Intraveinous injection of $GABA_A$ receptors embedded in modified liposomal membranes for people consuming alcohol and benzodiazepines at low or high concentrations

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Abstract

We use a liposomal technology in order to decrease alcohol concentration in the brain of patients consuming benzodiazepines with alcohol. In fact, it is common that benzodiazepines are consumed with alcohol in patients suffering from depression or anxiety disorders. An alternative treatment to reduce the effects of alcohol on the central nervous system in benzodiazepines consumers is to use $GABA_A$ receptors antagonists, preventing hyperpolarization of neurons. Unfortunately the use of $GABA_A$ receptors antagonists can increase excitability of neurons leading to convulsant effects, their use is reserved for pure research.

Introduction

In this theoretical model we focus on $GABA_A$ receptors, an ionotropic receptor stimulated by its endogenous ligand called γ-aminobutyric acid (GABA). Other ligands are able to stimulate this receptor, like ethanol (alcohol) or benzodiazepines. Note that the binding site of benzodiazepines is different from the binding site of GABA. When the receptor is stimulated, the $GABA_A$ receptor is open and is selectively permeable to chloride ions. The result is that the post-synaptic neuron is hyperpolarized (i.e there is an increase of potential membrane), reducing action potentials. Thus, GABA is the major inhibitory neurotransmitter in the central nervous system.
Benzodiazepines and alcohol consumers at the same time are a population-at-risk because these molecules cause inhibitory effect in the central nervous system and can lead to a coma. In the next paragraph we use a powerful tool based on electrophysiological equations, like the Nernst equation that is a special case of the Goldman-Hodgkin-Katz equation (GHK equation).

Liposomal technology

Because $GABA_A$ receptors are able to bind alcohol, we use this property to reduce the alcohol concentration in blood and consequently in brain (because the ethanol can cross the blood-brain barrier).
There are several evidences that we can embed a transmembrane protein (i.e $GABA_A$ receptor) in a modified liposomal membrane (figure 1) [1] [2].

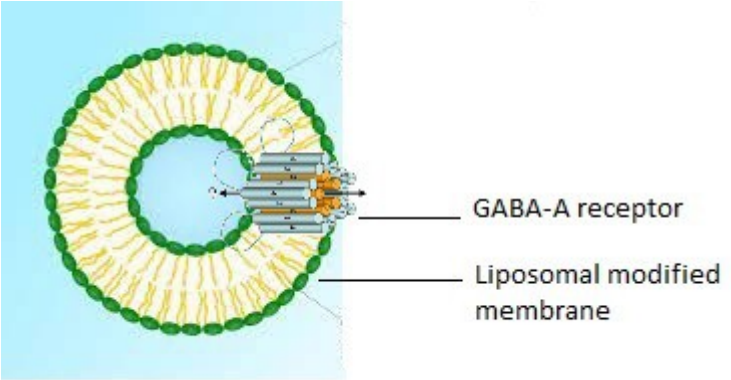

Figure 1: $GABA_A$ receptor is embedded in a modified liposomal membrane

$GABA_A$ receptors also bind to benzodiazepines, so the treatment should be increased to obtain the same effect.
An interesting thing is that GABA in the blood cannot cross the blood-brain barrier, so even if the $GABA_A$ receptor binds to GABA in the blood, the GABA in the brain is not affected, allowing hyperpolarization of neurons in the central nervous system and avoiding hyperexcitability of these neurons.
However, a study shows that decreased blood GABA rate can lead to mood disorders like depression or anxiety [3]. In this case, benzodiazepines can counterbalance the effects of the decreased blood GABA rate.

Another study suggests that it is possible to embed a protein that has a quaternary structure [4], like immunoliposomes that carry antibodies attached to their surface and bind to their antigens. This is interesting because $GABA_A$ receptors have also a quaternary structure and function as an immunoliposome because it selectively binds to several ligands (alcohol, benzodiazepines, GABA and others).

We use long-circulating liposomes that are modified and can stay in the blood much long (for hours) than non-modified liposomes. This is interesting because the levels of alcohol in blood decrease slowly.

Because it doesn't exist antibodies directed against alcohol [5], we have to use modified liposomes that we inject by intraveinous. Astudy suggests that intravenous injection of liposomes could be possible [6].

Because the intraliposomal concentrations are different from blood concentrations, we need to equilibrate the concentrations of Cl- and others components in the intraliposomal solution to avoid an osmotic shock [7]. Because we equilibrate the concentrations of intraliposomal Cl- and blood Cl-, the Nernst equation (equation 1) gives a membrane liposomal potential that tends to 0mV :

$$Em = \frac{RT}{zF} \ln \frac{[Cl-]ext}{[Cl-]int} (1)$$

Where R is the universal gas constant in J $K^{-1}mol^{-1}$
T is the temperature in Kelvins
z is the number of electrons transferred in the cell reaction or half-reaction
F is the Faraday constant in C mol^{-1}
Em is the liposomal membrane potential in mV

The Nernst equation is used when a biological membrane is permeable to only one ion and in our theoretical model this is the case.

Limits of the study and conclusion

Our theoretical model doesn't take into account the elimination of the complex liposomes/$GABA_A$receptors (urinary elimination for example).
Moreover, the reaction of the immune system is unknown.

To conclude, we can say that low or high concentrations of alcohol are decreased in the blood because alcohol binds to $GABA_A$receptors in the blood and consequently alcohol levels are also decreased in the brain for the same reason. Thus, people who consume alcohol with benzodiazepines at low or high concentrations should be protected from organs damaged at long-term.

References

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