builders to prevent gynecomastia side effects of anabolic testosterone-based steroid usage (Testosterone Propionate, Equipoise, Dianabol, etc).

Testosterone is also converted into the more potent Dihydrotestosterone (DHT) sex steroid via the 5-alpha reductase enzyme process (this can be prevented via medications such as Avodat/Dutasteride). DHT is responsible for follicle stimulation (body hair growth), and various other masculinization effects on the body.

- Commonly referred to as ’the male hormone’, it is responsible for differentiating the primary and secondary attributes of male/female cellular expression and genital definition.
- Increases muscle mass, metabolic rate, red blood cells and enhances bone density.
- Initiates protein synthesis, enhances cellular repair and growth.
- Promotes the release of growth hormone (HGH).

2.8.2 Estrogen

The “female hormone”. Typically known as 17b-estradiol, or E2. While estrogens are present in both men and women, they are usually present at significantly higher levels in women of reproductive age. They promote the development of female secondary sexual characteristics, such as breasts, and are also involved in the thickening of the endometrium and other aspects of regulating the menstrual cycle. In males, estrogen regulates certain functions of the reproductive system important to the maturation of sperm and may be necessary for a healthy libido.[8]

Primary Characteristics of Estrogen

- Protein synthesis: Increase hepatic production of binding proteins.
- Structural: Increase fat store, accelerate metabolism.
- Secondary Sexual Characteristics: promote formation/feminization.
- Lipids: Increase HDL, triglyceride.
- Lipids: Decrease LDL, fat deposition.
- Fluid balance: Salt (sodium) and water retention.
- Bones: Reduce bone resorption, increase bone formation.
- SHBG: Increase cortisol, increase levels of SHBG.
- Other: Maintenance of vessel tone and skin softness.

Types of Estrogen: Estrone, Estradiol, Estriol

- *Estrone (E1)* is primary form of estrogen and acts as the precursor to estradiol during steroidogenesis. Due to its lesser affinity to the estrogen receptor, larger quantities of estrone are required to get the same effects as a smaller quantity of estradiol. Thus it is normally converted to estradiol when that form is needed. Estrone can also be de-converted from estradiol, as needed by endocrine system regulatory processes.

- *Estradiol (E2)* is the major estrogen produced by ovaries and as a product of the Aromatase Process. Estradiol s the most biochemically efficient form of estrogen. Estradiol is capable of the widest range of estrogenic effects due to its high affinity for the estrogen receptors.

- *Estriol (E3)* is a metabolic product of estradiol metabolism. It is produced by the liver and is 8% as potent as estradiol and 14% as potent as estrone. Once estriol is bound to an estrogen receptor, it blocks estradiol from binding.

Estradiol level fluctuations during the menstrual cycle.

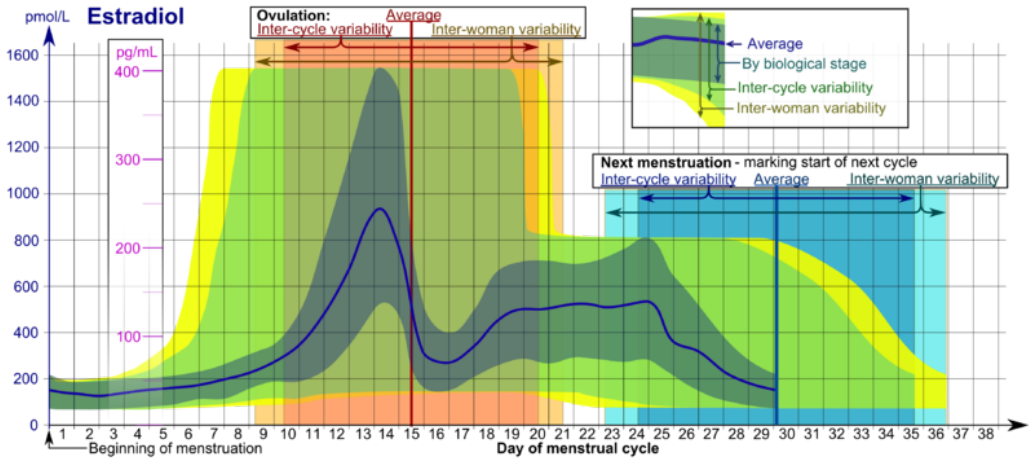


Figure 2.2: Estradiol level fluctuations during the menstrual cycle

Estrogen and Weight Loss

Estradiol can cause a reduction in weight, with only a minimal effect in insulin itself, but that does not mean it does not alter the body's reaction to insulin. Estradiol lowers insulin receptor number, and in very high doses even actual insulin sensitivity. It does so in various ways, not in the least by reducing GLUT4 recruitment and translocation in adipocytes, which results in less glucose uptake in fat cells. This will result in a negative energy balance and a greater activation of lipolysis, right where we want it, in the fat tissue. The effect of estradiol on insulin is quite acute, and clearly evident in the fact that short-term modulation drastically reduces glucose appearance (release) and disappearance (uptake), suggesting a dysfunctional glucose transport system.

The second way in which estradiol may increase fat loss, is its effect on growth hormone. Unlike testosterone, which stimulates the GH/IGF-1 axis, the effect of estrogen may actually be in reducing systemic (liver-derived) IGF-1, which lowers inhibition of Growth Hormone. In doing so it obviously reduces the anabolic capacity of the body (which is why we don't use estrogen to build muscle) but increases the fat burning capacity since whole-body IGF-1 is reduced, leading to a reduction in adipogenic markers (since IGF-1 and insulin activate the same cascades) and a concurrent increase in Growth Hormone, leading to further decreases in LPL and up-regulation of beta-adrenoreceptors. Estradiol may even reduce IGF-1, while increasing IGFBP-3.

A third way in which estradiol helps as a fat loss agent is by reducing appetite. It reduces sensations of hunger via modulation of melanin-concentrating hormone (MCH). Estradiol was able to completely abolish this increase in MCH, making it a very potent appetite suppressor during low-calorie diets.

2.8.3 Progesterone

Progesterone is an endogenous steroid and progestogen sex hormone. It belongs to a group of steroid hormones called the progestogens, and is the major progestogen in the body. Progesterone is also a crucial metabolic intermediate in the production of other endogenous steroids, including the sex hormones and the corticosteroids, and plays an important role in brain function as a neurosteroid.

Progesterone enhances the function of serotonin receptors in the brain, so an excess or deficit of progesterone has the potential to result in significant neurochemical issues. This provides an explanation for why some people resort to substances that enhance serotonin activity such as nicotine, alcohol, and cannabis when their progesterone levels fall below optimal levels.

Primary Characteristics of Progesterone

- Increases core temperature (thermogenic functionality).
- Reduces spasm and relaxes smooth muscle; bronchi are widened and mucus regulated.
- Acts as an anti-inflammatory agent and regulates the immune response.
- Normalizes blood clotting and vascular tone.
- Regulates zinc and copper levels, cell oxygen levels, and use of fat stores for energy.
- Assists in regulating the effects of estrogen.
- Plays an crucial role in the signaling of insulin release during glycogenesis while balancing blood sugar levels.
- Maintaining the uterine lining and preventing excess tissue buildup.
- Inhibiting breast tissue overgrowth.
- Increasing metabolism and promoting weight loss.
- Acting as a natural diuretic.
- Stimulating the production of new bone.
- Enhancing the action of thyroid hormones.
- Alleviating depression and reducing anxiety.
- Promoting normal sleep patterns.
- Preventing cyclical migraines.
- Restoring proper cell oxygen levels.
- Improving libido.

Progesterone converts to Estradiol and Testosterone during steroidogenesis.

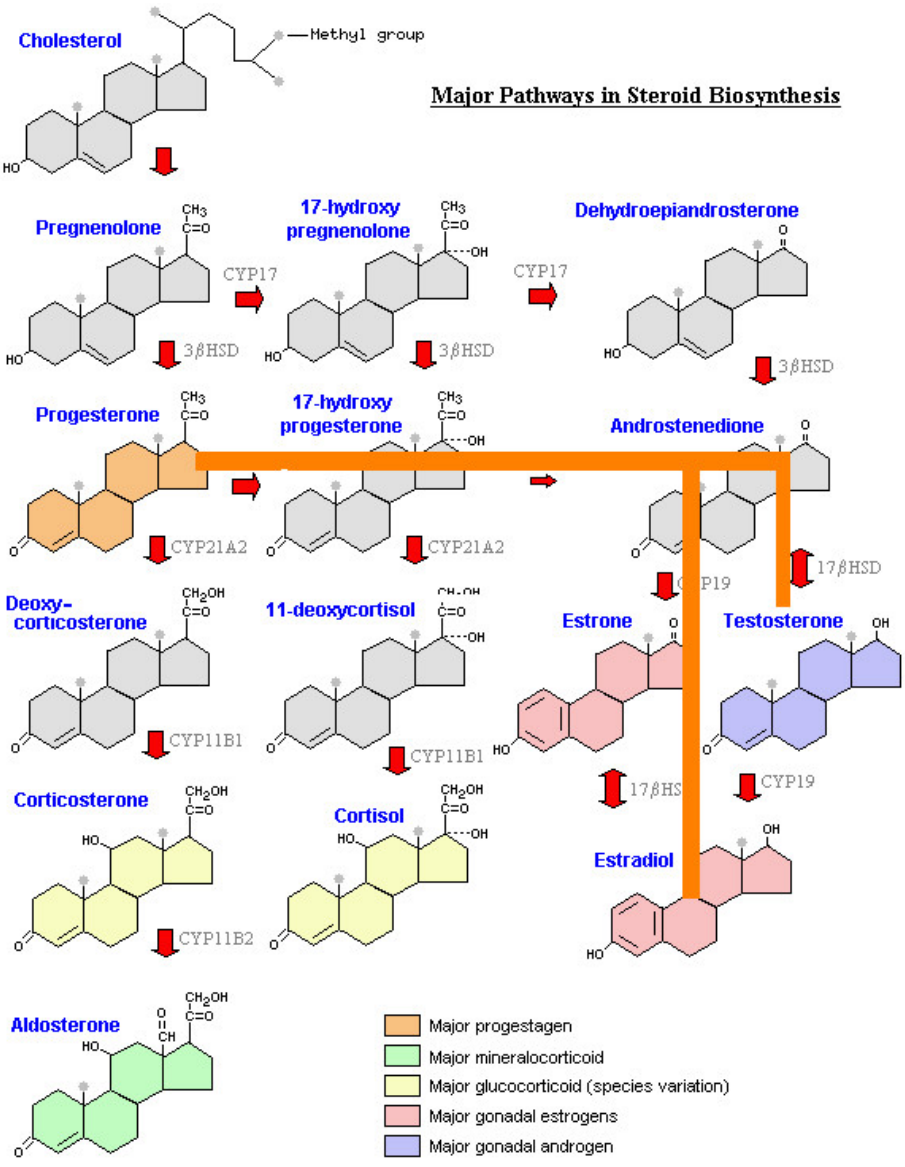


Figure 2.3: Progesterone during steroidogenesis

2.8.4 Growth Hormone

- Released from the pituitary gland during deep sleep.
- Provides us with a sense of well being, increases muscle mass, strengthens bones, reduces body fat, and strengthens our immune systems.

2.8.5 Dehydroepiandrosterone (DHEA)

The pre-cursor hormone that functions as hormonal fuel for conversion during steroidogenesis.

- The most abundant hormone in our bodies.
- Produced in the adrenal glands.
- Considered the mother hormone because it is used to produce other hormones such as estrogen, progesterone, testosterone and cortisol.
- Balanced levels of DHEA send messages to each of our 100 trillion cells to repair, rebuild, restore and revitalize.
- Improves our memory, mood, immune system and longevity.

Also known as androstenolone or prasterone (INN), as well as 3beta-hydroxyandrost-5-en-17-one or 5-androsten-3beta-ol-17-one, is an important endogenous steroid hormone. DHEA is produced from cholesterol through two cytochrome P450 enzymes. It is the most abundant circulating steroid hormone in humans, in whom it is produced in the adrenal glands, the gonads, and the brain, where it functions predominantly as a metabolic intermediate in the biosynthesis of the androgen and estrogen sex steroids. However, DHEA also has a variety of potential biological effects in its own right, binding to an array of nuclear and cell surface receptors, and acting as a neurosteroid. [26]

DHEA is a steroid hormone. High [ed: exogenous or supplemented] doses may cause aggressiveness, irritability, trouble sleeping, and the growth of body or facial hair on women [ed: this is due to DHEA being a pre-cursor to Testosterone, of which elevated levels lead to virilization/masculinization of the body). It also may stop menstruation and lower the levels of HDL ("good" cholesterol), which could raise the risk of heart disease. [26]

Although it predominantly functions as an endogenous precursor to more potent androgens such as testosterone and DHT, DHEA has been found to possess some degree of androgenic activity in its own right, acting as a low affinity & weak partial agonist of the androgen receptor. However, its intrinsic activity at the receptor is quite weak, and on account of that, due to competition for binding with full agonists like testosterone, it can actually behave more like an antagonist depending on circulating testosterone and dihydrotestosterone (DHT) levels, and hence, like an antiandrogen. [26]

DHEA and other adrenal androgens such as androstenedione, although relatively weak androgens, are responsible for the androgenic effects of adrenarche, such as early pubic and axillary hair growth, adult-type body odor, increased oiliness of hair and skin, and mild acne. Women with complete androgen insensitivity syndrome (CAIS), who have a non-functional androgen receptor and are immune to the androgenic effects of DHEA and other androgens, have absent or only sparse/scanty pubic and axillary hair and body hair in general, demonstrating the role of DHEA, testosterone, and other androgens in body hair development at both adrenarche and pubarche. As a neurosteroid, DHEA has important effects on neurological and psychological functioning. [25]

Regular exercise is known to increase DHEA production in the body. Calorie restriction has also been shown to increase DHEA in primates. Some theorize that the increase in endogenous DHEA brought about by calorie restriction is partially responsible for the longer life expectancy known to be associated with calorie restriction.[26] Catalpol and a combination of acetyl-carnitine and propionyl-carnitine on 1:1 ratio also improves endogenous DHEA production and release due to direct cholinergic stimulation of CRH release and an increase of IGF-1 expression respectively. [25]

DHEA is the precursor steroid to androgen and estrogen hormones, and is created by the adrenal gland. Exogenous DHEA can be supplemented for managing levels of this steroid available to the endocrine system. Excessive levels of DHEA can cause issues with androgenization/virilization, a negative consequence for women. Low levels of DHEA can impair neurological processes and hormonal balances. Exercise increases DHEA production in the body, which in turn enhances the body's ability to create and manage other hormones as well as manage neurological processes. Endogenous DHEA production can be improved by supplementing "Catalpol and a combination of acetyl-carnitine and propionyl-carnitine on a 1:1 ratio."

2.8.6 Cortisol

A glucocorticoid hormone involved in catabolic cellular processes.

- Produced in the adrenal cortex and adrenal gland.
- Designed to be a short term coping mechanism to deal with extreme stress.
- It functions to increase blood sugar through gluconeogenesis, to suppress the immune system, and to aid in the metabolism of fat, protein, and carbohydrates.
- When cortisol levels are too high the immune system is suppressed, insulin, blood pressure, and blood sugar levels increase which may lead to brain damage.
- Excessive levels of cortisol decreases bone formation, leading to osteoporosis. It transports potassium out of cells in exchange for an equal number of sodium ions which induces the metabolic shock syndrome known as hyperkalemia. Cortisol also reduces calcium absorption in the intestine, further compounding the potential for bone density reduction and/or inhibition.

2.8.7 Glucagon

A peptide hormone produced which functions in opposition to Insulin (which lowers glucose levels), thus Glucagon is responsible for increasing glucose levels in the bloodstream.

- The homeostatic (im)balance between insulin and glucagons dictates whether there is storage or depletion of energy stores.
- Produced in the pancreas and causes increases in blood glucose levels between meals by stimulating the breakdown of glycogen by the liver.
- Glucagon increases with age and promotes elevated glucose levels.

2.8.8 Thyroid (TSH,T3,T4)

A complex hormonal balance that is regulated via HPA-axis and HPG-axis homeostasis feedback loops.

- Controls our resting metabolic rate, modulates energy production and rest.
- we are very sensitive to any imbalance, with systemic negatives becoming obvious very rapidly in either over-stimulation or under-stimulation.

- High thyroid hormone levels increases the metabolic rate and can cause agitation and jittery/shakiness. An elevated heart rate is commonly experienced in excessive thyroid situations.
- Overly low thyroid hormone levels can cause depression, weight gain, slow heart rate, as well as trouble with concentration and focus.

2.8.9 Insulin

Insulin is a peptide hormone produced by beta cells in the pancreas. It regulates the metabolism of carbohydrates and fats by promoting the absorption of glucose from the blood to skeletal muscles and fat tissue and by causing fat to be stored rather than used for energy. Insulin also inhibits the production of glucose by the liver.

Except in the presence of the metabolic disorder diabetes mellitus and metabolic syndrome, insulin is provided within the body in a constant proportion to remove excess glucose from the blood, which otherwise would be toxic. When blood glucose levels fall below a certain level, the body begins to use stored glucose as an energy source through glycogenolysis, which breaks down the glycogen stored in the liver and muscles into glucose, which can then be utilized as an energy source. As a central metabolic control mechanism, its status is also used as a control signal to other body systems (such as amino acid uptake by body cells). In addition, it has several other anabolic effects throughout the body. [6]

Humulin R (regular human insulin injection [rDNA origin]) is a short-acting insulin that has a relatively short duration of activity as compared with other insulins. Humulin is identical in chemical structure to human insulin. Self-administered insulin therapy can be used to enhance the metabolic process. Most pharmacies in the USA will sell Humulin R without a prescription + insulin syringes. Typical doses range from 2iu to 10iu 30-minutes before the end of an intense workout. One *must* consume at a minimum of 10g/carb per 1iu of insulin injected within 30 min post-injection + a regular meal within the hour to prevent hypo-glycemia. It should be noted that Insulin is the most potent anabolic non-steroidal hormone in the human body and that elevated levels that do not have sufficient carbohydrates and protein to bind to and transport to muscle tissue will cause the body to go into hypo-glycemic shock. This is not recommended for a novice bodybuilder or anyone who does not have very strict control of their daily nutritional planning and execution. A lack of self control or simple mistake with exogenous insulin therapy can result in coma and death.

2.8.10 SHBG, Sex Hormone Binding Globulin

Testosterone and estradiol circulate in the bloodstream, bound mostly to SHBG and to a lesser extent serum albumin and corticosteroid-binding globulin (CBG) (AKA transcortin). Only a very small fraction of about 1-2% is unbound, or "free," and thus biologically active and able to enter a cell and activate its receptor. SHBG inhibits the function of these hormones.

SHBG (sex hormone binding globulin) is a protein created primarily by the liver that binds to sex steroids, and renders them inactive for as long as SHBG is bound to them. SHBG is a hormone reservation system... it has affinity binding preference as such: dihydrotestosterone (DHT) > testosterone > androstenediol > estradiol (E2) > estrone. [5] SHBG has both enhancing and inhibiting hormonal influences. It decreases with high levels of insulin, growth hormone, insulin-like growth factor 1 (IGF-1), androgens, prolactin and transcortin. High estrogen, and thyroxine cause it to increase. [4]

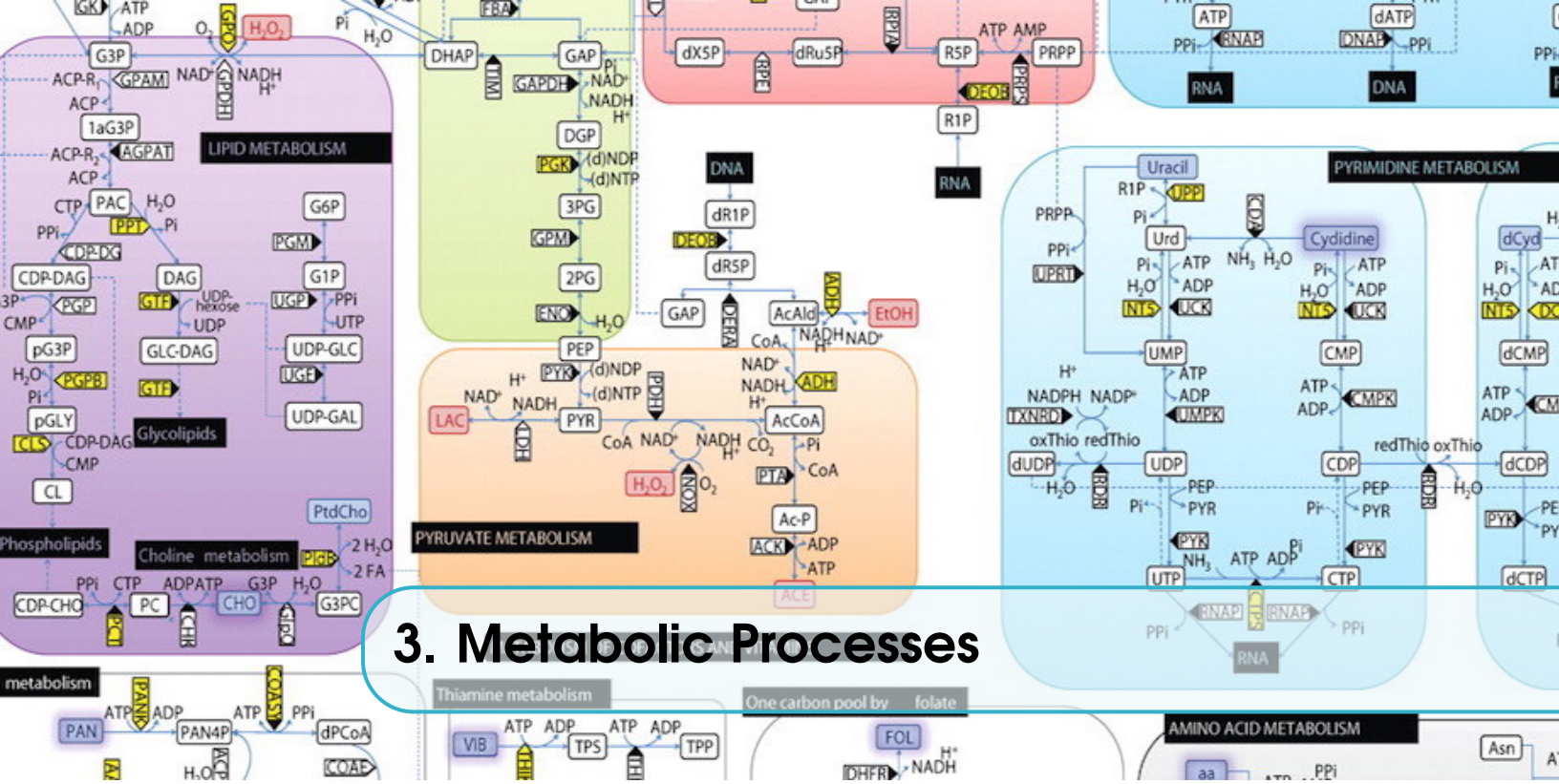
SHBG levels are decreased by androgens, administration of anabolic steroids, polycystic ovary syndrome, hypothyroidism, obesity, Cushing's syndrome, and acromegaly. Low SHBG levels increase the probability of Type 2 Diabetes. SHBG levels increase with estrogenic states (oral contraceptives), pregnancy, hyperthyroidism, cirrhosis, anorexia nervosa, and certain drugs. Long-term calorie restriction of more than 50 percent increases SHBG, while lowering free and total testosterone and estradiol. DHEA-S, which lacks affinity for SHBG, is not affected by calorie restriction. [4]

SHBG as affected by estrogen Hormone Replacement Therapy / Birth Control [3]: "Plasma SHBG levels were higher in the group treated with estrogen alone than in groups of women treated with sequential or combined HRT."

Exogenous Insulin and its effect on SHBG levels in newly diagnosed diabetes-type-2 patients [3]: "Insulin Therapy increases serum SHBG likely through improving insulin resistance and liver function." This is the opposite effect of Exogenous Insulin Therapy in non-diabetic patients. It can be inferred that insulin therapy brings diabetic patients back into homeostasis for proper insulin levels vs exogenous insulin therapy by non-diabetic patients which would decrease serum level SHBG levels due to excessive levels of insulin.

Primary effects of SHBG on hormone levels

- Higher SHBG = more of the Total Testosterone will be bound to it, thus reducing Free Testosterone... thus reducing virilization (masculinization effects) in women. Lower SHBG levels allow males to have additional masculinization due to the increase of Free Testosterone that can bind to androgen receptors. These factors are critical to understanding the hormonal balance and influence of SHBG on the overall functional ability of endogenous and exogenous sex-steroid levels. If SHBG is too high, your body will suffer for lack of sex-steroid levels that are needed for receptor bindings. The proper level of SHBG that determines your Free Testosterone and Free Estradiol depends on your fitness goals. Since you can modify SHBG levels via diet, you will want to tune your diet accordingly to your fitness goals.
- How diet affects SHBG levels: "One of the major controlling factors on SHBG synthesis is insulin. This intake of protein has been shown to increase insulin levels (32), and insulin has been shown to reduce SHBG levels (33, 34)." Thus a diet higher in protein = higher insulin levels = lower SHBG levels = more Free Testosterone = higher anabolic abilities and androgen receptor contact. [5]



3. Metabolic Processes

3.1 Introduction to Metabolism

Metabolism is the set of life-sustaining chemical transformations within the cells of living organisms. These enzyme-catalyzed reactions allow organisms to grow and reproduce, maintain their structures, and respond to their environments. The word metabolism can also refer to all chemical reactions that occur in living organisms, including digestion and the transport of substances into and between different cells, in which case the set of reactions within the cells is called intermediary metabolism or intermediate metabolism.

Metabolism is usually divided into two categories: catabolism, the breaking down of organic matter by way of cellular respiration, and anabolism, the building up of components of cells such as proteins and nucleic acids. Usually, breaking down releases energy and building up consumes energy.

The chemical reactions of metabolism are organized into metabolic pathways, in which one chemical is transformed through a series of steps into another chemical, by a sequence of enzymes. Enzymes are crucial to metabolism because they allow organisms to drive desirable reactions that require energy that will not occur by themselves, by coupling them to spontaneous reactions that release energy. Enzymes act as catalysts that allow the reactions to proceed more rapidly. Enzymes also allow the regulation of metabolic pathways in response to changes in the cell's environment or to signals from other cells.

This section will be extended in future revisions of the document. If you wish to know more, please consult a biochemistry textbook. We'll cover some of the more commonly discussed elements and features of the metabolism in the mean time.

R https://en.wikipedia.org/wiki/Metabolism

3.2 Elements of the Metabolic System

The human body is not a simple machine. It is capable of using multiple types of food (proteins, fats, carbohydrates) as sources of fuel and it will process and store that fuel in different ways depending on patterned behavior and immediate metabolic requirements. The body burns endogenous sources of stored fuel in a defined manner, with preferences for fuel types depending on the organ being fueled.

In exercise physiology we need to be aware of how we tune our nutritional needs to maximize our physical abilities based on our fitness goals. As such, choosing the proper fuels and in what ratios they are consumed is of primary importance. Whatever our end goal for fitness, we must maximize our efficiency of generating ATP - the “molecular unit of currency” for energy.

3.2.1 ATP, Adenosine triphosphate

Often called the "molecular unit of currency" of intracellular energy transfer. ATP transports chemical energy within cells for metabolism. It is one of the end products of photophosphorylation, cellular respiration, and fermentation and used by enzymes and structural proteins in many cellular processes, including biosynthetic reactions, motility, and cell division. [44]

3.2.2 Glutamine

Glutamine is the most abundant amino acid (building block of protein) in the body. The body can make enough glutamine for its regular needs. But during times of extreme stress (the kind you experience after heavy exercise or an injury), your body may need more glutamine than it can make. Most glutamine is stored in muscles, followed by the lungs where much of the glutamine is made. [48]

3.2.3 Metabolic Fuel

These include: glucose, fatty acids, and ketone bodies. Muscle differs from the brain in having a large store of glycogen. In fact, about three-fourths of all the glycogen in the body is stored in muscle.

This glycogen is readily converted into glucose 6-phosphate for use within muscle cells. Muscle, like the brain, lacks glucose 6-phosphatase, and so it does not export glucose. Rather, muscle retains glucose, its preferred fuel for bursts of activity. [41]

In actively contracting skeletal muscle, the rate of glycolysis far exceeds that of the citric acid cycle, and much of the pyruvate formed is reduced to lactate, some of which flows to the liver, where it is converted into glucose. [42] This is one of the reasons why proper liver health is so important for exercise physiology. Additionally, a healthy liver produces proper amounts of Albumin - the primary protein used to transport hormones and other vital resources in the bloodstream.

3.2.4 Liver Functions

The liver is essential for providing fuel to the brain, muscle, and other peripheral organs. Indeed, the liver, which can be from 2% to 4% of body weight, is an organism’s metabolic hub. Most compounds absorbed by the intestine first pass through the liver, which is thus able to regulate the level of many metabolites in the blood. [41]

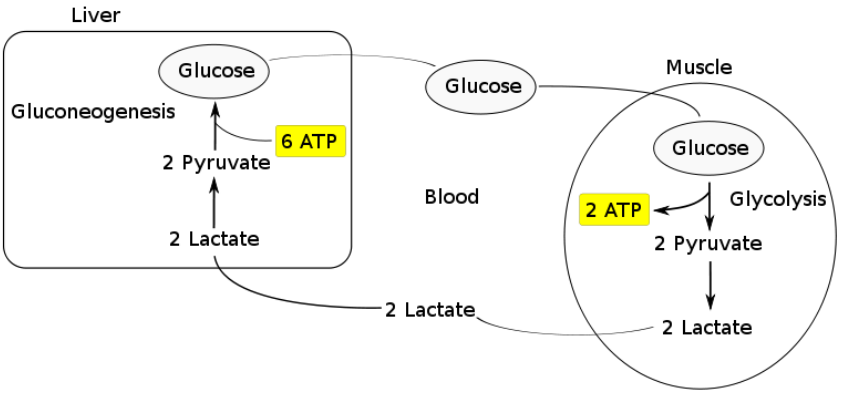


Figure 3.1: Metabolic activities of the liver.

3.2.5 Kidney, Hydration, Oxygen

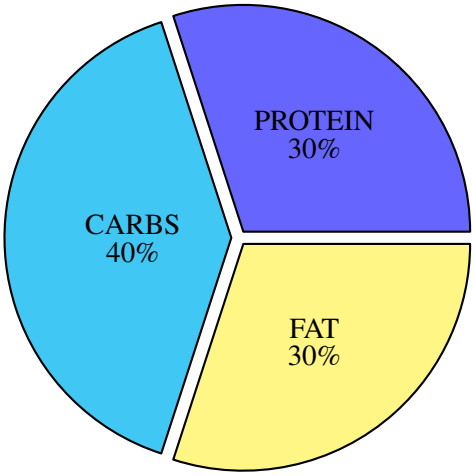
The major purpose of the kidney is to produce urine, which serves as a vehicle for excreting metabolic waste products and for maintaining the osmolarity of the body fluids. The blood plasma is filtered nearly 60 times each day in the renal tubules. Water-soluble materials in the plasma, such as glucose, and water itself are reabsorbed to prevent wasteful loss. The kidneys require large amounts of energy to accomplish the reabsorption. During starvation, the kidney becomes an important site of gluconeogenesis and may contribute as much as half of the blood glucose. [41]

3.3 Macro-nutrition for Fitness

Nutrition is the most important aspect of physical and mental health. You are what you eat, as the saying goes. The following graphics show standard ratios that can be applied to your diet for controlling body composition, aesthetics, and fitness goals. These are approximates. A +/- 5% range is acceptable for error margin on macro planning for nutrition plans.

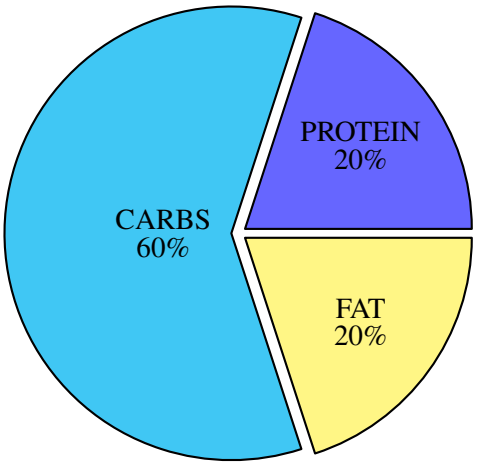
3.3.1 Macros: Bulking, Muscle

Bulking is all about gaining mass. Typically people want to add muscle so the following ratios are used.



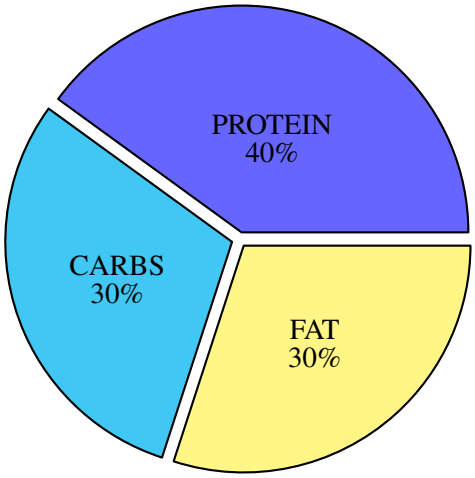
3.3.2 Macros: Bulking, Fat

In the rare event that one needs to gain fat instead of focusing on gaining muscle, the following ratios are appropriate.



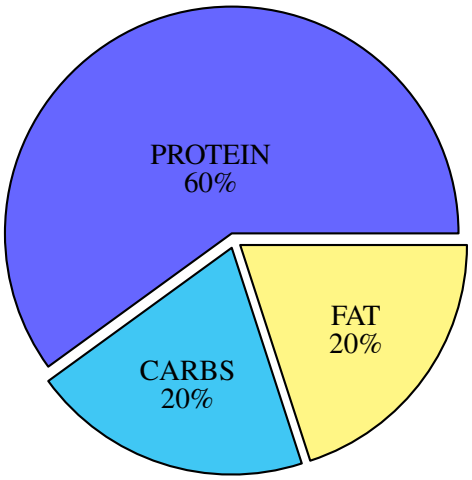
3.3.3 Macros: Maintaining Mass

Maintenance is a ratio that allows the body to keep fat and muscle at the same level; not gaining or losing weight or muscle structure/tone. Muscles will repair themselves after stress/exercise correctly while body fat percentage remains in a stable zone.



3.3.4 Macros: Cutting Mass

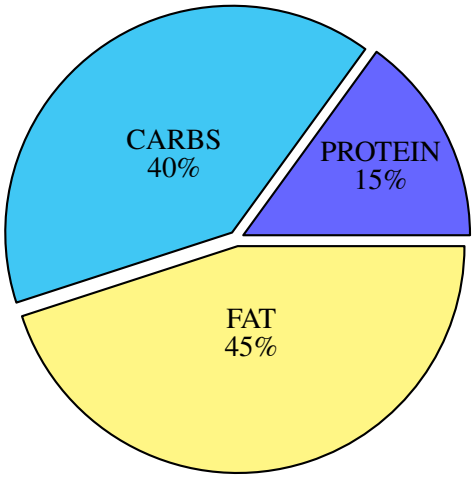
Cutting cycles involve high protein and fat while keeping carbs low. This helps the body switch to using fat as a fuel source, which is a denser and more efficient fuel but not as rapidly used as simple or complex carbs, nor protein; so it requires more energy to utilize and the glycemic index + insulin response cycle changes. Ketogenesis can be utilized in this method to rapidly lower body fat percentage.



3.3.5 Macros: Catabolic Atrophy

Want to lose muscle mass? Keep protein low to starve the muscle fibers from their primary fuel source that rebuilds/maintains mass and tone. Typically 0.5g/per-pound of body weight. Adjust with the same 0.5g/lb as your body weight reduces over time if you are concurrently losing weight while

letting muscles atrophy.



3.3.6 Managing Fat Intake

Notice that fat never goes below 15 percent of total calories. Since hormones are constructed from cholesterol and other fat molecules, getting any less than that can actually suppress normal hormone levels. This also has a negative effect on the bodily functions driven by those hormones, including growth and development, metabolism, reproduction, and mood. Low fat intake can also impair absorption of the fat-soluble vitamins A, D, E, and K. [31]

3.3.7 Nutrition for bulking

In order to achieve large gains in muscle mass along with significant body fat decreases, many hormonal events need to occur in the body. The amount of success that that can be achieved in these endeavors is determined by how much testosterone, growth hormone, and insulin are produced by the body and whether or not they are produced at the right times. These events are affected to a large extent by the quality, timing, amount, and ratio of the macronutrients consumed on a daily basis. [32]

3.3.8 Gender's role in macro-nutrition

Research suggests a variety of reasons that women have a greater reliance on fats for fuel during exercise, including [31]:

- Estrogen enhances epinephrine production, the primary hormone that stimulates lipolysis (fatty acid breakdown).
- Estrogen promotes the release of human growth hormone (HGH), which inhibits the uptake of carbohydrates and increases the mobilization of fatty acids from adipose tissue.
- Women have increased blood flow to adipose tissue, which could assist in fatty acid mobilization.
- Women have higher levels of intramuscular triglycerides (IMTG), a fat-based source of fuel that spares muscle glycogen during moderate to high intensity exercise. This sparing of muscle glycogen may actually give women an endurance edge when performing at high intensities against men.

- According to one study, men appear to rely more on stored carbohydrate for fuel than women when doing the same exercise.

3.4 Metabolic Transporters

What makes life possible is the transformation of the potential chemical energy of fuel molecules through a series of reactions within a cell, enabled by oxygen, into other forms of chemical energy, motion energy, kinetic energy, and thermal energy. The metabolic reactions are energy-transducing processes in which the oxidation-reduction reactions are vital for ATP (cellular energy) synthesis. [54]

3.4.1 Alanine

Alanine is an alpha-amino acid that is used in the biosynthesis of proteins. The L-isomer of Alanine, L-Alanine is second only to leucine in rate of occurrence, accounting for 7.8% of the primary structure in a sample of 1,150 proteins. The R-isomer version, D-Alanine occurs in bacterial cell walls and in some peptide antibiotics.

Alanine is a nonessential amino acid, meaning it can be manufactured by the human body, hence need not be obtained directly through diet. Alanine is found in a wide variety of foods including beans and rice, but is particularly concentrated in meats. Alanine can be manufactured in the body from pyruvate and branched chain amino acids such as valine, leucine, and isoleucine.

Alanine is most commonly produced by reductive amination of pyruvate. Because transamination reactions are readily reversible and pyruvate pervasive, alanine can be easily formed and thus has close links to metabolic pathways such as glycolysis, gluconeogenesis, and the citric acid cycle. It also arises together with lactate and generates glucose from protein via the alanine cycle. [66]

Alanine plays a key role in glucose–alanine cycle (aka Cahill Cycle) between tissues and liver. That process is covered in the "Alanine Cycle" section of this document.

3.4.2 Albumin

The primary transport protein, created by the liver. Serum albumin is the main protein of human blood plasma. It binds water, cations (such as Ca2+, Na+ and K+), fatty acids, hormones, bilirubin, thyroxine (T4) and pharmaceuticals - its main function is to regulate the colloidal osmotic pressure of blood. [46] Low serum levels of albumin can inhibit the functionality of all involved transports, thus negatively affecting healthy and mobility.

3.4.3 Insulin

Insulin is a peptide hormone produced by beta cells in the pancreas. It regulates the metabolism of carbohydrates and fats by promoting the absorption of glucose from the blood to skeletal muscles and fat tissue and by causing fat to be stored rather than used for energy. Insulin also inhibits the production of glucose by the liver. [6]

- Insulin is required to store energy (glucose as glycogen) and synthesize proteins from amino acids.
- Insulin allows us to use blood sugar in the fuel mix for our cells. produced in the pancreas after meals and when blood sugar is elevated.
- When insulin levels are low you feel tried because your cells do not receive enough glucose.
- When insulin levels are high insulin receptors shut down and you store excess glucose as body fat.

- Elevated insulin levels cause artery and vascular walls to swell, which decrease their diameter and makes it more difficult to circulate nutrients and oxygen.
- Elevated insulin levels of insulin are the norm for individuals who are overweight due to the fact that insulin production is greatly influenced by body weight.
- Eating excess carbohydrates and processed foods sends our insulin production through the roof and burns out our receptor sites making it extremely difficult for us to stop our cravings for sweets, which leads us on a downward spiral towards adult-onset diabetes and obesity.

3.5 Cycles of the Metabolic Process

3.5.1 Alanine Cycle

A glucose generating process involving the cycling of nutrients between skeletal muscle and the liver. When muscles degrade amino acids for energy needs, the resulting nitrogen is transaminated to pyruvate to form alanine. This alanine is shuttled to the liver where the nitrogen enters the urea cycle and the pyruvate is used to make glucose. [48]

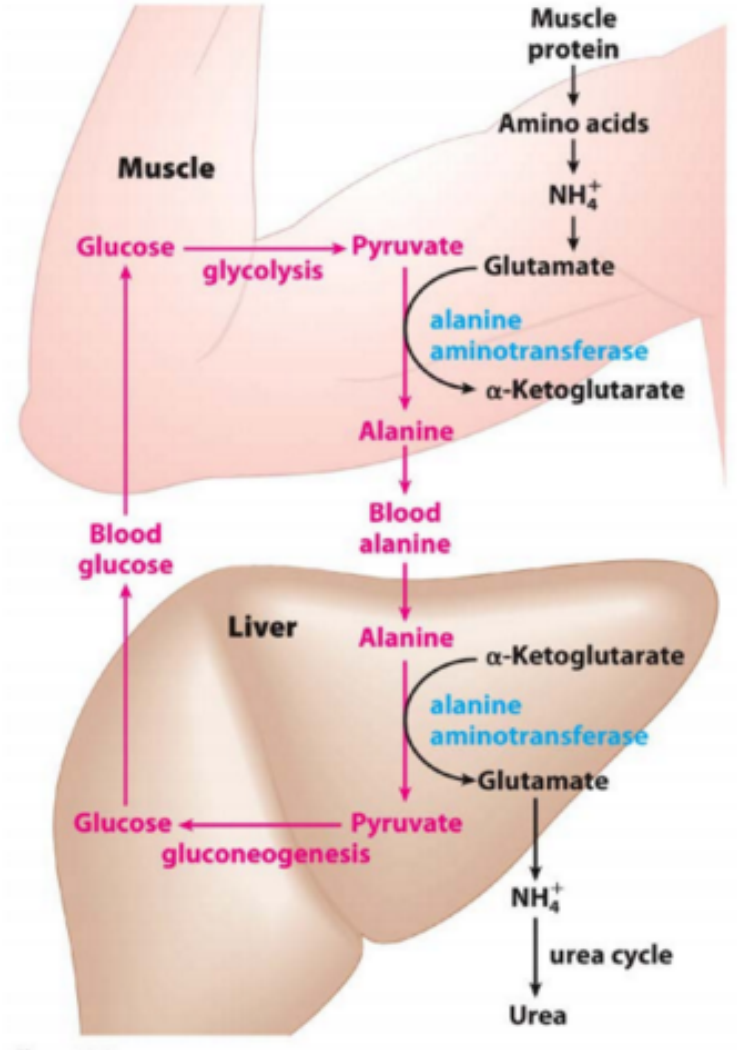


Figure 3.2: The Glucose - Alanine Cycle

3.5.2 Catabolic, Anabolic

Catabolism breaks down products into Urea (waste) + Fat and Glucose as potential energy. Anabolism creates tissue and muscle building materials. Losing weight is primarily a catabolic process where building muscle mass is primarily an anabolic process.

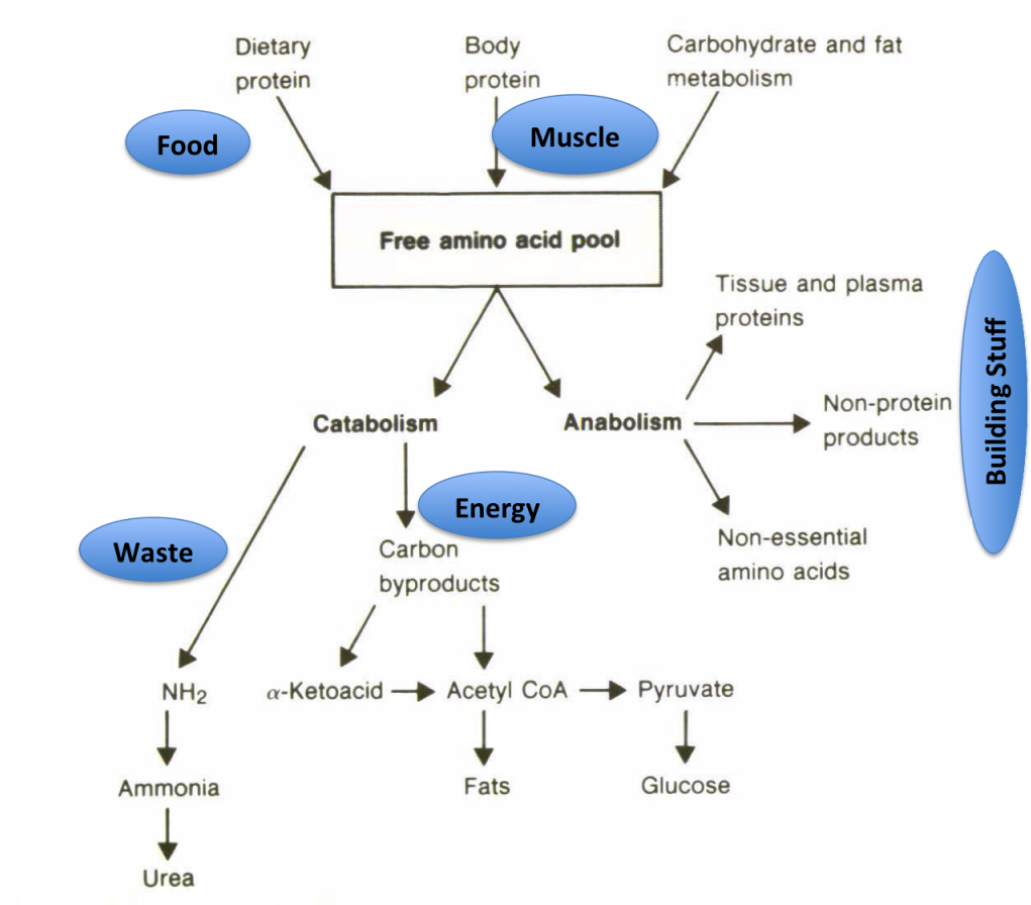


Figure 3.3: Losing mass vs Gaining mass

3.5.3 GFA Cycle

The Glucose Fatty Acid cycle describes interrelationships of glucose and fatty acid oxidation as defined by fuel flux and fuel selection by various organs. This cycle is not a metabolic cycle such as can be defined by the TCA cycle as an example, but defines the dynamic interactions between these two major energy substrate pools. The glucose-fatty acid cycle was first proposed by Philip Randle and co-workers in 1963 and is, therefore, sometimes referred to as the Randle cycle or Randle hypothesis. [65]

The Randle cycle is a biochemical mechanism involving the competition between glucose and fatty acids for their oxidation and uptake in muscle and adipose tissue. The cycle controls fuel selection

and adapts the substrate supply and demand in normal tissues. This cycle adds a nutrient-mediated fine tuning on top of the more coarse hormonal control on fuel metabolism. This adaptation to nutrient availability applies to the interaction between adipose tissue and muscle. Hormones that control adipose tissue lipolysis affect circulating concentrations of fatty acids, these in turn control the fuel selection in muscle. Mechanisms involved in the Randle Cycle include allosteric control, reversible phosphorylation and the expression of key enzymes. The energy balance from meals composed of differing macronutrient composition is identical, but the glucose and fat balances that contribute to the overall energy balance change reciprocally with meal composition. [67]

3.5.4 Glycogenesis

Glycogenesis is the formation of glycogen from glucose. Glycogen is synthesized depending on the demand for glucose and ATP (energy). If both are present in relatively high amounts, then the excess of insulin promotes the glucose conversion into glycogen for storage in liver and muscle cells.
In the synthesis of glycogen, one ATP is required per glucose incorporated into the polymeric branched structure of glycogen. actually, glucose-6-phosphate is the cross-roads compound. Glucose-6-phosphate is synthesized directly from glucose or as the end product of gluconeogenesis.

http://chemistry.elmhurst.edu/vchembook/604glycogenesis.html

3.5.5 Glycogenolysis

In glycogenolysis, glycogen stored in the liver and muscles, is converted first to glucose-1- phosphate and then into glucose-6-phosphate. Two hormones which control glycogenolysis are a peptide, glucagon from the pancreas and epinephrine from the adrenal glands.

Glucagon is released from the pancreas in response to low blood glucose and epinephrine is released in response to a threat or stress. Both hormones act upon enzymes to stimulate glycogen phosphorylase to begin glycogenolysis and inhibit glycogen synthetase (to stop glycogenesis).

Glycogen is a highly branched polymeric structure containing glucose as the basic monomer. First individual glucose molecules are hydrolyzed from the chain, followed by the addition of a phosphate group at C-1. In the next step the phosphate is moved to the C-6 position to give glucose 6-phosphate, a cross road compound.

Glucose-6-phosphate is the first step of the glycolysis pathway if glycogen is the carbohydrate source and further energy is needed. If energy is not immediately needed, the glucose-6-phosphate is converted to glucose for distribution in the blood to various cells such as brain cells.

http://chemistry.elmhurst.edu/vchembook/604glycogenesis.html

3.5.6 Gluconeogenesis

Gluconeogenesis is the process of synthesizing glucose from non-carbohydrate sources. The starting point of gluconeogenesis is pyruvic acid, although oxaloacetic acid and dihydroxyacetone phosphate also provide entry points. Lactic acid, some amino acids from protein and glycerol from fat can be

converted into glucose. Gluconeogenesis is similar but not the exact reverse of glycolysis, some of the steps are the identical in reverse direction and three of them are new ones. Without going into detail, the general gluconeogenesis sequence is given in the graphic on the left.

Notice that oxaloacetic acid is synthesized from pyruvic acid in the first step. Oxaloacetic acid is also the first compound to react with acetyl CoA in the citric acid cycle. The concentration of acetyl CoA and ATP determines the fate of oxaloacetic acid. If the concentration of acetyl CoA is low and concentration of ATP is high then gluconeogenesis proceeds. Also notice that ATP is required for a biosynthesis sequence of gluconeogenesis.

Gluconeogenesis occurs mainly in the liver with a small amount also occurring in the cortex of the kidney. Very little gluconeogenesis occurs in the brain, skeletal muscles, heart muscles or other body tissue. In fact, these organs have a high demand for glucose. Therefore, gluconeogenesis is constantly occurring in the liver to maintain the glucose level in the blood to meet these demands.

http://chemistry.elmhurst.edu/vchembook/604glycogenesis.html

3.5.7 Lipolysis

Lipolysis is the breakdown of lipids and involves hydrolysis of triglycerides into glycerol and free fatty acids. The following hormones induce lipolysis: epinephrine, norepinephrine, ghrelin, growth hormone, testosterone, and cortisol. [63]

Lipolysis is the biochemical pathway responsible for the catabolism of triacylglycerol (TAG) stored in cellular lipid droplets. The hydrolytic cleavage of TAG generates non-esterified fatty acids, which are subsequently used as energy substrates, essential precursors for lipid and membrane synthesis, or mediators in cell signaling processes. Consistent with its central importance in lipid and energy homeostasis, lipolysis occurs in essentially all tissues and cell types, it is most abundant, however, in white and brown adipose tissue. [64]

Nutritional regulation of lipolysis occurs at multiple levels in response to changing metabolic conditions and nutrient intakes. Acute, rapid regulation of adipose tissue lipolysis occurs in order to maintain the supply of energy substrates during the postabsorptive state and to allow for efficient storage of excess fuels following a meal. Chronic exposure to extreme nutritional states, such as obesity or starvation, also induces metabolic adaptations that include changes in lipolysis. [65]

3.5.8 Steroidogensis

This is the life-cycle process of steroid synthesis and conversion.

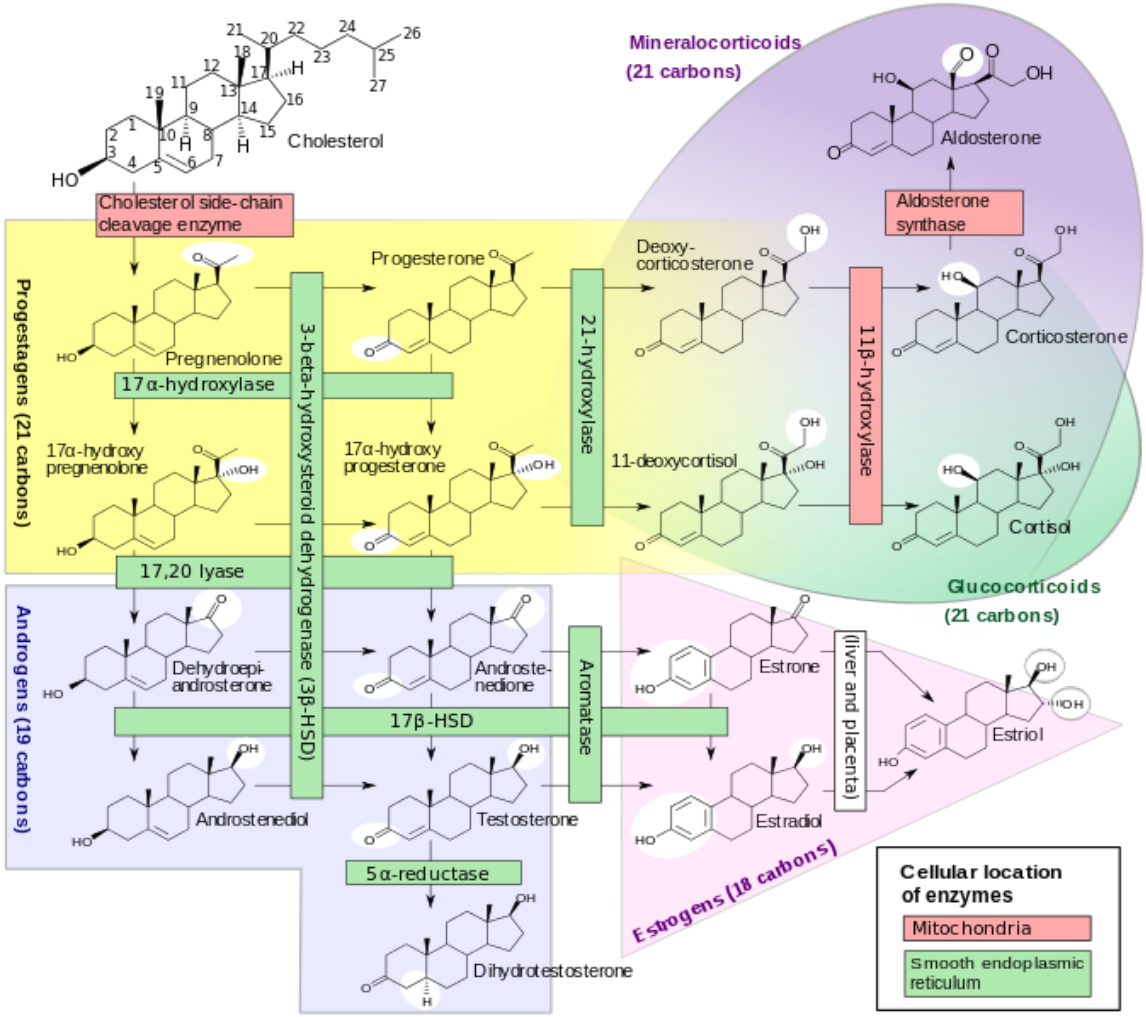


Figure 3.4: The Steroidogenesis Process

3.5.9 Steroidogensis

This is the life-cycle process of steroid synthesis and conversion.

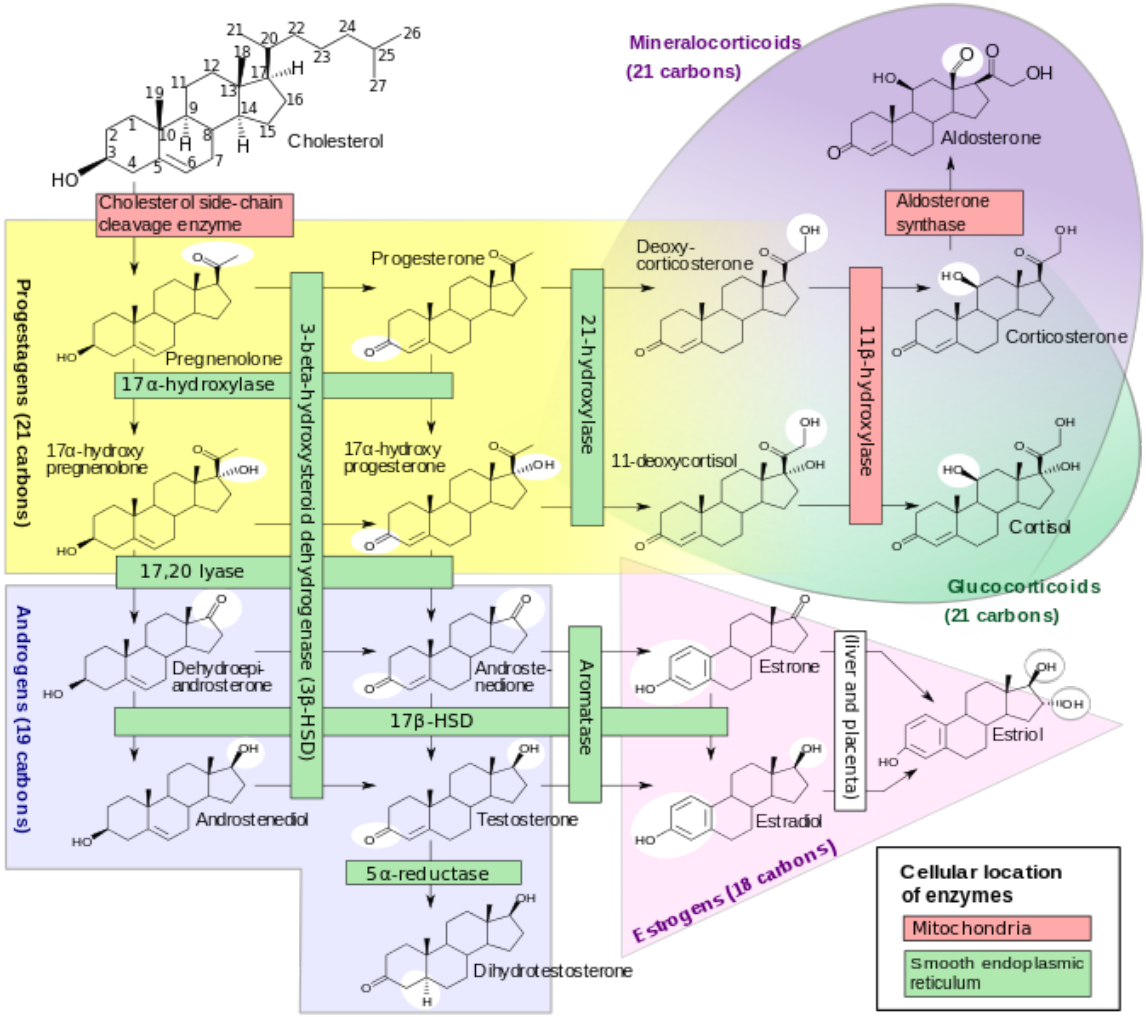


Figure 3.5: The Steroidogenesis Process

3.5.10 Wake, Sleep Cycles

We all need to rest in order to be at our peak fitness levels. As demonstrated in the figure below, rest promotes many essential metabolic processes.

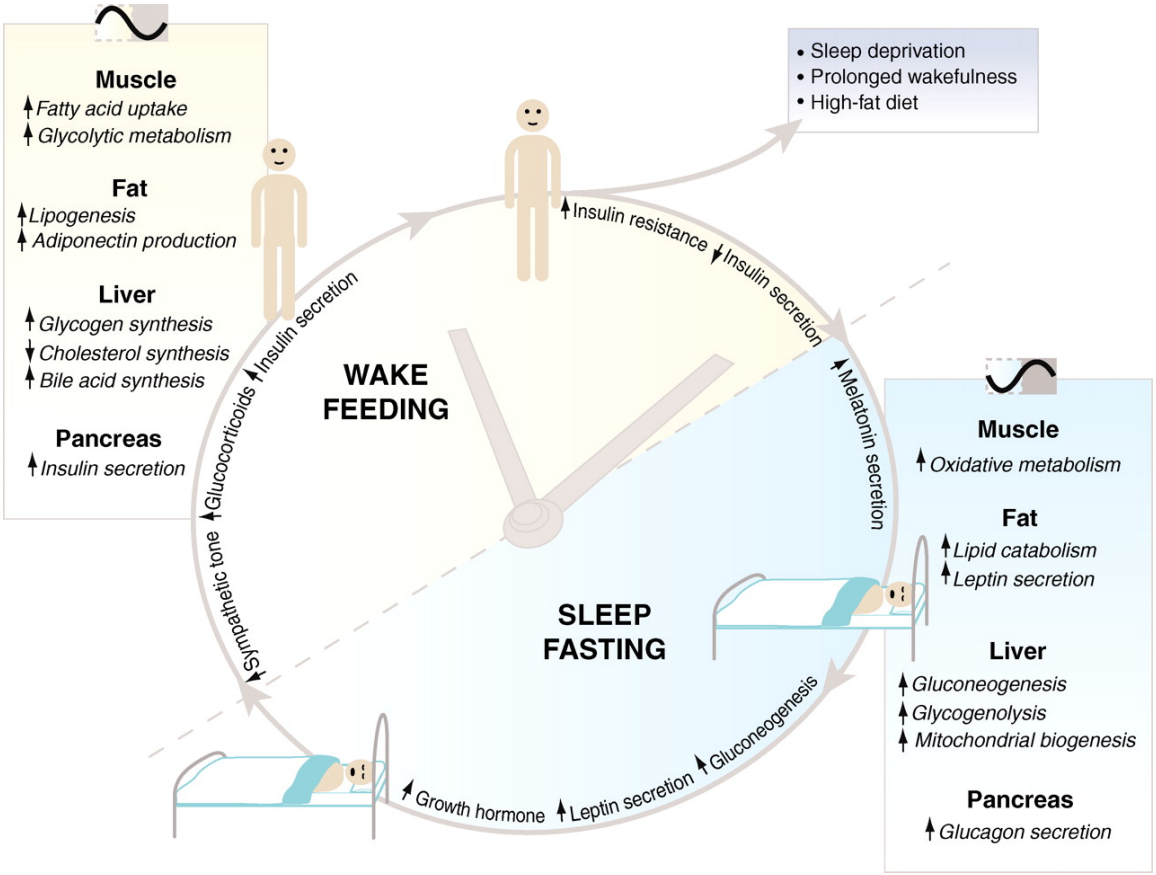


Figure 3.6: Wake vs Sleep Cycles

4. Supplementation, Exogenous

4.1 Introduction to Supplementation

Sometimes you just need more than food and genetics can offer.

4.2 Stimulants

Stimulants (also referred to as psychostimulants) are psychoactive drugs that induce temporary improvements in either mental or physical functions or both. Examples of these kinds of effects may include enhanced alertness, wakefulness, and locomotion, among others. Due to their rendering a characteristic "up" feeling, stimulants are also occasionally referred to as "uppers". Depressants or "downers", which decrease mental and/or physical function, are in stark contrast to stimulants and are considered to be the functionally opposite drug class. Stimulants are widely used throughout the world as prescription medicines and without prescription both as legal substances and illicit substances of recreational use or abuse.[52]

4.2.1 Amphetamine

In 2015, a systematic review and a meta-analysis of high quality clinical trials found that, when used at low (therapeutic) doses, amphetamine produces modest, unambiguous improvements in cognition, including working memory, episodic memory, and inhibitory control, in normal healthy adults; the cognition-enhancing effects of amphetamine are known to occur through its indirect activation of both dopamine receptor D1 and adrenoceptor A2 in the prefrontal cortex.

Therapeutic doses of amphetamine also enhance cortical network efficiency, an effect which mediates improvements in working memory in all individuals. Amphetamine and other ADHD stimulants also improve task saliency (motivation to perform a task) and increase arousal (wakefulness), in turn promoting goal-directed behavior.

Amphetamine is used by some athletes for its psychological and performance-enhancing effects,

such as increased stamina and alertness. In healthy people at oral therapeutic doses, amphetamine has been shown to increase physical strength, acceleration, stamina, and endurance, while reducing reaction time. Amphetamine improves stamina, endurance, and reaction time primarily through reuptake inhibition and effluxion of dopamine in the central nervous system. At therapeutic doses, the adverse effects of amphetamine do not impede athletic performance; however, at much higher doses, amphetamine can induce effects that severely impair performance, such as rapid muscle breakdown and elevated body temperature.

Amphetamine stimulates the medullary respiratory centers, producing faster and deeper breaths. Amphetamine also has a slight analgesic effect and can enhance the pain relieving effects of opioids.

https://en.wikipedia.org/wiki/Amphetamine#Physical

4.2.2 Beta Alanine

Beta-alanine is technically a non-essential beta-amino acid, but it has quickly become anything but non-essential in the worlds of performance nutrition and bodybuilding. Also known by its trademarked name CarnoSyn, it has become a shining star due to claims that it raises muscle carnosine levels and increases the amount of work you can perform at high intensities.

Beta-alanine, or 3-aminopropionic acid is a naturally-occurring beta-amino acid and a component of the histidine dipeptides carnosine and anserine, as well as vitamin B5, or pantothenic acid. Structurally, beta-alanine is a hybrid between the potent neurotransmitters L-glycine and GABA, which may explain why consumers often claim to experience a caffeine-like response from it. Beta-alanine is even gaining support within the scientific community for being secondarily classified as a neurotransmitter.

Your body can produce beta-alanine in at least three ways. It can be released during the breakdown of histidine dipeptides, such as carnosine or anserine, or it can be formed as a secondary byproduct of a reaction that converts L-alanine to pyruvate. Additionally, beta-alanine can be formed during digestion, when intestinal microbes remove a carbon atom from L-aspartate, releasing both beta-alanine and CO2.

When consumed as a dietary supplement, beta-alanine passes from the bloodstream into skeletal muscle via a beta-alanine and taurine transporter that's dependent upon both sodium and chloride availability. Once it enters a skeletal muscle cell, it binds with the essential amino acid L-histidine to form the dipeptide carnosine. That's where the fun really begins. Supplementation with beta-alanine has been shown to increase muscle carnosine concentrations by up to 58 percent in just four weeks, and 80 percent in 10 weeks. [10]

4.2.3 Caffeine

Caffeine is a central nervous system (CNS) stimulant of the methylxanthine class. It is the world's most widely consumed psychoactive drug, but — unlike many other psychoactive substances — it is legal and unregulated in nearly all parts of the world. There are several known mechanisms of action to explain the effects of caffeine. The most prominent is that it reversibly blocks the action of

adenosine on its receptor and consequently prevents the onset of drowsiness induced by adenosine. Caffeine also stimulates certain portions of the autonomic nervous system.

R https://en.wikipedia.org/wiki/Caffeine

4.2.4 Clenbuterol

Clenbuterol is not an anabolic steroid, but rather a stimulant that belongs to a classification of compounds known as sympathomimetics. This classification (or 'family') contains other compounds that the average person might be more familiar with, such as: caffeine, ephedrine, albuterol, amphetamines, cocaine, and many others. It is indeed quite a broad drug category, and each of the compounds in this family are related to each other, and more or less carry many similarities and operate in a similar manner through similar pathways. Clenbuterol's effect on the nervous system involves its interaction with adrenoreceptors, which are located in many different tissues and cell types in the body. When Clenbuterol binds to these adrenoreceptors, different effects in different tissue types (depending on the tissues stimulated) will manifest. One effect in particular that we are concerned with is Clenbuterol's effect in adipose (fat) tissue.

There are two different adrenoreceptors in the body – alpha and beta receptors – and within those two different types, there are 9 subtypes. For example, alpha-1, alpha 2, beta-1, beta-2 receptors, etc. The difference between Clenbuterol and other compounds in the stimulant family lie in their different capabilities to stimulate different subtypes, multiple subtypes, or focus on one subtype. Clenbuterol in particular I known for its very strong and almost exclusive stimulation of the beta-2 adrenoreceptors, and therefore this is why Clenbuterol is commonly referred to as a beta-2 receptor agonist. It is within fat tissue that, when beta-2 receptors are stimulated by Clenbuterol, initiate lipolysis (the breakdown of fat into free fatty acids). It has gained plenty of popularity among just bodybuilders and athletes because of this, but among entertainment celebrities, and by proxy, common people looking to drop a few pounds of fat.

Clenbuterol's original use as a medicine in the prescription drug market was (and still currently is) as a bronchodilator in the treatment of asthma. Upon activation of beta-2 receptors in the cell lining of the bronchial tubes, it will initiate bronchial dilation (opening and expansion of the airways) in the lungs, nose, and throat. Almost all sympathomimetic stimulants exert this effect, but Clenbuterol and Albuterol are highly effective in particular for this purpose. Clen has also been used medically in the treatment of other conditions, such as hypertension, cardiovascular shock or slowdown, heart arrhythmias, migraine headaches, allergic reactions and swelling, histamine reactions, and anaphylactic shock.

Although Clenbuterol is a beta-2 receptor agonist, it does exhibit effects on other receptor subtypes as well, with emphasis on the beta-2 subtype. By comparison, Ephedrine is known for stimulating multiple beta and alpha receptors by an equal degree rather than stimulation of one receptor subtype by a large degree.

One important point of note is that through continued consistent use, Clenbuterol will downregulate beta-2 receptors in the body in response to its stimulation of those receptors, and it occurs very quickly. The manifestation of this effect is diminished fat loss during use until the fat loss reaches a

complete stop. There are two methods of remedying this effect. The first is to introduce time off from use of the drug (2 weeks minimum). The second is through the use of Ketotifen Fumarate, an anti-histamine drug that is known for upregulating beta-2 receptors. Benadryl has been rumored to have the same effects as Ketotifen Fumarate on beta-2 receptors, but this has found to be simply untrue because although Benadryl is an antihistamine like Ketotifen, it operates on a very different pathway.

Perhaps the most unique of Clenbuterol side effects is the commonly reported side effect of muscle cramping. This is also a reported side effect of Clenbuterol's close sibling compound, Albuterol. The cause of this is through Clenbuterol's depletion of Taurine in the body. Studies have demonstrated that the use of Clenbuterol depletes levels of the amino acid Taurine both in muscle tissue as well as serum blood plasma. Taurine alongside Magnesium, Potassium, and Sodium play very crucial roles in the regulation of bioelectrical nerve impulses and signals that govern the contraction and relaxation of all muscle tissue types. When Taurine is depleted, involuntary and often intense and painful muscle contractions that lead to cramps can result. It has been found that supplementation with Taurine at 2.5 – 5 grams per day can mitigate this side effect.

When it comes to Clenbuterol and the heart and cardiovascular system, the vast majority of these negative effects involve cardiac hypertrophy, enlargement of ventricles, and cardiac necrosis. Without a doubt, Clenbuterol tends to place a great degree of strain on the cardiovascular system and this should be a consideration for all potential users. Other common Clenbuterol side effects include tremors ("shaky hands"), insomnia, sweating and perspiration, increased blood pressure and headaches, and nausea. Clenbuterol side effects can also include adverse or unique allergies and reactions such as hives and rashes.

See "Celbuterol References" in Bibliography for more information.

4.2.5 Ephedrine

Ephedrine is not an anabolic steroid, but instead belongs to a particular category of compounds known as sympathomimetics (more commonly known as stimulants). It is a sympathomimetic amine that acts upon both the alpha and beta adrenoreceptors. This makes Ephedrine an alpha and beta adrenergic receptor agonist. In contrast to Clenbuterol, another similar sympathomimetic, Clenbuterol is much more selective as it almost exclusively targets the beta-2 adrenoreceptors in the body. Ephedrine is a member of a large family of these sympathomimetic stimulant compounds, which includes others such as: Caffeine, Albuterol, Ephedrine, Dextroamphetamine, Methamphetamine, Cocaine, and many others. It is a very broad category of compounds. All of these compounds, which include Caffeine, Albuterol, Clenbuterol, Ephedrine, Epinephrine, Norepinephrine, and so on and so forth, are all related to one another and could be considered siblings or 'cousins' to each other. Because of this they are related in many ways and carry many similarities.

All of the mentioned compounds (stimulants/sympathomimetics) will act upon the nervous system and essentially increase the activity of the CNS (Central Nervous System), among other effects. Ephedrine will also increase the secretion of Norepinephrine (also known as Noradrenaline) in the body, which will further assist to act upon alpha and beta receptors in the body. The actions that Ephedrine has upon the alpha and beta receptors will trigger different effects in different cell types

and tissues in the body. For example, much like Clenbuterol, Ephedrine when acting upon the alpha and beta receptors of the cells lining the bronchial pathways, will cause bronchial dilation (the opening of the bronchial pathways). This is especially important for asthma patients, which Ephedrine has been used for in traditional Chinese medicine for hundreds of years. When Ephedrine acts upon the alpha and beta receptors of fat cells, it will initiate the process of lipolysis (fat breakdown) whereby free fatty acids are mobilized and released from the fat cell for consumption by the body as fuel/energy. The actions of Ephedrine upon the CNS will also increase the ability to generate nerve impulses more efficiently, and therefore allow the user to generate stronger and more forceful muscle contractions (often very beneficial for weight training, power lifters, and bodybuilders). As one can easily see, the applications of Ephedrine go far beyond the scope of simple fat loss.

As a fat loss agent, Ephedrine is perhaps on par with Clen in popularity and is perhaps even more commonly known than Clenbuterol. Ephedrine as a compound and medication has been known to man for thousands of years, and is considered a very old medicine. It has been used in traditional Chinese medicine for thousands of years and its use dates back in China to the Han Dynasty. In china it is known as Ma Huang, and was used in its natural form from the Ephedra Sinica (known in China as 'Ma Huang') plant, which contains the active compound Ephedrine within it. The synthesis of Ephedrine was performed in 1885 by Japanese chemist Nagi Nagayoshi, and the industrial mass-scale manufacture of Ephedrine in China was underway in the 1920s by the pharmaceutical company Merck.

Ephedrine will exhibit various effects on the body through its ability to directly interact with alpha and beta receptors, as well as its ability to enable the increased secretion of Norepinephrine[5]. The best analogy to use in terms of Ephedrine's activity in the body would be its comparison to Clenbuterol in relation to a hammer and nails analogy: Clenbuterol's action of selectively activating Beta-2 receptors is the equivalent of having several nails sticking out of a wooden surface, and a hammer is used to hammer one specific nail on the head, while Ephedrine is the equivalent of using a larger sledgehammer to hit multiple nails on the head to drive them into the wood. Although not a perfect analogy, this explains Ephedrine's activity with a fair amount of accuracy. Through its activity with the alpha and beta receptors, as described earlier, it will initiate the process of fat loss in fat cells in the body. Its interaction with the same receptor types on other cells, such as the CNS, will increase the ability for additional force generation by skeletal muscles and thereby improve performance in a more short-term immediate sense.

See "Ephedrine References" in Bibliography for more information.

4.2.6 Pseudo-Ephedrine

See Ephedrine.

4.3 Enzyme Modulation

4.3.1 Cytochrome P450 (CYP450)

Cytochrome P450 enzymes are present in most tissues of the body, and play important roles in hormone synthesis and breakdown (including estrogen and testosterone synthesis and metabolism), cholesterol synthesis, and vitamin D metabolism. Cytochrome P450 enzymes also function to metabolize potentially toxic compounds, including drugs and products of endogenous metabolism such as bilirubin, principally in the liver. [20]

A subset of cytochrome P450 enzymes play important roles in the synthesis of steroid hormones (steroidogenesis) by the adrenals, gonads, and peripheral tissue. CYP19A (P450arom, aromatase) in endoplasmic reticulum of gonads, brain, adipose tissue, and elsewhere catalyzes aromatization of androgens to estrogens. [20]

Steroids are oxidized mainly by cytochrome P450 oxidase enzymes, such as CYP3A4. These reactions introduce oxygen into the steroid ring and allow the cholesterol structure to be broken up by other enzymes, to form bile acids as final products. These bile acids can then be eliminated through secretion from the liver in the bile. The expression of this oxidase gene can be upregulated by the steroid sensor PXR when there is a high blood concentration of steroids. [29]

Steroid hormones, lacking the side chain of cholesterol and bile acids, are typically hydroxylated at various ring positions and/or oxidized at the 17 position, then conjugated with sulfate or glucuronic acid and excreted in the urine. [29]

4.3.2 Grapefruit

Grapefruit contains natural compound sources that modulate the CYP450 enzyme. To study the effects of grapefruit and grapefruit products on body weight and metabolic syndrome, 91 obese patients were randomized to either placebo capsules and 7 ounces (207 mL) of apple juice, grapefruit capsules with 7 ounces (207 mL) of apple juice, 8 ounces (237 mL) of grapefruit juice with placebo capsule, or half of a fresh grapefruit with a placebo capsule three times a day before each meal. Metabolic syndrome parameters were measured at the beginning and end of 12 weeks. [21]

After 12 weeks, the fresh grapefruit group had lost 1.6 kg, the grapefruit juice group had lost 1.5 kg, the grapefruit capsule group had lost 1.1 kg, and the placebo group had lost 0.3 kg. The fresh grapefruit group lost significantly more weight than the placebo group ($P < .05$). A secondary analysis of those with the metabolic syndrome in the four treatment groups demonstrated a significantly greater weight loss in the grapefruit, grapefruit capsule, and grapefruit juice groups compared with placebo ($P < .02$). [21]

There was also a significant reduction in 2-hour post-glucose insulin level in the grapefruit group compared with placebo. Half of a fresh grapefruit eaten before meals was associated with significant weight loss. In metabolic syndrome patients the effect was also seen with grapefruit products. Insulin resistance was improved with fresh grapefruit. Although the mechanism of this weight loss is unknown it would appear reasonable to include grapefruit in a weight reduction diet. [21]

Grapefruit and grapefruit juice have been found to interact with numerous drugs (at least 85 known

by 2013), in many cases resulting in adverse effects. Organic compounds that are furanocoumarin derivatives interfere with the hepatic and intestinal enzyme CYP450 isoform CYP3A4 and are believed to be primarily responsible for the effects of grapefruit on the enzyme. Bioactive compounds in grapefruit juice may also interfere with P-glycoprotein and organic anion transporting polypeptides (OATPs), either increasing or decreasing the bioavailability of a number of drugs. [1]

4.3.3 Cimetidine (Tagamet)

This Over The Counter (OTC) medication, which functions as a proton pump in the digestive system, Inhibits the activity of CYP450 enzyme and decreases the levels of AST + ALT liver enzymes which will aid in treatment of hepatotoxicity (liver stress or damage). If GGT (gamma-glutamyl transferase) is in an elevated status in conjunction with elevated AST/ALT this indicates liver damage, whereas standard range GGT in presence of elevated AST/ALT indicates liver stress. This is important because some exogenous supplements used in high level fitness training can put stress on the liver, especially during the cutting phases where low body-fat percentages + low dietary fat intake is being observed in the athlete. Cimetidine also is a potentiator, meaning that it increases and prolongs the effects of opiate medication.

We observed the levels of ALT, AST, blood sugar in model group increased significantly, then kept increasing through the study.The decrease of CYP450, CYP2E1 in therapeutic groups was obvious.There was an obvious difference of ALT, AST between therapeutic group and model group, while the other indexes be not obviously distinguished from each other.The hepatic injury in therapeutic groups was significantly lessened. So cimetidine can prevent nonalcoholic hepatic injury, inhibit the expressions of CYP450 and CYP2E1, and decrease the expression of ALT and AST, but have no effect on blood sugar, insulin, TG, TC and lipoprotein. [1]

4.4 Liver Health

4.4.1 R-ALA, ALA

Lipoic acid (LA), also known as alpha-lipoic acid (ALA), and thioctic acid are a organosulfur compounds derived from octanoic acid. ALA is made in animals normally, and is essential for aerobic metabolism. It is also manufactured and is available as a dietary supplement in some countries where it is marketed as an antioxidant, and is available as a pharmaceutical drug in other countries. [15] R-ALA is an essential supplement for use in liver detoxification and hepatotoxicity treatment.

4.4.2 Tauroursodeoxycholic acid (TUDCA)

TUDCA is an ambiphilic bile acid. It is the taurine conjugate form of ursodeoxycholic acid (UDCA). Humans are found to have trace amounts of TUDCA. TUDCA is produced in several countries for the treatment of gallstones and liver cirrhosis. [16] TUDCA is an essential supplement for use in liver detoxification and hepatotoxicity treatment.

4.4.3 N-acetyl-L-cysteine (NAC)

Acetylcysteine has also been hypothesized to exert beneficial effects through its modulation of glutamate and dopamine neurotransmission as well as its antioxidant properties. Acetylcysteine is sold as a dietary supplement commonly claiming antioxidant and liver protecting effects. Extensively liver metabolized; CYP450 minimal. Urine excretion 22-30% with a half-life of 5.6 hours in adults. Acetylcysteine is the N-acetyl derivative of the amino acid L-cysteine, and is a precursor in the formation of the antioxidant glutathione in the body. The thiol (sulfhydryl) group confers antioxidant effects and is able to reduce free radicals. [17] NAC is an essential supplement for use in liver detoxification and hepatotoxicity treatment.

4.4.4 Silybum (Milk Thistle)

For many centuries extracts of milk thistle have been recognized as "liver tonics." Milk thistle has been reported to have protective effects on the liver and to greatly improve its function. It is typically used to treat liver cirrhosis, chronic hepatitis (liver inflammation), toxin-induced liver damage including the prevention of severe liver damage from Amanita phalloides (’death cap’ mushroom poisoning), and gallbladder disorders. [18] Milk Thistle is an essential supplement for use in liver detoxification and hepatotoxicity treatment.

4.5 Blood Pressure Modulators

4.5.1 ACE Inhibitors

An angiotensin-converting-enzyme inhibitor (ACE inhibitor) is a pharmaceutical drug used primarily for the treatment of hypertension (elevated blood pressure) and congestive heart failure.

This group of drugs cause relaxation of blood vessels, as well as a decreased blood volume, which leads to lower blood pressure and decreased oxygen demand from the heart. They inhibit the angiotensin-converting enzyme, an important component of the renin-angiotensin-aldosterone system. Frequently prescribed ACE inhibitors include perindopril, captopril, enalapril, lisinopril, and ramipril. [56]

4.5.2 Clonidine

An alpha-2 adrenergic agonist + imidazoline receptor agonist: treat high BP, ADHD, anti-anxiety, migraine, flushing, diarrhea, and certain pain conditions. Clonidine does not slow down the heart rate like beta-blockers so it can be used during exercise for high blood pressure treatment. [57]

Potentially allows for HR increase during high intensity workouts while lowering BP, useful in some cases however it reduces sympathetic CNS reactions as a result of norepinephrine reuptake inhibition. Will negatively affect desirable properties of sympathomimetic stimulants like Clenbuterol.

4.5.3 Propranolol

A nonselective beta blocker which works by blocking beta-adrenergic receptors: It is used to treat high blood pressure, a number of types of irregular heart rate, thyrotoxicosis, capillary hemangiomas, performance anxiety, and essential tremors. It can negatively affect T3 thyroid activity and can decrease the intended benefits of Clenbuterol.

4.6 Receptor Blockers

Many medications exist that assist in blocking the various receptor types. Many purposes exist that this class of medications could be prescribed for, some of which are out of the scope of this document. As such, not all use cases will be covered.

4.6.1 Androgens Blockers

Also called "anti androgens". These are used to block sex hormones from attaching to Androgen Receptors (AR). Anti-androgens are used to treat an array of medical conditions that are dependent on the androgen pathway.

Anti-androgens are often prescribed for men with prostate cancer, benign prostatic hyperplasia, hypersexuality, and male contraception, and for trans women undergoing gender reassignment. For women, anti-androgens are often prescribed for severe cases of acne, amenorrhea, seborrhea, hirsutism, androgenic alopecia, hidradenitis suppurativa, and hyperandrogenism. These are also used as ancillary medications for female bodybuilding in Post-Cycle Therapy.

Most Common AR Antagonists

- Bicalutamide: the strongest, pure non-steroidal AR blocker.
- Cimetidine: mild AR affinity, but useful for reducing oxidation of estrogen.
- Cyproterone: a very strong progestin based AR blocker.
- Spironolactone: relative of aldosterone, a strong AR blocker. Potassium sparing diuretic.

Less Common AR Antagonists

- Flutamide
- Nilutamide
- Enzalutamide
- Apalutamide
- Megestrol acetate
- Chlormadinone acetate
- Canrenone
- Drospirenone
- Ketoconazole
- Topilutamide

Androgen synthesis inhibitors

- CYP17A1 (17a-hydroxylase, 17,20-lyase) inhibitors: cyproterone acetate, spironolactone, danazol, gestrinone, ketoconazole, abiraterone acetate
- 3b-Hydroxysteroid dehydrogenase inhibitors: danazol, gestrinone, abiraterone acetate
- 17b-Hydroxysteroid dehydrogenase inhibitors: danazol, simvastatin
- CYP11A1 (cholesterol side-chain cleavage enzyme) inhibitors: aminoglutethimide, danazol
- HMG-CoA reductase inhibitors: statins (e.g., atorvastatin, simvastatin)

Androgen synthesis inhibitors: Anti-gonadotropins

- Progestogens: progesterone, cyproterone acetate, medroxyprogesterone acetate, megestrol acetate, chlormadinone acetate, spironolactone, drospirenone
- GnRH agonists: buserelin, deslorelin, gonadorelin, goserelin, histrelin, leuprorelin, nafarelin, triptorelin
- GnRH antagonists: abarelix, cetrorelix, degarelix, ganirelix

Note: As can be seen above, some antiandrogens, such as cyproterone acetate, megestrol acetate, spironolactone, and abiraterone acetate, act via multiple mechanisms of action, including both AR antagonism and androgen synthesis inhibition through enzyme inhibition and/or gonadotropin suppression.

R See the "Androgen Blockers" section of the bibliography for relevant sources.

4.6.2 DHT Blockers

These prevent the conversion of Free Testosterone -> DHT (dihydrotestosterone). Used in MtF transgender/transexual healthcare and to prevent male pattern baldness in cis-male patients. Also heavily used in prostate cancer treatment as well as ancillary medication during on-cycle and post-cycle bodybuilding.

- Dutasteride: type I,II,III 5-alpha reductase blocker.
- Finasteride: type I,II 5-alpha reductase blocker.
- Alfatradiol: stereoisomer of the endogenous steroid hormone 17b-estradiol

R See the "Androgen Blockers" section of the bibliography for relevant sources.

4.7 (SERMS) Estrogen Receptor Modulators

Commonly referred to as SERMS, Selective Estrogen Receptor Modulators. These are used to treat breast cancer, gynocomastia, and in female-to-male transgender/transexual hormone replacement therapy. Commonly seen in bodybuilding when anabolic steroids are used. Some are prescribed drugs for ovulation induction to reverse anovulation or oligoovulation.

R See the "Estrogen" section of the bibliography for additional sources.

4.7.1 Anastrazole

Also known as Arimidex, Anastrazole is a non-steroidal aromatase-inhibiting drug approved for treatment of breast cancer after surgery, as well as for metastasis in both pre and post-menopausal women. The severity of breast cancer can be increased by estrogen, as sex hormones cause hyperplasia, and differentiation at estrogen receptor sites. Anastrozole works by inhibiting the synthesis of estrogen. Anastrozole binds reversibly to the aromatase enzyme through competitive inhibition, inhibits the conversion of androgens to estrogens in peripheral tissues (extra-gonadal). Anastrozole

has been tested for reducing estrogens, including estradiol, in men. Excess estradiol in men can cause benign prostatic hyperplasia, gynecomastia, and symptoms of hypogonadism. It can also contribute to increased risk of stroke, heart attack, chronic inflammation, prostate enlargement and prostate cancer. Some athletes and body builders use anastrozole as part of their steroid cycle to reduce and prevent symptoms of excess estrogen–gynecomastia, emotional lability and water retention. Study data suggests dosages of 0.5 mg to 1 mg a day reduce serum estradiol by approximately 50% in men, which differs in postmenopausal women. [58]

4.7.2 Clomifene

Clomifene, also known as Clomid, is a non-steroidal SERM. It inhibits estrogen receptors in the hypothalamus, inhibiting negative feedback of estrogen on gonadotropin release, leading to up-regulation of the hypothalamic–pituitary–gonadal axis. Clomifene has been found very effective in the treatment of secondary male hypogonadism in many cases. Clomifene is used by males (especially steroid users at the end of a cycle) to reduce the physical effects caused by high estrogen levels, such as gynecomastia. The drug binds to estrogen receptors to prevent the hormone from binding and therefore taking effect. It also restores the body's natural production of testosterone. It is included on the World Anti-Doping Agency list of illegal doping agents in sport. [59]

4.7.3 Nolvadex

Nolvadex, also known as Tamoxifen, a selective estrogen-receptor modulator that works both by decreasing factors that increase the growth of breast cells and increasing factors that decrease the growth of breast cells. Tamoxifen is used to prevent estrogen-related gynecomastia, resulting from elevated estrogenic levels. Tamoxifen itself is a prodrug, having relatively little affinity for its target protein, the estrogen receptor. It is metabolized in the liver by the cytochrome P450 isoform CYP2D6 and CYP3A4 into active metabolites such as 4-hydroxytamoxifen (afimoxifene) and N-desmethyl-4-hydroxytamoxifen (endoxifen) which have 30-100 times more affinity with the estrogen receptor than tamoxifen itself. These active metabolites compete with estrogen in the body for binding to the estrogen receptor. In breast tissue, 4-hydroxytamoxifen acts as an estrogen receptor antagonist so that transcription of estrogen-responsive genes is inhibited. [60]

4.8 (SARMS) Androgen Receptor Modulators

4.8.1 Cyproterone Acetate

Cyproterone acetate (abbreviated as CPA), also sold under brand names such as Androcur among others, is a synthetic, steroidal antiandrogen, progestin, and antigonadotropin. It is primarily used in the treatment of androgen-related conditions by virtue of its ability to suppress androgenic activity in the body, an effect which it mediates by preventing endogenous androgens from interacting with the androgen receptor and by suppressing androgen biosynthesis. CPA is also used for its progestogenic effects, for instance, as a component of some combined oral contraceptive pills in combination with ethinyl estradiol.

Pharmacological activity

- Progesterone receptor (PR) agonist (Kd = 15 nM; IC50 = 79 nM)
- Glucocorticoid receptor (GR) antagonist (Kd = 45 nM; IC50 = 360 nM)
- 21-Hydroxylase, 3b-hydroxysteroid dehydrogenase (3b-HSD), 17a-hydroxylase, and 17,20-lyase inhibitor
- Pregnane X receptor (PXR) agonist (and thus CYP3A4 and P-glycoprotein inducer)

CPA is equally potent as a progestogen and antiandrogen. It is the most potent progestin of the 17a-hydroxyprogesterone group, being 1200-fold more potent than hydroxyprogesterone acetate, 12-fold more potent than medroxyprogesterone acetate, and 3-fold more potent than chlormadinone acetate.

CPA may also have a slight direct inhibitory effect on 5a-reductase, though the evidence for this is sparse and conflicting. In any case, the combination of CPA and finasteride, a well-established, selective 5a-reductase inhibitor, has been found to result in significantly improved effectiveness in the treatment of hirsutism relative to CPA alone, suggesting that if CPA does have any direct inhibitory effects on 5a-reductase, they must not be particularly marked.

Pharmacokinetics
The pharmacokinetics of CPA are complicated due to its lipophilic nature. Although the mean elimination half-life is usually estimated to be around 40 hours, this primarily reflects its accumulation in adipose cells. Elimination from the bloodstream is considerably quicker, and the amount stored in fat may be affected by food intake. Therefore, it is recommended that CPA be given in divided doses 2–3 times per day, or in the form of a long-acting injection.

CPA is metabolized by CYP3A4, forming the major active metabolite 15b-hydroxycyproterone acetate. This metabolite retains antiandrogen activity, but has reduced activity as a progestogen. As a result, the co-administration of CPA with drugs which inhibit CYP3A4 may increase its potency as a progestogen.

Antiandrogenic Effects
CPA is a potent androgen receptor (AR) competitive antagonist.

- It directly blocks endogenous androgens such as testosterone (T) and dihydrotestosterone

(DHT) from binding to and activating the AR, and thus prevents them from exerting their androgenic effects in the body. However, CPA, like spironolactone and other steroidal antiandrogens such as chlormadinone acetate and medroxyprogesterone acetate, is not actually a pure antagonist of the AR – that is, a silent antagonist – but rather is a very weak partial agonist.

- CPA generally behaves purely as an antiandrogen, as it displaces much more efficacious endogenous androgens such as T and DHT from interacting with the receptor and thus its net effect is usually to lower physiological androgenic activity. But unlike silent antagonists of the AR such as flutamide, CPA, by virtue of its slight intrinsic activity at the receptor, is inherently incapable of fully abolishing androgenic activity in the body and will always maintain at least some degree of it.

- In accordance with its, albeit weak, capacity for activation of the AR, CPA has been found to stimulate androgen-sensitive carcinoma growth in the absence of other androgens, an effect which could be blocked by co-treatment with flutamide. As a result, CPA may not be as effective in the treatment of certain androgen-sensitive conditions such as prostate cancer compared to non-steroidal antiandrogens with a silent antagonist profile at the AR such as flutamide, bicalutamide, and enzalutamide.

Progestogenic Effects
CPA is a very potent progestin. Through its action as a progestogen, CPA has been found to significantly increase prolactin secretion and to induce extensive lobuloalveolar development of the mammary glands of female rhesus macaques. In accordance, a study found that CPA, in all cases, induced full lobuloalveolar development in trans women treated with the drug in combination with estrogen for a prolonged period of time. Pregnancy-like breast hyperplasia was observed in two of the subjects. In contrast, the same study found that men with prostate cancer treated with a non-progestogenic antiandrogen such as flutamide or bicalutamide and no estrogen showed only moderate and incomplete lobuloalveolar development of the breasts. Based on the above research, it was concluded by the study authors that combined estrogenic and progestogenic action is required in trans women for full, female-like histologic breast development including lobuloalveolar maturation. Also, it was noted that lobuloalveolar maturation reverses upon discontinuation of CPA after surgical castration, indicating that continued progestogen treatment is necessary to maintain the histology.

Antigonadotropic Effects
CPA has powerful antigonadotropic effects. In humans, it blunts the gonadotropin releasing hormone (GnRH)-induced secretion of gonadotropins, and accordingly, markedly suppresses the plasma levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Consequently, progesterone (P4), androstenedione, T, DHT, and estradiol (E2) are also markedly lowered, while an elevation in sex hormone-binding globulin (SHBG) and prolactin levels is observed. The antigonadotropic effects of CPA are mediated by hyperactivation of the PR. However, its inhibition of steroidogenic enzymes may also contribute to its ability to suppress sex hormone levels.

See the "Androgen Blockers" section of the bibliography for additional sources.

4.8.2 Spironolactone

Spironolactone is one of the more commonly prescribed antiandrogens and functions as a potent SARM. It is used in the treatment of prostate cancer, hirsuitism, and in male-to-female transexual hormone replacement therapy, as well as several other medical purposes. It is a potent potassium sparing diuretic, which means that it causes the body to retain potassium.

Pharmacological activity of Spironolactone

- Mineralocorticoid receptor (MR) antagonist (IC50 = 24 nM)
- Androgen receptor (AR) antagonist/very weak partial agonist (IC50 = 77 nM)
- Progesterone receptor agonist (EC50 = 740 nM)
- Glucocorticoid receptor antagonist (IC50 = 2,410 nM)
- Steroid 11b-hydroxylase, aldosterone synthase (18-hydroxylase), 17a-hydroxylase, and 17,20-lyase inhibitor
- Pregnane X receptor (PXR) agonist (and thus CYP3A4[55] and P-glycoprotein inducer)

Pharmacokinetic Properties
Spironolactone has an onset of action of about 2–3 hours after taking the first dose, with a half-life of about 1–2 hours. It is highly plasma protein bound. Spironolactone is metabolized by the liver, from which it is partially eliminated with the majority being handled by the kidneys. Minimal amounts are handled by biliary excretion. The bioavailability of spironolactone improves significantly when it is taken with food.

Antiandrogenic Effects
Spironolactone mediates its antiandrogenic effects via multiple actions, as follows.

- Direct blockade of androgens from interacting with the androgen receptor. It should be noted however that spironolactone, similarly to other steroidal antiandrogens such as cyproterone acetate, is not a pure, or silent, antagonist of the androgen receptor, but rather a weak partial agonist with the capacity for both agonist and antagonist effects.

- Inhibition of 17a-hydroxylase and 17,20-desmolase, enzymes in the androgen biosynthesis pathway, which in turn results in decreased testosterone and dihydrotestosterone (DHT) levels.

- Activation of the progesterone receptor, as, in sufficient amounts, this results in an antigonadotropic effect due to negative feedback on the hypothalamic-pituitary-gonadal axis, which in turn reduces sex steroid production and by extension androgen levels.

- Inhibition of 5a-reductase, the enzyme responsible for converting testosterone into the 3- to 10-fold more potent androgen dihydrotestosterone (DHT). It is not as effective as more potent and selective 5a-reductase inhibitors like finasteride.

- Acceleration of the rate of metabolism/clearance of testosterone by enhancing the rate of peripheral conversion of testosterone into estradiol. This is termed "the aromatase process".

Estrogenic Effects
Spironolactone has some indirect estrogenic effects which it mediates via several actions.

- By acting as an antiandrogen, as androgens suppress both estrogen production and action, for instance in breast tissue.

- Displacement of estrogens from sex hormone-binding globulin (SHBG). This occurs because spironolactone binds to SHBG at a relatively high rate, as do endogenous estrogens and androgens, but estrogens like estradiol and estrone are more easily displaced (ed: from SHBG binding affinity) than are androgens like testosterone. As a result, spironolactone blocks relatively more estrogens from interacting with SHBG than androgens, resulting in a higher ratio of free estrogens to free androgens.

- Inhibition of the conversion of estradiol to estrone, resulting in an increase in the ratio of estradiol to estrone. This is important because estradiol is approximately 10 times as potent as estrone as an estrogen.

- Enhancement of the rate of peripheral conversion of testosterone to estradiol, thus further lowering testosterone levels and increasing estradiol levels.

Progestogenic
Spironolactone has weak progestogenic properties. Its actions in this regard are a result of direct agonist activity at the progesterone receptor, but with a half-maximal potency approximately one-tenth that of its activity at the androgen receptor. They may also serve to augment the gynecomastia caused by the estrogenic effects of spironolactone, as progesterone is known to play a role in breast development.

See the "Androgen Blockers" section of the bibliography for additional sources.

4.9 Hormone Supplementation

Hormones, anabolic or not, are supplemented for various reasons. Some are used purely for medical reasons and some are commonly used in fitness, bodybuilding, and pro-sports. Many are illegal in non-medical situations and are banned from global sporting events.

4.9.1 Anabolics, Cutting

Cutting cycles are primarily used to trim down from a bulking cycle, or as a focus to create very dense lean muscle mass. Weight gain is typically slower when compared to a bulking cycle and different macronutrition ratios are used.

- Anavar (Oxandrolone)
- Equipoise (Boldenone Undecylenate)
- Halotestin (Methyltestosterone)
- Masteron (Drostanolone)
- Primobolan (Methenolone)
- Trenbolone (Trenbolone)
- Winstrol (Stanozolol)

4.9.2 Anabolics, Bulking

Bulking is the process of putting on muscle mass in a rapid manner. This is non-lean muscle mass, and is commonly done before a cutting cycle in order to "bulk up".

- Anavar (Oxandrolone)
- Anadrol (Oxymetholone)
- Dianabol (Methandrostenolone / Methandienone)
- Deca NPP (Nandrolone Phenylpropionate)
- Deca Durabolin (Nandrolone Decanoate)
- Trenbolone (Trenbolone)

4.9.3 Anabolics, Female

The following list are commonly used by female body builders, though often not discussed due to the social stigma combined with inherent risk of masculinization and irreversible changes to the body, sex drive, and vocal chords. The potential for life altering changes is far more severe compared to usage by men. Lower doses are used, sometimes in the range of 50% to 10% of the dose used by men.

- Anavar (Oxandrolone)
- Equipoise (Boldenone Undecylenate), note: will aromatize to estrogen.
- Masteron (Drostanolone), note: will consume endogenous estrogen.
- Primobolan (Methenolone)
- Winstrol (Stanozolol)

4.9.4 Anabolics, Medical

Most anabolic steroids have a historical and present-day purpose in the medical community. The usage in fitness and sports is primarily an offshoot of the medical properties that make these compounds useful from a scientific perspective.

Name	Purpose
Anavar	cancer, HIV/AIDS, osteoporosis
Anadrol	osteoporosis, anaemia, HIV/AIDS, cancer
Nandrolone	anaemia, osteoporosis, neoplasia, RBC increase
Dianabol	increase Growth Hormone levels by 40%, protein synthesis, glycogenolysis
Equipoise	race Horses, increase nitrogen retention, protein synthesis, appetite stimulant
Halotestin	neoplasms, male hypogonadism, delayed puberty (male)
Primobolan	no approved prescriptive use
Masteron	lowers cholesterol, antineoplastic breast cancer, aromatase inhibitor
Testosterone	Trans-male HRT, TRT cis-male, androgen deficiency
Trenbolone	primarily for livestock to increase muscle growth and appetite
Winstrol	wasting diseases, RBC production, promote bone density, appetite stimulant

4.9.5 Anabolics, Properties

The following comparisons can be made between the anabolic steroids.

Name	Anabolic	Androgenic	Half Life	Efficiency	Derivative
Test Propionate	100	100	0.8 day	80%	Testosterone
Test Phenylpropionate	100	100	1.5 day	66%	Testosterone
Test Isocaproate	100	100	4 days	72%	Testosterone
Test Enanthate	100	100	4.5 days	70%	Testosterone
Test Cypionate	100	100	5 days	69%	Testosterone
Test Decanoate	100	100	7.5 days	62%	Testosterone
Test Undecanoate	100	100	20.9 days	61%	Testosterone
Trenbolone Acetate	500	500	1 day	87%	Nandrolone
Trenbolone Enanthate	500	500	4.5 days	70%	Nandrolone
Masteron Propionate	130	40	0.8 days	80%	DHT
Masteron Enanthate	130	40	4.5 days	70%	DHT
Deca NPP	125	37	1.5 days	67%	Nandrolone
Deca Durabolin	125	37	7.5 days	64%	Nandrolone
Equipoise	100	50	14 days	61%	Testosterone
Primobolan (oral)	88	57	5 hours	100%	DHT
Primobolan (inject)	88	57	4.5 days	70%	DHT
Halotestin (oral)	1,900	850	7 hours	100%	Testosterone
Anadrol (oral)	320	45	14 hours	100%	DHT
Dianabol (oral)	210	60	5 hours	100%	Testosterone
Winstrol (oral)	320	30	8 hours	100%	DHT
Winstrol (inject)	320	30	1 day	87%	DHT
Anavar (oral)	300-600	24	10 hours	100%	DHT

4.9.6 Anabolics, Side Effects

All anabolic steroids have side effects. Some are worse than others.

Name	Aromatizes	Liver	Cardio	Cholesterol	Other
Testosterone	Yes	Mild	Mild	Mild	HPTA disruption
Trenbolone	No	Moderate	Moderate	Moderate	Neuro-degenerative
Masteron Propionate	No	Moderate	No	Moderate	Aromatase Inhibitor
Deca	Yes	Low	Mild	Moderate	Acne prone
Equipoise	Yes	Low	Low	Low	Long term taper
Primobolan (oral)	No	Low	Low	Low	HPTA disruption
Primobolan (inject)	No	Low	Low	Low	HPTA disruption
Halotestin	No	High	Mild	Mild	Very aggressive
Anadrol	No	Severe	Severe	Severe	Water retention
Dianabol	Yes	Moderate	Mild	Mild	Acne prone
Winstrol (oral)	No	High	High	High	HPTA disruption
Winstrol (inject)	No	Mild	High	High	HPTA disruption
Anavar	No	Mild	Mild	Mild	Protein synthesis

4.9.7 Estrogens, Properties

The following comparisons can be made between the estrogen types. Types that have a high variation in application/metabolization of the estradiol are marked with N/A as their efficiency value varies widely on an individual basis due to dermal environment differences between patients.

Name	Half Life	Efficiency
Estradiol Valerate (gel)	6-12 hours	0.06-0.1%
Estradiol Valerate (oral)	35 hours	60%
Estradiol Valerate (sublingual)	12 hours	75%
Estradiol Valerate (matrix patch)	3-4 days	N/A
Estradiol Valerate (reservoir patch)	7-8 days	N/A
Estradiol Benzoate (injection)	4-5 days	98%
Estradiol Valerate (injection)	7-8 days	98%
Estradiol Cypionate (injection)	11 days	98%

Injectable Estrogens Compared

Estrogen supplementation is available in three esters for intramuscular/subcutaneous injection purposes. Each ester has slightly different properties in regard to pharmacokinetics. The following data is provided via research source [70] for estradiol cypionate, valerate, and benzoate esters.

- In order to assess the pharmacokinetic properties of estradiol cypionate, valerate, and benzoate, the daily plasma levels of estradiol and estrone were analysed in groups of 10, 9, and 10 subjects, respectively, before and during 3 weeks after the intramuscular administration of a single dose of 5.0 mg in 1.0 ml arachis oil.

- In order to minimize the contribution of endogenous estrogens to the plasma levels, all subjects were receiving a combined oral contraceptive consisting of levonorgestrel (150 ug) and ethinyl estradiol (30 ug) for three months prior to the study and during the study period.

- The administration of estradiol cypionate gave significantly lower peak levels of estradiol and

estrone than that of the valerate and benzoate. Peak plasma levels of estradiol and estrone were reached in approximately 4 days following the administration of estradiol cypionate and in a significantly shorter time (approximately 2 days) following the administration of both the valerate and benzoate. One hour after the injection of the esters, the average percentage increases in plasma estradiol and estrone levels were significantly higher in the valerate and benzoate groups compared to the subjects receiving estradiol cypionate.

- The average duration of elevated estrogen levels was shortest in the benzoate group (4–5 days) followed by the valerate (7–8 days) and cypionate (approximately 11 days). In none of the subjects studied were elevated estradiol and/or estrone levels encountered 2 weeks after the injection of the various esters.

- The data suggest that among the three esters studied, the valerate provides the most predictable pharmacokinetic behavior.

4.9.8 Estrogens, Administration

In order to assess the advantages and disadvantages of the various therapy regimens, it is important to know the pharmacokinetics and metabolism of the preparation used. Thereby it must be noted that there are great inter-individual differences in absorption and metabolism that account for the individual variations in serum level, effects and side effects. Attention to the time-related differences in estrogen levels after administration and their accumulation or decrease during longterm application are a prerequisite for correct interpretation of the hormone analysis, should these be considered necessary in certain cases for monitoring or prevention. [69]

Sublingual Administration
Due to the rapid absorption and low metabolization rate, very high estradiol levels are observed after sublingual administration of estradiol. This is followed by a rapid decrease in estrogen level.

- 0.25 mg micronized estradiol: a maximum estradiol level of 300 pg/ml is reached within one hour of sublingual administration.

- 1.0 mg micronized estradiol: a maximum estradiol level of 450 pg/ml is reached within one hour of sublingual administration.

Oral Administration
Within a short time of administration of e.g. 2 mg estradiol valerate, the estrogen serum concentration rises to a maximum of about 40 pg/ml on average on the first day, and up to 80 to 100 pg/ml after daily administration.

- The maximum estradiol concentration is not reached until after about 5 hours, and the decrease is also gradual, so that an increased estradiol level can be found for several hours. Accordingly, the terminal half-life time of oral estradiol is fairly long at 35 hours.

- In the further course of treatment with estradiol valerate, estradiol and its metabolites accumu-

late in the serum, so that on day 21 of treatment the serum levels of estradiol and estrone are about +50%, that of estrone sulfate +25% and that of estradiol sulfate +65% higher than on day 1. See "Plasma Saturation Curves" in the section of this document for a visual example.

Dermal Patch: Reservoir Type
The reservoir patch contains an alcoholic gel with 2, 4 or 6 mg estradiol. After application, the estradiol dissolved in alcohol diffuses through the membrane into the horny layer and reaches the capillaries in the dermis. The diffusion depends on the concentration gradient between the reservoir and the capillaries, whereby the alcohol not only facilitates diffusion but also reduces metabolization of the estradiol in the skin. The system is only efficient as long as the patch sticks and the alcohol solution is present. The reservoir patch is available with different doses, whereby release rates of 25, 50, or 100 ug per day are indicated.

- After the application of a 50 ug patch, the estradiol levels increase rapidly and reach a maximum of 40–60 pg/ml after 30 hours. Then they decrease again, reaching a level of 30 pg/ml after 48 hours and the baseline value after 72 hours. When the first patch is applied, the levels are slightly lower, but the steady state is already reached with the second patch. With the 25 ug patch, the estradiol levels are 30–40 pg/ml, and with the 100 ug patch they are between 60 and 110 pg/ml.
- With transdermal treatment, there are also strong intra-individual fluctuations of the estradiol level, ranging from 30 to 65 pg/ml with the 50 ug patch and from 60 to 100 pg/ml with the 100 ug patch. Usually, a strong decrease in estradiol is observed on the third day, since diffusion becomes weaker with the disappearance of the alcohol. In about 30% of the women, the values are fairly low due to poor absorption.

Dermal Patch: Matrix Type
In the matrix patch, the estradiol is distributed in the adhesion layer consisting of an acryl or vinyl acetate polymer, and it diffuses into the skin when the matrix is applied, whereby various absorption enhancers (fatty acids, fatty acid esters, lecithin) facilitate the penetration. The diffusion rate of the matrix system is fairly constant, so that the estradiol levels are still around 50% of the maximum value after 4 days. Therefore, the matrix patch lasts seven days, even though some manufacturers recommend changing it twice a week.

- Once the matrix patch has been applied, the maximum estradiol level is reached after only 12 hours, whereby the values are 30–45 pg/ml with the 25 ug patch, 40–80 pg/ml with the 50 ug patch, and 90–140 pg/ml with the 100 ug patch. In addition, there are matrix patches with a release rate of 37.5 ug and 75 ug per day.

- The observation that the estradiol level is higher in the evening than in the morning, possibly due to circadian fluctuations in the circulation of the skin, is interesting.

Dermal Gel
The administration of an alcohol-water gel containing estradiol, which is applied to a certain area of the abdomen or upper arm, follows a different principle. The hormone penetrates very rapidly, until the gel has dried (within 2 minutes). Thereby, the horny layer acts as a store from which the estradiol gradually diffuses into the capillaries of the dermis and reaches the circulation.

- There are two different types of such preparations. One of them contains a dose of 1.5 mg estradiol in 2.5 g gel (0.06% estradiol) and is always applied to the same area of skin. As a result, the horny layer is saturated with estradiol, and the estradiol level correlates with the surface of the treated skin. Consequently, an increase in estradiol level is observed during the first four or five days, until the steady state is reached. When 1.5 mg estradiol is applied to 400 square-cm skin surface daily, serum levels of 70 to 90 pg/ml are reached.

- The other preparation contains 0.1% estradiol hemi-hydrate (crystal water), and it is applied to different areas of skin. After application of 1.5 g gel with 1.5 mg estradiol, the estradiol level increases to a peak value of about 30 pg/ml within 6 hours. After repeated daily administration, a steady state with a maximum estradiol level of 80 pg/ml is reached after 4 hours. Here, too, the horny layer serves as a store, but the skin is not saturated with estradiol since the area of application is changed every day. Therefore, the estradiol levels do not correlate with the treated skin surface.

Intramuscular Injection
The intramuscular injection of an estradiol ester produces a microcrystalline primary deposit at the injection site or a secondary deposit in the fatty tissue, from which the ester is released gradually and broken down into estradiol in the liver.

- After the injection of 4 mg estradiol valerate, a maximum estradiol level of about 400 pg/ml is reached within two days, which decreases again gradually and reaches a level of about 150 pg/ml after 10 days with a total half-life of 14 days.

- If, on the other hand, the more lipophilic estradiol cipionate is used, the peak estradiol level of 340 pg/ml is lower, but the increase and decrease last much longer than after an injection with estradiol valerate.

Subcutaneous Injection
It is often debated whether or not subcutaneous (under the skin) or intramuscular (inside the muscle) is a more effective route of administration for injectable estrogen. The following details have been studied in research reference [71].

- Both pharmacokinetics and pharmacodynamics of the once-a-month combined injectable contraceptive medroxyprogesterone acetate (MPA) plus estradiol cypionate (E2-Cyp) were compared after intramuscular (IM) or subcutaneous (SC) injection in women of reproductive age.

- A comparative analysis showed that the main pharmacokinetic (peak serum concentration, peak serum time, area under the serum concentration vs. time curve, absorption half-life and elimination half-life) and pharmacodynamic parameters, such as follicular development and ovulation, were similar in the subcutaneous vs. intramuscular groups.

- The results presented herein demonstrate that the injection of 25 mg of MPA plus 5 mg of E2-Cyp has similar efficacy and safety with either the SC or IM route of administration.

The SC option can be considered a viable self-administered contraceptive option that might increase women's compliance to contraceptive use.

4.9.9 Progestins, Properties

The following comparisons can be made between the progesterone types.

Name	Half Life	Efficiency	Type
Progesterone (oral)	24 hours	60%	Bio-Identical
Progesterone (injection)	24 hours	98%	Bio-Identical
17 Hydroxyprogesterone Caproate	7.8 days	98%	Synthetic
Medroxyprogesterone Acetate	3 months	85%	Synthetic

4.10 Hormones, Administration

There are many ways to get exogenous hormones into your blood stream. Some are more efficient than others.

4.10.1 Routes of Administration

Hormones are typically used via the following routes of administration.

Method	Bioavailability	Liver Processing	Note
Oral, Swallowed	Low	High	Highest liver stress
Oral, Sublingual	High	Low	10-15min absorption time
Dermal Patch	Moderate	Low	Propensity for patches to fall off
Dermal Gel	Low	Low	Prone to sweat and clothing issues
Injection, Intramuscular	High	Low	Most efficient method
Injection, Intravenous	High	Low	Uncommon

4.10.2 Plasma Saturation Curves

Injectable hormones all have a plasma saturation curve. This must always be taken into account when doing blood tests, as you want to test for the compound during the median timeframe of the compound's half life. Take Estradiol Valerate for example: it has a 14 day half life. So if we want to know the median plasma concentration for a given dose then we will want to have the estrogen blood test done on day 7 (1/2 way through the half life period). You can see that visualized on the "injectable estradiol valerate" graph below.

It's also important to understand when using injectables, that in order to have the most consistent amount of change with the least amount of side effects, you want to have the smallest peaks (maximal plasma saturation) and valleys (minimum plasma saturation) in your saturation curves as possible. You can do this via smaller volume injections more frequently vs a large weekly or large bi-weekly injection. Some anabolics and some progesterones have very short half-lives (eg: Test Propionate, Masteron Propionate, Tren Acetate) and must be injected more frequently, while others like Equipoise and Estradiol Valerate both have a longer 14 day half life.

The formula used for calculating the rate of compound release at a given day t is defined as follows. You can reference the Hormone Supplementation section for information on half-life and efficiency rates for different hormone types.

$A * N(t)$

Where A is the decay constant equal to $ln\ (2)/h$, with h being the half life of the compound given in days; and $N(t)$ is the half-life equation given by the equation:

$N(t) = n * e\hat{(}-t/A)$

Where n is the effective dose of the compound in mg and t is given in days. If you are administering a compound with less than 100% bioavailability, as most injectables are, then you will calculate the

effective dose as n = (Total Dose * Efficiency %). Example: 100mg of Masteron Propionate at 80% efficiency = 80mg effective dose n.

Example: Daily vs Weekly Intramuscular Injection

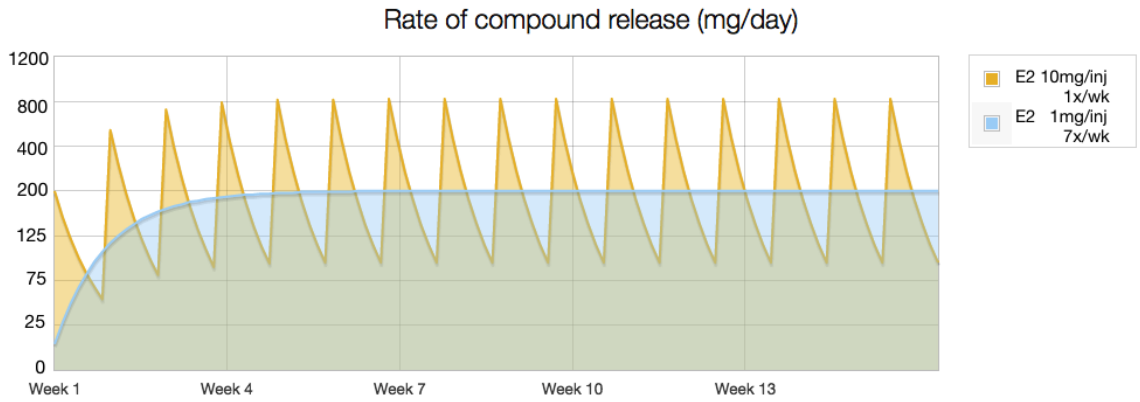


Figure 4.1: Plasma peak/valley: Weekly vs Daily Injection of Estradiol Valerate

If you want the peaks and valleys to be small and you're using a compound that has a long half life the solution is to break up the doses into smaller amounts. See the graph above for a comparison that shows how a once-weekly injection of 10mg has the same median plasma level as a daily 1mg injection. The important part to note is how the daily injection has no peak or valley while the single weekly injection creates a dramatic sawtooth profile of plasma saturation levels. The daily injection cycle offers plasma saturation levels that are consistent enough to warrant smaller injections the compound (7mg total) during the same one week period to get the same median level as a larger once per-week injection (10mg total).

Plasma Saturation: Oral Estrogen Supplementation

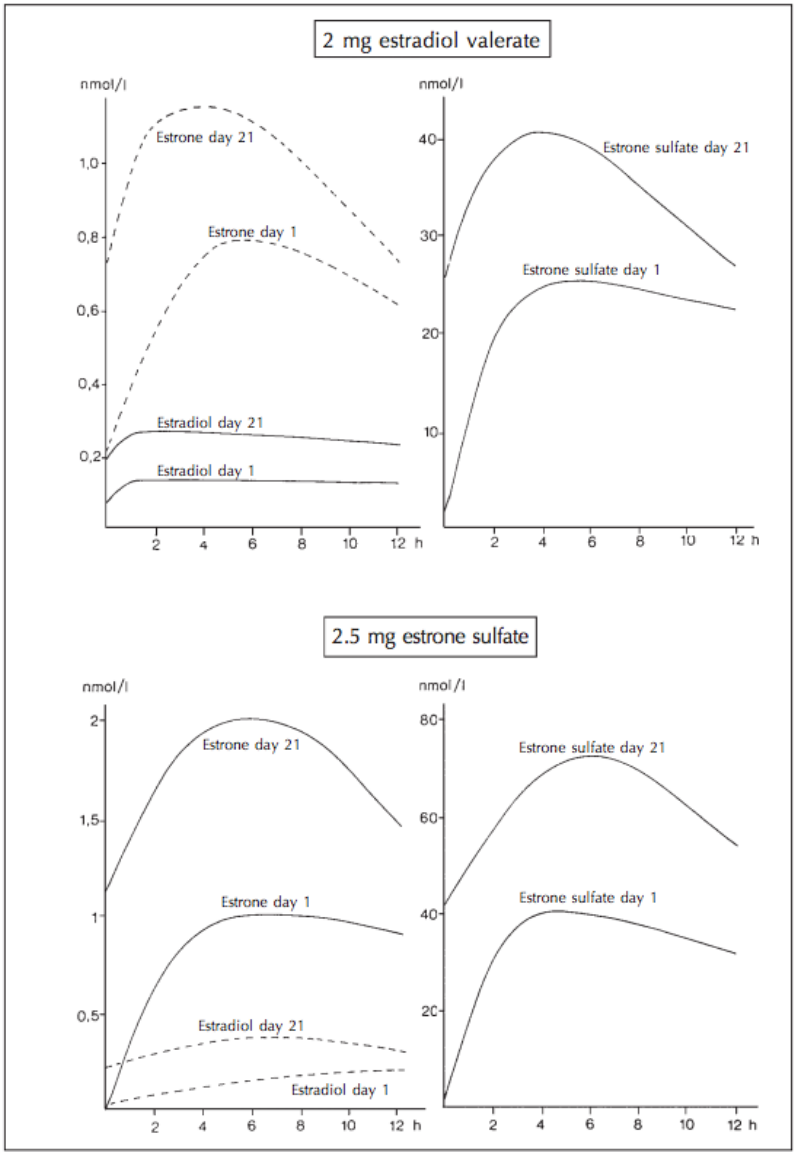


Figure 4.2: Average serum concentration curve for estradiol, estrone and estrone sulfate following oral administration of 2 mg estradiol valerate (above) or 2.5 mg estrone sulfate (below). [69]

4.10.3 Front Loading Injectables

Let's use pictures to describe this methodology for "getting up to speed" with the plasma saturation curve. Both of these cycles show 16 "primary effect weeks" and then a tapering off period where the injectable compound is metabolized and gradually eliminated from the blood stream.

The Front Loaded cycle doesn't waste any time getting the patient into the desired plasma saturation level vs the non-Front Loaded cycle that takes it's sweet ass time to get going. In a cycle where you want to maximize the potential changes in a given time period, front loading is a critical element of hormone administration.

The cycles below are just an example. It uses Equipoise because the 14 day half life compound is a good visual representation for the graphical description of front loading vs regular cycles. It is a commonly front-loaded compound. The doses below are not a suggestion of a real cycle and should not be taken as anything but a means to explain the concept in visual terms. To see how other compounds graph you can visit http://steroidgraph.com or break out your TI-86 and use the equations shown in the Plasma Saturation Curves section.

Front Loading an Injectable

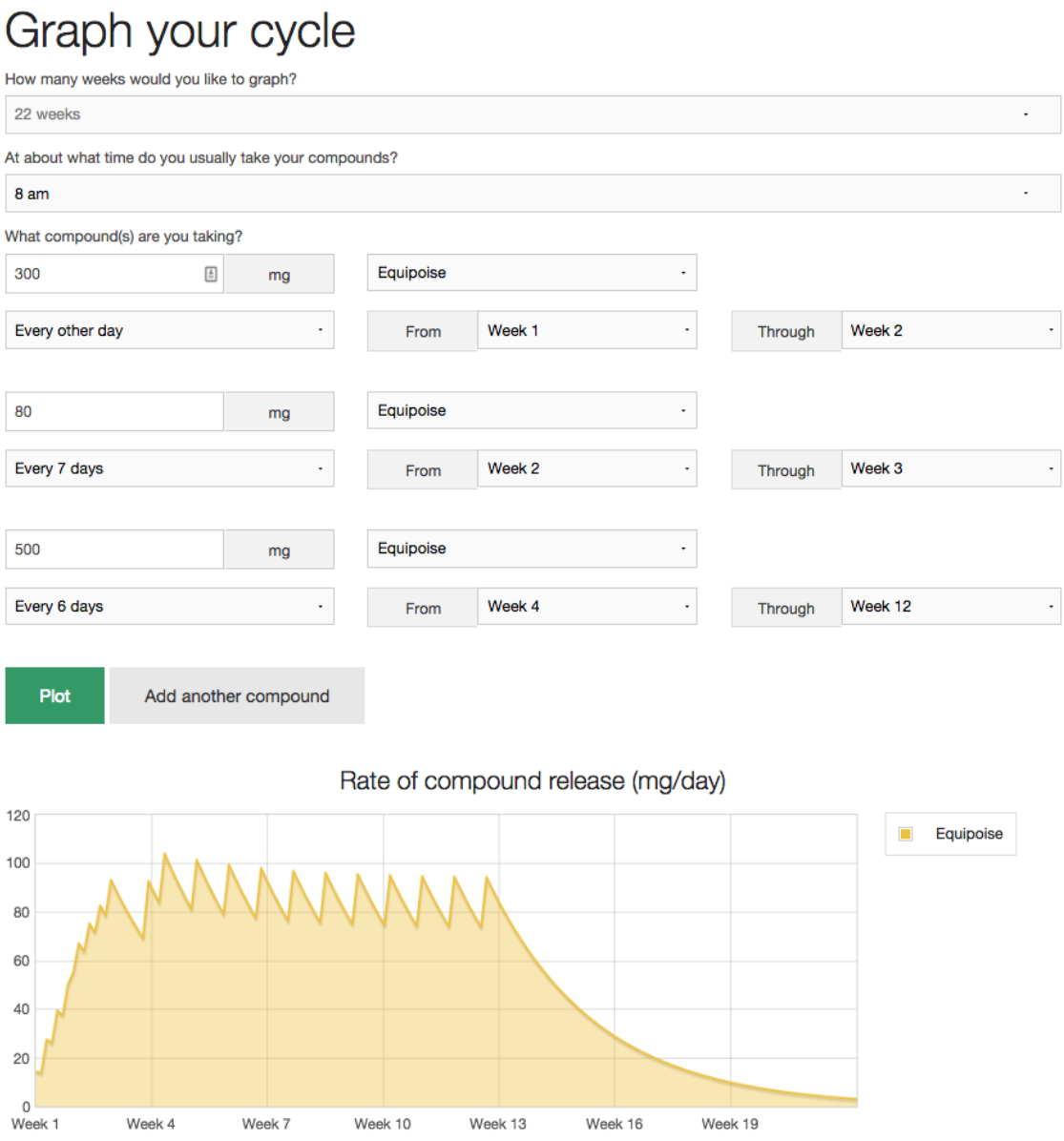


Figure 4.3: Up To Speed Quick! A front loaded cycle.

Standard Loading an Injectable

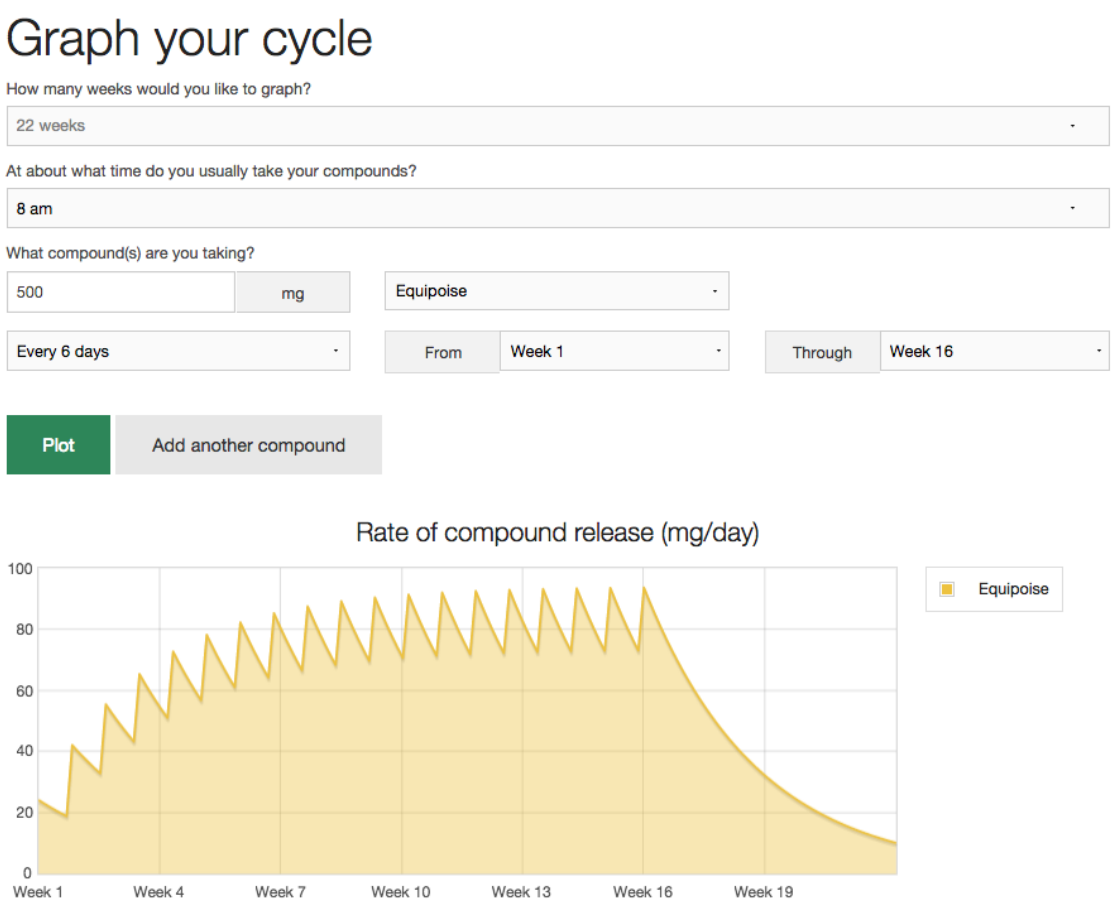
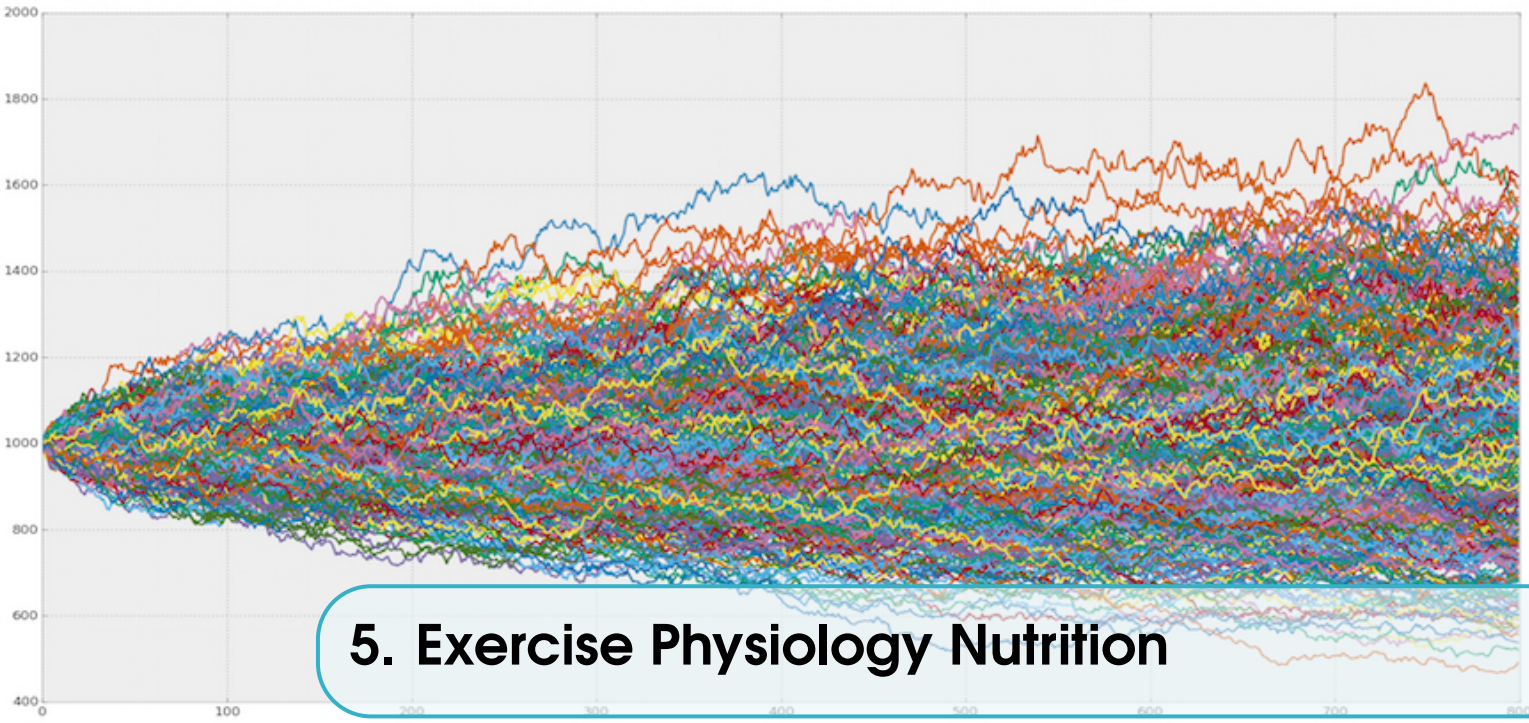


Figure 4.4: Up To Speed Slowly. A regular cycle.



5. Exercise Physiology Nutrition

5.1 Types of Fat

Healthy fat sources are comprised of Monounsaturated Fats, Polyunsaturated Fats, Medium-Chain Triglycerides (MCT oils), and Omega-3 Fatty Acids. Unhealthy fat sources are Saturated Fats and Trans-Unsaturated Fatty Acids. Fatty acids, stored as triglycerides in an organism, are an important source of energy because they are both reduced and anhydrous.

The energy yield from a gram of fatty acids is approximately 9 kcal (37 kJ), compared to 4 kcal (17 kJ) for carbohydrates. Since the hydrocarbon portion of fatty acids is hydrophobic, these molecules can be stored in a relatively anhydrous (water-free) environment.

Carbohydrates, on the other hand, are more highly hydrated. For example, 1 g of glycogen can bind approximately 2 g of water, which translates to 1.33 kcal/g (4 kcal/3 g). This means that fatty acids can hold more than six times the amount of energy per unit of storage mass.

Put another way, if the human body relied on carbohydrates to store energy, then a person would need to carry 31 kg (67.5 lb) of hydrated glycogen to have the energy equivalent to 4.6 kg (10 lb) of fat. [42]

5.1.1 Monounsaturated fat

This is a type of fat found in a variety of foods and oils. Studies show that eating foods rich in monounsaturated fats improves blood cholesterol levels, which can decrease your risk of heart disease. Monounsaturated fats may benefit insulin levels and blood sugar control. Examples include: avocados, egg yolks, olives, nuts, peanut butter, canola oil, olive oil, high-oleic sunflower oil. [33]

5.1.2 Polyunsaturated fat

This is a type of fat found mostly in plant-based foods and oils. Evidence shows that eating foods rich in polyunsaturated fats (PUFAs) improves blood cholesterol levels, which can decrease your

risk of heart disease. PUFAs may also help decrease the risk of type 2 diabetes. [33]

5.1.3 Medium-Chain Triglycerides

Medium-chain triglycerides are generally considered a good biologically inert source of energy that the human body finds reasonably easy to metabolize and are absorbed rapidly by the body. Some studies have shown that MCTs can help in the process of excess calorie burning, thus weight loss. MCTs are also seen as promoting fat oxidation and reduced food intake. [37]

They have potentially beneficial attributes in protein metabolism, but may be contraindicated in some situations due to their tendency to induce ketogenesis and metabolic acidosis. [37][38][39] Examples include: coconut oil, palm kernel oil

5.1.4 Omega-3 fatty acids

This type of fat helps protect the cardiovascular system, aids in liver health, and aids in the metabolic process. [33][34][35]

- As an anti-arrhythmic agent, Omega-3 helps prevent abnormal rhythms of the heart (cardiac arrhythmias), such as atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation.

- Omega-3 helps regulate hepatic lipid metabolism, adipose tissue function, and inflammation. There are plant sources of omega-3 fatty acids. However, the body doesn't convert it and use it as well as omega-3 from fish.

- Sources include: salmon, and other fish, grass-fed beef, chia seeds, ground flax seeds, soybeans, tofu, edamame, beans, wild rice, and walnuts.

5.1.5 Saturated fat

This is a type of fat that comes mainly from animal sources of food, such as red meat, poultry and full-fat dairy products. Saturated fat raises total blood cholesterol levels and low-density lipoprotein (LDL) cholesterol levels, which can increase your risk of cardiovascular disease. Saturated fat may also increase your risk of type 2 diabetes. [34]

5.1.6 Trans-Unsaturated Fat

This is a type of fat that occurs naturally in some foods in small amounts. But most trans fats are made from oils through a food processing method called partial hydrogenation. By partially hydrogenating oils, they become easier to cook with and less likely to spoil than do naturally occurring oils. Research studies show that these partially hydrogenated trans fats can increase unhealthy LDL cholesterol and lower healthy high-density lipoprotein (HDL) cholesterol. This can increase your risk of cardiovascular disease. [34]

5.2 Protein for exercise physiology

Protein is the key building nutrient for a variety of bodily tissues, many of which support muscle growth (enzymes, skin, hair, nails, bones, and connective tissue are all constructed from protein). Protein makes up 15-20% of one's body weight and is thus, next to water, the body's second most abundant substance. [36]

5.2.1 Protein Type Efficiency

Protein	Srv Size	Calories	Protein	Carbs	Fat	Efficiency	Caloric N
Whey	41g	140cal	30g	3g	1g	4.6cal/g	21.4g @ 100cal
Casein	43g	160cal	30g	6g	1.5g	5.3cal/g	18.8g @ 100cal
Turkey	28g	54cal	8g	0g	21g	6.75cal/g	14.8g @ 100cal
Pork	84g	206cal	23g	0g	12g	8.95cal/g	11g @ 100cal
Chicken	140g	335cal	38g	0g	19g	8.89cal/g	11g @ 100cal
Tofu	124g	94cal	10g	2.3g	6g	9.4cal/g	10.6g @ 100cal
Soy Bean	186g	830cal	68g	56g	37g	12.2cal/g	8g @ 100cal

5.2.2 Nitrogen Balance

Nitrogen balance is a method of determining protein metabolism via input-output efficiency and the outcome of being anabolic or catabolic in terms of protein synthesis, balance or degradation.

- Positive Nitrogen Balance: Protein intake is at a level that encourages weight gain.
- Neutral Nitrogen Balance: Protein intake is at a level that maintains body weight.
- Negative Nitrogen Balance: Protein intake is at a level where weight loss occurs or muscle proteins are at risk of being catabolized to make up the deficit.

5.2.3 Whey: daytime protein

The use of whey protein as a source of amino acids and its effect on reducing the risks of diseases such as heart disease, cancer and diabetes has been the focus of ongoing research as of 2007. Whey is an abundant source of branched-chain amino acids (BCAAs), which are used to stimulate protein synthesis. [23]

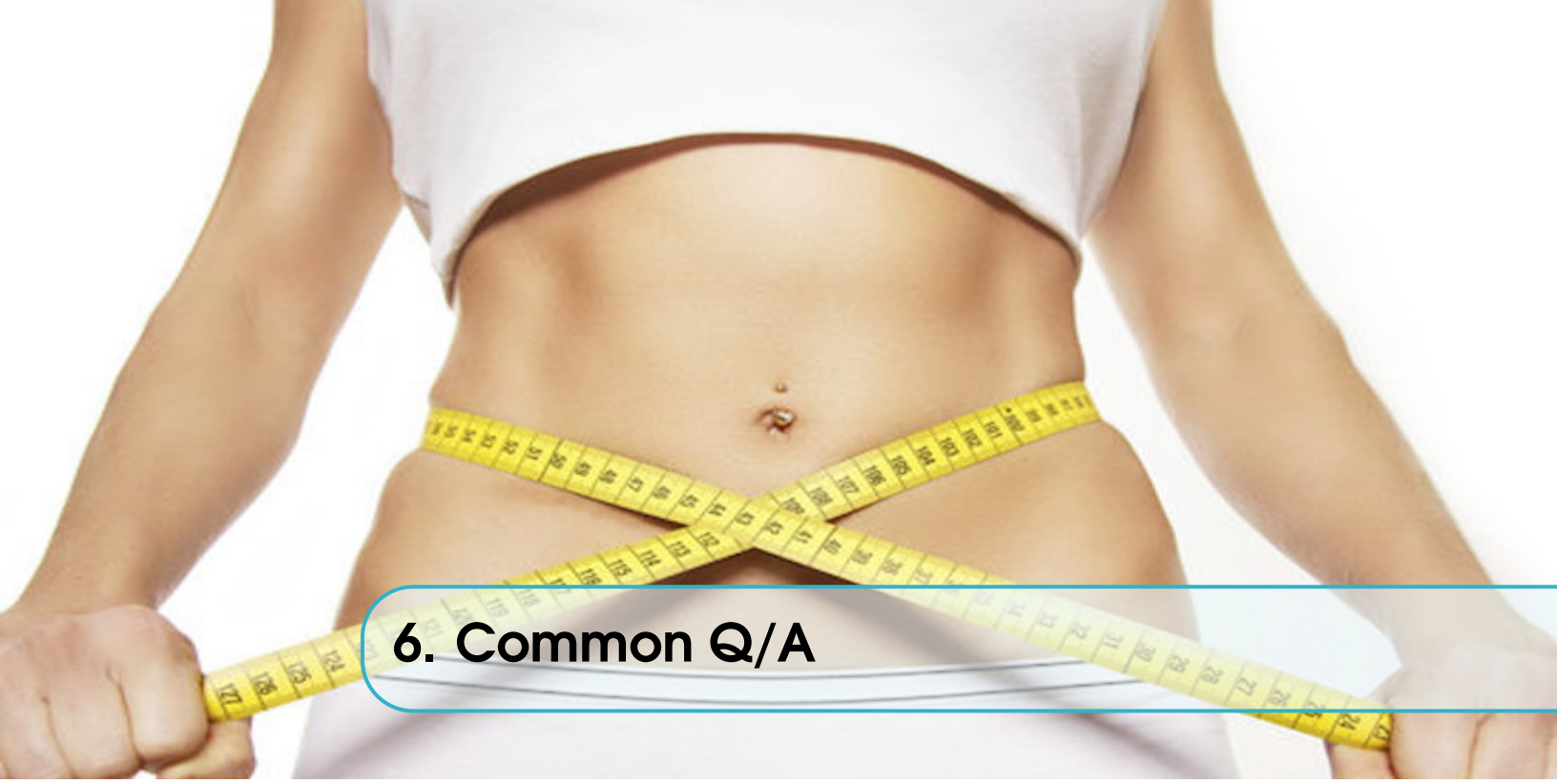
When leucine is ingested in high amounts, such as with whey protein supplementation, there is greater stimulation of protein synthesis, which may speed recovery and adaptation to stress (exercise). Whey has approximately three grams of leucine per serving and the threshold for optimal protein synthesis is three grams. [23]

As with other forms of protein, consumption of whey protein shortly after vigorous exercise can boost muscle hypertrophy. Scientific evidence has shown that proteins high in essential amino acids (EAA), branched chain amino acids (BCAA), and particularly leucine (Leu) are associated with increased muscle protein synthesis, weight loss, body fat loss, and decreased plasma insulin and triglyceride profile. [23]

5.2.4 Casein: nighttime protein

An attractive property of the casein molecule is its ability to form a gel or clot in the stomach, which makes it very efficient in nutrient supply. The clot is able to provide a sustained slow release of

amino acids into the blood stream, sometimes lasting for several hours. This slower absorption allows for longer periods of restful nutrient digestion. [22]



6. Common Q/A

If you would like to have a question answered for the next release of this document, please email eve@cmplx.io for list subscription along with your question.

6.1 Fitness Troubleshooting

The following are answers to some of the more common fitness questions.

6.1.1 How can I lose weight in general?

Question: I keep hearing about negative energy balance? What does that means for weight loss and how do I successfully and consistently lose weight?

I find it's most efficient and healthy to do weight loss in plateaus... two weeks of moderate weigh loss followed by 1-2 weeks of maintenance BMR calories to get the body to recover and stay at the same weight while glucose stores are replenished, then another two weeks of weight loss, repeat. If you do not plateau occasionally you will have health issues and it will become very difficult to continue losing weight efficiently while remaining a productive member of society and not consumed by malaise, depression, and illness.

One must keep the immune system very healthy when you're on caloric restriction; that means always take a good multi-vitamin, always drinking 80-120oz of actual water every day (not kombucha or gatorade or whatever but actual plain water - it's really good for you!), get a good sleep - rest is where you recover and you can't be healthy without proper rest. Keep your mental health in good shape while you do this too - don't rush. Learn the science behind it, enjoy the process and set realistic goals based on statistics.

So... onto the science of it. Energy balance and dietary protein intake are critical factors that contribute to the regulation of skeletal muscle mass by influencing whole-body and skeletal muscle

protein metabolism. The following text comes from source [61], which also contains additional information if desired.

The consequences of negative energy balance on total body and skeletal muscle mass are well established. In general, total body mass decreases in response to sustained periods of negative energy balance, and the proportion of body mass loss is 75% adipose tissue and 25% fat-free mass (FFM). Although the predominant change in body composition is the loss of body fat, which may be beneficial, the concomitant decrease in skeletal muscle mass may negatively affect metabolic processes, muscular function, and physical performance.

- In overweight and obese individuals attempting to lose weight, decreases in muscle mass may down-regulate metabolic processes, such as protein turnover and basal metabolic rate (BMR), thus compromising healthy weight management.
- Healthy, normal-weight individuals such as athletes and military personnel may also undergo periods of negative energy balance resulting from dietary energy restriction, increased energy expenditure, or the combined effects of both. Decreased FFM in this population may be of greater concern, decreasing physical performance and increasing susceptibility to injury.
- Popular strategies to attenuate muscle loss during negative energy balance include nutritional interventions that provide dietary protein in excess of the current recommended dietary allowance (RDA), as several studies have described a potential muscle-sparing effect, consequent to consuming higher protein diets.

In a recent systematic review of publications from 1993 to 2009, Weinheimer reported that in more than half of the studies reviewed, energy restriction induced weight loss of 5–10% of the initial body mass. More than one fourth of this change in total body mass was a result of decreases in FFM. Layman et al. demonstrated a greater retention of FFM and loss of body fat in overweight women adhering to a hypoenergetic diet (7113 kJ/d or 1700 kcal/d) than those consuming higher levels of dietary protein compared with those who consumed the RDA for protein.

The catabolic nature of negative energy balance and the protective effect of dietary protein were also demonstrated in postmenopausal obese women who consumed diets ranging from 0.5 to 1.5 g protein per kg of body weight for 20 wk. In that study, the extent of muscle loss in response to negative energy balance was proportional to dietary protein intake. Specifically, all volunteers lost FFM (-1.4 kg and -4.3 kg in the high and low protein groups, respectively). However, the percentage of total weight loss due to decreases in FFM was significantly lower for those women consuming high (17.3%) versus low (37.5%) protein diets. Others have also demonstrated benefits of consuming higher protein diets during prolonged periods of negative energy balance, with consistent reports documenting the attenuation of the loss of FFM after weight loss. Taken together, these investigations indicate that a certain degree of lean mass protection is gleaned from the consumption of a higher protein diet during prolonged periods of energy deficit.

6.1.2 How can I lose muscle?

Question: I'm curious if you think that losing muscle mass is possible, especially on the neck?

It's absolutely possible. The body is capable of incredible change, you just have to choose to do

so. It's not a matter of mass or fat/muscle % that is important in terms of reduction; it's honestly a matter of planned and controlled starvation while ensuring that your organs and mind have enough of the proper healthy calories in order to lose weight efficiently, consistently, over a period of time.

Losing mass is a catabolic situation. You cannot lose muscle in some areas while gaining it in others if you're intaking enough protein to build muscle. Your body will strive to distribute protein efficiently to all muscles that need it while repairing damaged ones as a priority. You can purposefully workout the muscles you want to reduce if you keep protein intake low enough to starve the muscles from repairing via protein synthesis; I've spot targeted muscle groups to induce atrophy via catabolism that way... it's painful, and it takes mental dedication to starve your body of protein while also working the muscles with not enough fuel... it's hard on the organs too, you have be careful, and stimulants help the process there but also carry other risks.

About Nitrogen Balance [62]: keeping a negative nitrogen balance in your nutrition plan will enhance catabolic muscle atrophy. Ways to induce a lower nitrogen balance include, but are not recommended due to health risks. Remaining caloric deficient will equate to weight loss, but one must have a healthy balance of all macros to not damage vital organs and mental health while continuing to lose weight.

- Protein consumption is crucial are far as enhancing nitrogen balance is concerned. A negative nitrogen balance may result from consuming an insufficient amount of high biological value proteins, poor quality proteins (lunch meats, fatty meats, and vegetables for example), or protein sources lacking an optimal balance of the essential amino-acids.
- On a more serious level, a continued negative nitrogen balance will result in the body consuming its own blood products to support the internal organs.
- A severe lack of protein equates to fewer of the antibodies which are needed to fight infection - bacterial infections may result from this. Proteins importance, in this instance, is underscored by the fact that regardless how many nutrients are consumed at this point, death will occur if protein is not supplied.
- Insufficient carbohydrate and fat consumption. To support protein synthesis, good quality fats and carbohydrates should be available for energy purposes. If one consumes primarily protein, without considering the importance of the other macronutrients, the body may metabolize protein for energy purposes, thus lowering the nitrogen balance - valuable amino acids will be shuttled to vital organs thus depriving the muscles of exactly what they need for growth.
- Overtraining: Training involves breaking down muscle tissue. Protein and rest help to regenerate these tissues. Too much training, coupled with insufficient protein consumption will hasten a negative nitrogen balance. Following a training session, muscles soak up nutrients (including protein) like a sponge. If training is undertaken too frequently without proper rest, these nutrients might eventually fall short of supporting continued growth.

We see additional information on the topic from source [61]: Nitrogen balance methodology is widely used as a holistic assessment of protein balance, allowing one to gain valuable insight regarding the relationship between energy status, dietary protein, and skeletal muscle mass. In general, when energy intake is sufficient to meet energy demand, increasing the protein content of the diet imparts no added influence on nitrogen retention. However, increasing dietary protein intake may offset the increase in nitrogen excretion and negative nitrogen balance that generally occurs during periods

of energy deficiency. For example, nitrogen balance and basal metabolic rate were preserved in premenopausal women who consumed a higher protein diet (1.4g per kg) during a 10-wk period of negative energy balance induced by dietary restriction coupled with a modest increase in physical activity.

In a second study, Pikosky et al. demonstrated negative nitrogen balance in healthy young volunteers in response to a 7 day period of negative energy balance (-1000 kcal/day) elicited solely by an increase in aerobic-type physical activity when protein was consumed at levels similar to the current RDA (0.9g per kg). However, doubling dietary protein intake (1.8g per kg) abrogated the increased nitrogen excretion and resultant negative nitrogen balance that occurred after the 7 day energy deficit. Again, these results indicate that lean body mass may be defended in response to negative energy balance by consuming a diet that provides protein at levels above the RDA, regardless of whether the energy deficit is caused by diet or physical activity.

In general, acute periods of negative energy balance associated with fasting result in increased whole-body proteolysis, amino acid oxidation, and nitrogen excretion, which become less pronounced and plateau over an extended period of time as the body adapts to conserve energy and protein reserves (e.g., muscle protein). For example, Nair et al. reported a significant up-regulation of whole-body proteolysis and oxidation after a 72-h fast; however, longer duration studies observed a reversal of this response, as whole-body proteolysis and protein synthesis were decreased by 20% after a 4-wk period of negative energy balance in overweight adults consuming the RDA for dietary protein (3). The down-regulation of protein turnover was proportional to the loss of FFM, which accounted for nearly 25% of the total body mass lost. Recent experimental evidence from Campbell et al. confirms these findings because whole-body protein synthesis and proteolysis were decreased in postmenopausal overweight women who consumed 1.0g protein per kg during a 13-wk period of moderate negative energy balance (-500 kcal per day). Together, these data suggest that whole-body protein turnover, an energy-requiring process, is down-regulated in response to sustained energy deficit, perhaps to conserve endogenous protein stores when dietary protein intake is equivalent to the current RDA.

Sub Question: Would a low protein diet work best or just low calorie?

You need to do both in order to lose any kind of muscle. If you just wanted to lose weight, like if you had a BMI of 25+ then you'd focus on high protein %, low carb, low fat diet while also cutting overall calories. In order to target muscle mass loss while also losing weight you need low protein %, moderate carb, moderate fat + reduction in calories. A general rule is that a 500 calorie per-day caloric deficiency = 1lb of weight loss per week; which is a 3500 calorie deficit per week.

If you target muscle mass by keeping protein low then you induce catabolic muscle atrophy because you're starving muscle of their building blocks and they cannot maintain their shape/density and thus shrink. See the "Macro-nutrition for fitness" sections of this document for more information.

6.1.3 Muscle maintenace while in a catabolic state, possible?

Question: Can I keep muscle mass in some areas while I'm targeting other muscle groups for catabolic atrophy? Say I want to do bicep curls to keep my arms toned while I'm on a protein

deficient nutrition plan for overall muscle loss.

The easy way to look at this question is to see the musculature as a system that needs 100% of protein (the #grams that equates to 100% is variable from person to person) to maintain the current build. If you break down muscle tissue via weights or exercise then you will need more than 100%, as the 100% will be going to maintain the current size of the musculature + additional protein will be needed to repair the damaged/worked-out muscles. If you do bicep curls while in a catabolic protein deficient state you will atrophy those muscles more than others because the muscle fiber tissue will be broken down during curls but your body will not have sufficient protein to repair them, which will prove the opposite of your intended goal.

You can think of it like a mechanic that sits around and maintains a car every day; his energy is pretty static most of the time while doing simple maintenance but if you blow a tire and need new shocks then he's going to expend more energy during the day working on those repairs while still needing his usual energy to do generic daily maintenance. If you don't give him extra energy then he's not going to repair the extra damage very efficiently or maybe not at all (and that's how you lose muscle mass). While your body remains caloric deficient, especially protein deficient, the baseline energy that's required for body maintenance comes from 1) your caloric intake + 2) your body burning fat and muscle tissue to make up the caloric deficit.

So what you'll get is a situation where it's difficult to impossible to gain muscle mass in one place while losing it in another if you are on a caloric and protein deficient nutrition plan. There simply isn't enough protein to keep the baseline musculature operational at the same size, let alone build bigger muscles.

If you want to build one set of muscles while having the others reduce, then the common tactic is to not be caloric or protein deficient, then work out the target muscles to build them while ignoring the muscles you want to atrophy. Muscles atrophy from disuse; which is one of the reasons that bodybuilders and racers get kind of fluffy fat in the off-season, they're not working out as hard so a percentage of the musculature metabolizes into fat.

The fitness community commonly discusses the following method for aesthetic change where muscle atrophy & targeted bulking is desired: do a cutting cycle where you are caloric and protein deficient and lose muscle mass to the degree you see fit, then once you're at that target start a mini-bulk cycle where you increase protein intake and are not caloric deficient. During the mini-bulk you only workout the muscles you want to get bigger while ignoring the ones you don't want to get bigger. The muscle tissue repair process will allow the body to increase the size of those muscle. Keep doing that until you're at your aesthetic goal. Don't overdue to the calories or protein though, or you'll get fluff around other parts of the body while you're working out the target muscles. In between mini-bulks you can do non-caloric-deficient cutting cycles to metabolize/burn-off any fat that you don't want. Tuning the nutrition plan to proper macro ratios (referenced in section 3.3) during the cuts and mini-bulks are where the most efficient losses/gains will be seen.

6.1.4 What food is good for a low protein diet?

Low calorie nutrition plans are all about maximizing the types of food that are vegetarian in nature and which make you feel full while being low in caloric density. This allows your stomach to "feel full" without being loaded up with heavy calories. Apples, spring salads with light dressing, tomatoes, carrots, and similar foods will all achieve this goal.

You will still need some protein in your diet so plan accordingly; tofu is a good source, edamame and other soy bean varieties, black beans (not refried), are all going to make you feel full without being highly caloric in density. In the chart below we'll see why Whey protein, the most efficient in grams of protein per calorie for building muscle mass is also the least efficient for inducing muscle atrophy. See the "Macro-nutrition for fitness" sections of this document for more information on percentages.

When I'm on a protein restricted nutrition plan I keep protein between 5-15% of my macros. So, let's say for the sake of easy math... that the daily calories are 1000. That means...

- 1000 * 5% = 50 cal of protein = N grams of protein
- 1000 * 10% = 100 cal of protein = N grams of protein
- 1000 * 15% = 150 cal of protein = N grams of protein

Now, take N and look at the values from the protein efficiency chart below. We'll use the following equation to solve for N. *Whey protein: 41g srv = 140cal 30g = 140cal:30g protein -> 140cal|100cal = 30g|Ng -> 100*30 -> 3000/140 = N grams protein -> 21.4g protein for 100 calories*

Protein Type Efficiency

Protein	Srv Size	Calories	Protein	Carbs	Fat	Efficiency	Caloric N
Whey	41g	140cal	30g	3g	1g	4.6cal/g	21.4g @ 100cal
Casein	43g	160cal	30g	6g	1.5g	5.3cal/g	18.8g @ 100cal
Turkey	28g	54cal	8g	0g	21g	6.75cal/g	14.8g @ 100cal
Pork	84g	206cal	23g	0g	12g	8.95cal/g	11g @ 100cal
Chicken	140g	335cal	38g	0g	19g	8.89cal/g	11g @ 100cal
Tofu	124g	94cal	10g	2.3g	6g	9.4cal/g	10.6g @ 100cal
Soy Bean	186g	830cal	68g	56g	37g	12.2cal/g	8g @ 100cal

So, if you're keeping macros at 10% protein (which equates to 100 calories in a 1000 calorie per day) that means the most efficient way to induce catabolic muscle atrophy is to eat the least efficient sources of protein in order to have the least amount of protein you can get for that 100 calorie intake.

Divide the #s above by 0.5 to get 5% protein intake, multiply by 1.5 to get 15% protein macros.

As you can see... eating primarily soy protein for a 5-10% caloric intake is not a lot of protein, and you'll lose muscle really quickly. Keep in mind that you generally want to eat 15g per day at a minimum to maintain basic organ functionality, so choose wisely and don't overdo it. You can apply the same formulas to other types of food, since it's not just the primary protein sources that have protein - bread has protein, yogurt and ice cream have protein, etc. Get used to reading all of the nutrition labels and use a food/nutrition tracking app like MyPlate, MyFitnessPal, FitBit, etc. Track

everything with those - they will make this whole process a lot easier while also providing useful statistics to look back on.

I find it's most efficient and healthy to do weight loss in plateaus; Two weeks of moderate weigh loss followed by 1-2 weeks of maintenance BMR calories to get the body to recover and stay at the same weight while glucose stores are replenished, then another two weeks of weight loss, repeat. If you do not plateau occasionally you will have healthy issues and it will become very difficult to continue losing weight efficiently while remaining a productive member of society and not consumed by malaise, depression, and illness.

Have to keep the immune system very healthy when you're on caloric restriction; that means always take a multi-vitamin, always drink 80-120oz of water every day, get a good sleep (rest is where you recover and you can't be healthy without proper rest). Keep your mental healthy in good shape while you do this too - don't rush. Learn the science behind it, enjoy the process and set realistic goals based on statistics.

6.1.5 Can I lower blood pressure while still exercising?

Yes, you would want to reduce sodium intake to 1000-1500mg/day in order to keep blood pressure at a metabolic minimum. If this does not affect enough change then you can look into an ACE inhibitor medication or other types, like Clonidine. Stay away from Beta Blockers like Propranolol since these will lower blood pressure as well as heart rate, which complicates fitness activities.

6.1.6 Fitness and asthma?

I've always had a hard time with exercise due to light asthma. What can I do?

Get a prescription for clenbuterol or albuterol. It's a sympathomimetic stimulant that is prescribed for asthma + it signals the cells to burn fat as a fuel source first, and is an incredible metabolic stimulant. Clenbuterol is what you want for serious fat burning weight loss. See the Clenbuterol section of this document for more information.

6.1.7 How can I lose belly fat?

The belly is primarily about diet, particularly simple sugars. Cut out processed sugars and other sources of simple carbohydrates, only drink non-sweetened water/coffee/tea, keep your macros clean and organic. Do crunches and sit ups every day, every day. Couple more per day and suddenly your core is tightened up and flat (doesn't have to be a six pack but you need strong core muscles to stay flat and tight).

6.1.8 What is BMR?

BMR stands for Basal (or base) Metabolic Rate. That's the bare minimum of calories you need to maintain current weight without any additional exercise. When it comes to weight loss you have three options when it comes to basic metabolic facts.

- Burn more calories via exercise and don't eat more than your BMR. The caloric deficit is made up by your metabolism consuming endogenous sources (your fat).

- Eat less than BMR and don't exercise at all = creates a negative caloric balance, same metabolic process as the previous method but without the exercise.
- Eat less than BMR + exercise = most rapid method of weight loss.

`http://www.bmi-calculator.net/bmr-calculator/`

6.1.9 Cardio based weight loss: HIIT or LIIT?

Cardio, does it matter if I use High Intensity Interval Training or Low? What kind of cardio exercise is used to simply lose weight?

It depends on your overall fitness goal. Personally, I always train in Heart Rate zones regardless of HIIT or LIIT because it allows me to understand how my heart is functioning so that I can maximize the intensity intervals. HIIT is good for maximizing caloric burn or for doing interval training where you have some kind of intensity or speed goal (like with bike racing or running or other competition where that matters), but if you are simply wanting to lose weight and muscle mass then you only need to be concerned with average weekly caloric deficits. eg: 500cal deficit per day is a standard equation to = 1lb/week weight loss (which = 3500cal deficit per week). So you manage it with some simple math. Daily (BMR + calories burned in fitness = daily caloric net), do that for each day and you get your weekly deficit. Then divide by 500 and you get pounds-per-week of loss.

Regardless of goal, I always recommend training by heart rate zones to prevent burnout too early on in the workout. I warm up for 10-15min below 140bpm, then increase 140-150 for another 10-15min, then stay between 150-165 for the remainder with dips to 140s every 30min or so (or in between weight sets) + increases from 165-175 if I feel really good. then I always warm down for 15-20min so I don't get messed up from lactic acid rush. Owning a good heart rate monitor is essential for statistics based fitness.

6.1.10 What are some sample routines for women bodybuilders?

Question: What do you usually do and how can I get ripped?

Last summer I'd warm up on the elliptical for 30min and then do 60-90min free weights and/or rowing, then elliptical to warm down. With rowing at my peak I'd do super sets of 50rep x 115lbs and then decrease by 10lbs each successive set of 50 until I couldn't do any more.

Then I'd switch to the next workout depending on day of the week (is it arms/shoulders day, arms/back, leg day, core day, etc) I did the same routine for tricep pull downs, spider curl bars (though usually doing sets of 15-30 instead, starting at 100lbs and working down in super sets)... a whole mess of different types of dumbbell routines. With squats, same idea... sets of 20-50 but starting at 135lbs and working my way down. Weights are going to vary from person to person, it's just numbers and unless you're competing for some record then it's basically irrelevant what those numbers are; just make it burn and feel good and then do some more! Going too hard too fast can lead to injury and prevent you from achieving fitness goals. Modulate your exercises and listen to your body.

I never did chest/pectorals ever - I like my boobs the way they are, and that was part of my aesthetic goal. I never did any max-out or low rep sets because I didn't want to get huge, though I got pretty big regardless, but nothing like how big male bodybuilders get by any means. My intake of protein was 1.5-2g per pound of body weight during the month of August. I started at 178lbs @ 15% body fat and cut down to 164lbs @ 6% body fat. Lots of fun!

6.2 Endocrine Troubleshooting

The following are answers to several common endocrinology questions.

6.2.1 Do hormones change fat distribution?

What do you think about the notion that if you lose fat deposited under the influence of Testosterone and then gain it back under high Estrogen that it will go to the female areas?

That is absolutely true. No doubt about it - this is one of the core aspects of how hormones work in terms of cellular change for a body in endocrine transition.

6.2.2 How can I reduce body hair?

Body hair growth is controlled by androgen receptor modulation. Hair follicles get stimulated particularly well by DHT, dihydrotestosterone levels. Women with hirsuitism, and androgen disorder, generally take one of three types of androgen receptor blockers, which are also covered in the "Androgen Blockers" section of this document: spironolactone, dutasteride / finasteride, or bicalutamide. Bicalutamide in particular is especially useful because it attaches to the androgen receptor and prevents any activation; while also being non-steroidal in nature and thus tends to cause less systematic issues by comparison to the other blockers.

6.2.3 Estradiol tests for dosage changes?

My doctor wants me to get an E2 test to determine if my HRT blood levels are correct for the current dose, what should I know before doing the test?

You always need 4 weeks of consistent dosage to see how the body stabilizes. Take the test in the morning before you take your usual dose so that the medication does not throw off the test results.

6.2.4 Estrogen injections and blood test?

On what day of the injection cycle should I get an estradiol test done?

The common day for E2 tests is day 7 after injection - otherwise the plasma concentration curve will be at a non-midterm of the half life and the reading will be either way too high or too low and the endocrinologist may interpret your dosage incorrectly. The half life for estradiol valerate is 14 days, with a "not exactly logarithmic" shaped curve to it. See the "Estrogens, Properties" section of this document for a visual description of plasma concentration when doing a weekly injection.

6.2.5 When should I have testosterone blood tests?

My doctor wants me to get a testosterone test to determine if my blood levels are correct. When should I get this test done?

Due to the manner in which the body fluctuates testosterone production and suppression, the highest level of Testosterone occurs in the early morning. It is commonly desired that Testosterone tests be run prior to 9am in the morning. You do not have to fast for this test.

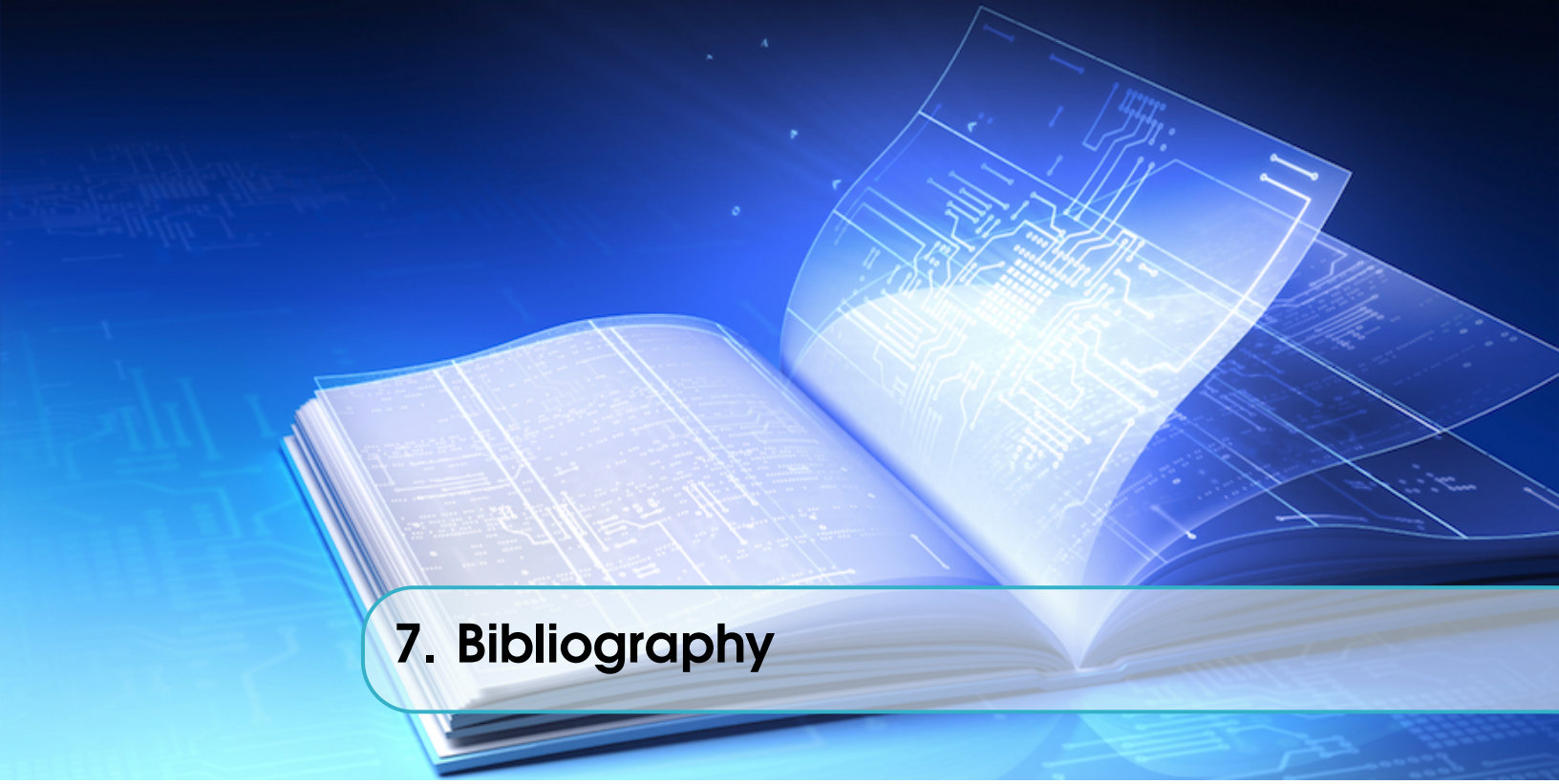
6.2.6 What is all of this about blocking DHT?

If your Testosterone is suppressed by other means, is Finasteride/Dutasteride still effective?

If there is still Free Testosterone (not bound by SHBG) in your system while concurrently taking an androgen blocker then a 5-AR blocker like Finasteride / Dutasteride will be useful to suppress the conversion of T -> DHT. If there is an "undetectable" level of Free T in your system then it's basically a waste of money to take a 5-AR blocker.

I've heard Bicalutamide tends to reduce body hair pretty significantly and/or change them to clear or lighter hairs.

Though results vary person to person in intensity + are dose dependent. Body hair reduction is a common effect of this medication and one reason that is it commonly used. Bicalutamide is a pure, non-steroidal androgen receptor blocker. It does not do anything except bind to the AR and prevent any free T or DHT from binding and activating the AR, thus body hair production has less stimulation and the follicles will tend to shut down.



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