Propofol, a powerful anesthetic, can be used safely in medical settings, but proves deadly when used recreationally. Figure 1 shows the results of a five year study in South Korea in which there were 131 cases of Propofol related deaths. Of these, 49 of these autopsies revealed that the body contained only propofol at the time of death, and 82 of the deaths occurred as a result of propofol combined with other drugs.

Propofol binds to the GABA<sub>A</sub> receptor, which consists of an integral ion channel protein embedded in the membrane of neurons in the brain that is activated by the neurotransmitter molecule gamma aminobutyric acid, or GABA. When propofol binds to the GABA<sub>A</sub> receptor, a conformational change occurs, holding the neurotransmitter GABA in its binding site and keeping the ion channel open. This allows more chloride ions to diffuse into the cell. Resting potential becomes more negative so even with the diffusion of Na<sup>+</sup> ions during nerve stimulation, the threshold cannot be reached and the action potential is generated. Since the neurons cannot communicate normally, a person given propofol remains unconscious.

The lower part of the GABA<sub>A</sub> receptor, located in the cytoplasm of a neuron, has an unidentified molecular structure. Phe 393 variants in the A and D chains prevent propofol from acting on the GABA<sub>A</sub> receptor. The DSHA SMART Team modeled the similar nicotinic receptor to better understand the structure of the GABA<sub>A</sub> receptor and the role of the Phe 393 variants in the action of propofol can lead to the development of more effective anesthetics.

**Propofol Sensitivity Data**

Figure 3: Propofol enhances GABA-evoked currents in a cell expressing the wild type receptor, but does not in a cell expressing the mutant F385A receptor. Therefore, these mutated residues must be essential in the allosteric response of the GABA<sub>A</sub> receptor to propofol.

Figure 4: These traces show currents carried by a single glycine receptor protein (which is similar to the GABA<sub>A</sub> receptor). When the trace drops, the receptor is open. The upper traces show that the wild-type receptor is open more often when propofol is present versus when it is not present. The lower traces show that the mutant receptor is less responsive to Propofol.

Figure 5: Propofol is more effective in wild-type receptors because it holds the channels open longer than the mutant type; however, there is not a difference in how big the current is through an individual receptor.

**References:**


The GABA<sub>A</sub> receptor is an essential target of anesthetics in the brain. Through studying the action of propofol on this receptor, scientists hope to determine how the cytoplasmic region affects channel function. By better understanding the structure of this neurotransmitter, a wider range of anesthetics can be developed for use in a medical setting. Future research is needed to understand the exact interaction of propofol and other anesthetics with the GABA<sub>A</sub> receptor, and to provide further insights into the molecular mechanisms of the brain.