Alastair S. Deng
High School Senior
Benjamin Franklin High School, New Orleans, LA

Ashley Henderson[1], Sarah Melton[1], Jessye Garriet, Tamara Morris[1], and Peter Winsauer[1]
[1] Louisiana State University Health and Science Center, Department of Pharmacology

"Effects of Shisa7 on $GABA_A$ Receptors and Learning"

The γ-aminobutyric acid type-A ($GABA_A$) receptor is a ligand-gated chloride ion channel. Its endogenous ligand is GABA, which is the major inhibitory neurotransmitter of the central nervous system. In addition, the $GABA_A$ receptor complex has allosteric binding sites for several other types of ligands that include drugs from classes such as the benzodiazepines and barbiturates. These drugs are positive $GABA_A$ modulators that can be used as pharmacotherapies for anxiety and insomnia.

Previous experiments have suggested that genetically modifying the proteins around the $GABA_A$ receptor allosterically modifies the effects of drugs that bind to this receptor complex and can alter learning and memory (Han, Li et al. 2019). For example, recent data has shown that the deletion of SHISA7, a transmembrane protein that regulates the conformational activity of the $GABA_A$ receptor complex, leads to a decrease in the effects of benzodiazepines in mice (Han, Li et al. 2019). We aim to demonstrate the role of SHISA7 in the effects of benzodiazepines on learning by knocking down SHISA7 in rats trained to respond under a complex behavioral baseline of learning; that is, a repeated-acquisition baseline. Under this baseline, rats acquire a four-response sequence on three keys under a second-order variable-ratio (VR) schedule of food reinforcement. When responding under this baseline stabilized, the rats were administered varying doses of the benzodiazepine alprazolam to establish a dose-effect curve ranging from an ineffective to a maximally effective dose. Further, by establishing dose-effect curves before and after SHISA7 knockdown, we will be able to determine whether this protein plays a direct role in the effects of $GABA_A$ modulators such as the benzodiazepines on learning and memory. Currently, we are finalizing the dose-effect curve for the rats before SHISA is knocked down. Alprazolam (1-18 mg/kg) significantly and dose-dependently decreased response rate and increased percent error. Using western blot analysis, we were also able to demonstrate that rats administered the SHISHA7 shRNA knockdown virus 24, 48, and 72 hours before sacrifice reduced the SHISA7 protein in the cerebellum, but there was little or no reduction of SHISHA7 in the frontal cortex compared to control.

If the dose-effect curves show significant changes after SHISA knockdown, these data would confirm the initial evidence indicating that this family of proteins is critical for the function of the $GABA_A$ receptor complex and its role in learning. Moreover, these results would show that SHISA7 can alter the effects of drugs that bind to the $GABA_A$ receptor complex.