Effects of PICK1 Inhibitor on Reinstatement of Cocaine-seeking Behavior
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This summer I had to opportunity to continue working under Dr. Heath Schmidt in the Department of Biobehavioral Health Sciences of Penn's School of Nursing, thanks to the CURF Jumpstart for Juniors grant. Dr. Schmidt's work focuses largely on identifying the neurobiological mechanisms underlying cocaine addiction. The goal of our study was to characterize the role of protein-interacting C Kinase 1 (PICK1) in cocaine seeking using a novel, selective peptide inhibitor of PICK1 called TAT11-N-PEG4-DATC5 in a rodent model of cocaine addiction/relapse. Previous evidence suggests that PICK1 may play a critical role in the reinstatement of drug-seeking behavior. Cocaine reinstatement is associated with rapid internalization of AMPA receptors containing the GluA2 subunit, resulting from PKC-mediated phosphorylation of GluA2. PICK1, through its interactions with PKC, facilitates the phosphorylation of GluA2 and thus plays an important role in the reinstatement of cocaine seeking. Thus, we hypothesized that TAT11-N-PEG4-DATC5 would attenuate the reinstatement of cocaine seeking through inhibition of PICK1.

Initially, rats were allowed to lever press for infusions of cocaine during daily two-hour drug self-administration sessions. Once responding for cocaine became stable, the cocaine was replaced with a non-rewarding saline solution. Eventually, rats learned that cocaine was no longer available to them and they stopped pressing the lever previously associated with the delivery of cocaine. When cocaine taking was extinguished, we modeled relapse by giving the rats an acute priming injection of cocaine to reinstate drug-seeking behavior.

In our experiment, we wanted to test whether administration of the PICK1 inhibitor prior to the cocaine injection would attenuate reinstatement of cocaine-seeking behavior. First, we pretreated rats with systemic infusions of the PICK1 inhibitor. Systemic administration of the inhibitor attenuated cocaine priming-induced reinstatement of drug seeking. To determine the neural circuits mediating these effects, we next administered the inhibitor directly into the brain. Consistent with our systemic study, we found that intra-cranial infusions of the PICK1 inhibitor reduced cocaine seeking. Taken together, these results identified a novel role for PICK1 in cocaine seeking and suggest that peptide inhibitors of PICK1 may represent efficacious medications for preventing cocaine craving and relapse.

Working under Dr. Schmidt was an invaluable experience. I developed skills and techniques that I could not have imagined I would possess at this stage in my education. For example, I am now able to perform surgery to implant a catheter into the jugular vein of a rat, through which drugs can be administered intravenously for experimentation. I can also administer microinfusions into specific brain regions and use histology to verify the cannula placements post mortem. Furthermore, through my research I have gained a much better understanding of neuroscience and biology as a whole, which will help me on my path to one day becoming a successful doctor. Finally, I learned the value of being part of a close-knit team, where the combination of being reliable and relying on each other allowed us to accomplish more than seemingly possible. Thank you to CURF, Dr. Schmidt, and the Schmidt Lab!