# KP222 Molecular Recognition of Barbiturate Enantiomers in Agonist Binding Site of Nicotinic Acetylcholine Receptor

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## 1. Introduction

Specific theory of anesthesia has been suggested that general anesthetics act on a discreet site of neuronal membrane proteins, because optical isomeric anesthetics act differently. However, the isomers of 2-hexanol and 2-heptanol do not show different anesthetic effect [1].

We pose here question to this theory. Present study investigates enantiomeric barbiturate binding and interactions at binding site of nicotinic acetylcholine receptor (nAChR), and to elucidate mechanism of enantiomeric molecular recognition and discuss role of enantioselectivity in anesthesia.

## 2. Method

Binding of optical isomeric barbiturates was studied by docking simulation. 2BG9 ( Protein Data Bank ) was used as nAChR structure [2]. To verify reproductivity of simulation, binding of nicotine to nAChR was simulated and compared with prior experimental data [3]. Its channel inhibitors, amobarbiturate, amylbarbiturate, (R/S)-isobarbiturate ( isobarb ) and (R/S)-pentobarbiturate were used for docking. Docking was performed with ASEDock2005 ( Ryoka system, Japan ) on Molecular Operating Environment ( MOE, Chemical Computing Group, Canada ) [4]. MMFF94x force field was used. MOE-ligand interactions was used to find interactions.

## 3. Results and Discussion

The simulated binding site of nicotine and experimental data were identical. Isobarb bound to the agonist binding site and its carbonyl groups hydrogen-bonded to Thr190 and Asp 152 of the site (Fig. 1). Comparing (R)-isobarb and (S)-isobarb bindings, barbiturate rings almost superimposed each other and alkyl radicals partially superimposed, respectively (Fig. 2). Binding energies of (R) and (S)-isobarb did not differ each other. Major binding group was barbiturate ring ($R_1$), and the contributions of alkyl radicals ($R_2$, $R_3$) were minor. Enantiomeric isomer has been considered to have quite different affinity to the site with lock-and-key specificity. However, in case that single binding group dominates the binding, enantiomeric effect for binding was relatively small. Thus, enantiomeric drugs of $R_1 >> R_2$, $R_3$ type binding would show minimal pharmacological difference.

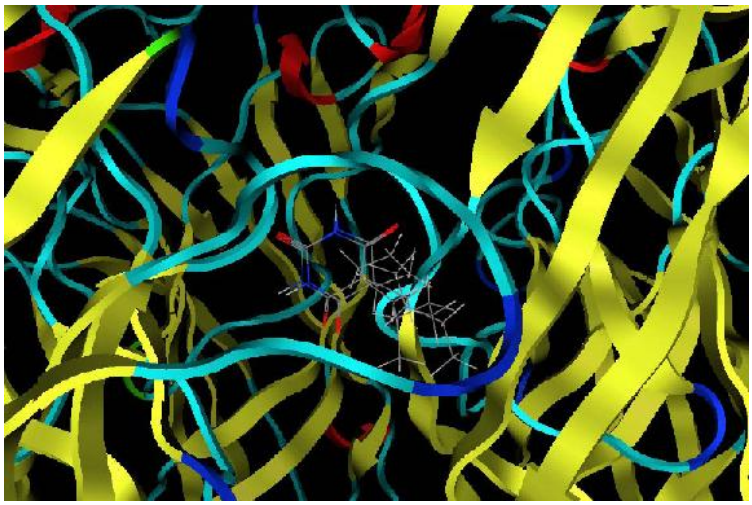

**Fig. 1** (R)-isobarb and (S)-isobarb both bound to the same agonist binding site of AchR

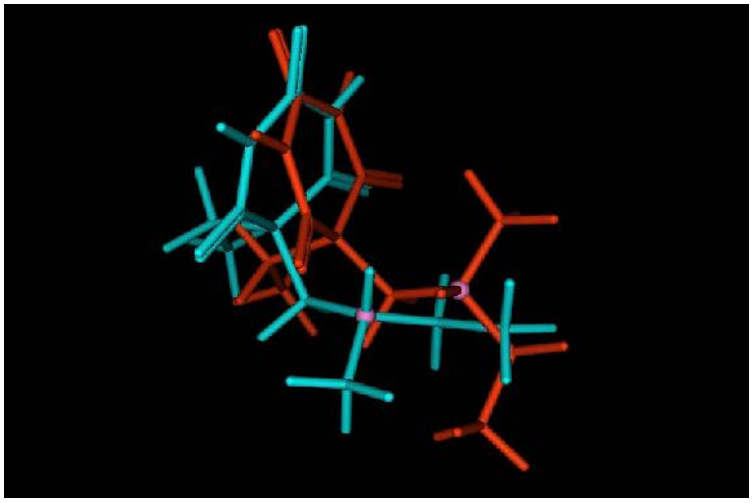

**Fig. 2** Barbiturate rings of (R)-isobarb and (S)-isobarb are almost superimposed each other

## 4. Summary

These results suggest that docking simulation with ASEDock is reliable, barbiturates bind to the agonist binding site of nAChR, the barbiturate ring is the crucial structure to exhibit anesthetic effects, and enantioselectivity of barbiturate does not affect binding conformation and energy.

## References


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