Experience-Dependent Neuroplasticity in Dopamine-Linked Models of Anabolic Androgenic Steroid Abuse and Huntington's Disease

By Grace Kim, Junior, Neuroscience Major

Background

Vivek Shah is a senior at the University of Southern California majoring in Business Administration with a minor in Natural Sciences. Vivek aspires to attend medical school in the near future and has been active in many extracurricular activities, including research in neurological diseases.

His career in the laboratory began during his sophomore year while volunteering at the Keck medical center, Vivek had the opportunity to walk a patient down to her car. He soon learned that the patient was a medical student working in the laboratory of Drs. Michael Jakowec and Giselle Petzinger and would be willing to help connect them due to his interest in neuroscience. A few weeks after this meeting, Vivek contacted Dr. Jakowec and in January of 2011, began working as a student researcher.

Research on the molecular basis of the chronic Anabolic Androgenic Steroid (AAS) abuse

Vivek has been involved with three main research projects in the Jakowec lab. In his first project, Vivek looked at molecular mechanisms to support behavior seen in an animal model of chronic Anabolic Androgenic Steroid (AAS) abuse. The focus of the project was to answer three questions: 1) Will AAS abuse cause an increase in aggression? 2) Does steroid abuse increase motivation for aggression? 3) How does AAS abuse affect impulsivity? Vivek's main role in the project was to provide support from a molecular biology perspective to behavioral observations in the AAS model.

To answer the first question, a foreign rat was placed in the home of a rat under the AAS abuse model to see whether steroid abuse would cause an increased likelihood of fighting and if fighting would last for longer periods of time. As expected, rats on chronic doses of steroids fought the intruder rat more frequently and for longer amounts of time than the control.

The second question was answered by giving rats the chance to fight with an intruder. If the rat wanted to fight, he would have to poke a lever. Increased likelihood to push the lever indicated an increase motivation for aggression. It was found that chronic steroid abuse did not lead to increased motivation to be aggressive.

Finally, to determine how steroid abuse would affect impulsivity, rats were trained so that after a poke on the nose, they would receive food, but if they waited for some time to poke the lever, they would receive more food. Findings showed that rats chronically on steroids tended to wait longer to receive food; they were less impulsive. This finding was further supported by the fact that when a female rat was placed in a male rat's cage, the rats with high levels of testosterone did not attack the female unless she attacked him. The rat would only attack back if she was not nesting.

With these behavioral data in hand, Vivek sought to explore the molecular basis of behavior – specifically, the mechanisms of the brain responsible for such behavior. He focused on studying the Mesolimbic pathway, a pathway in the brain known to be associated with the reward. Vivek examined various regions of the brain including the Prefrontal Cortex (PFC), Caudate Putamen (CPU), and the Accumbens (Acc). He measured change of levels of Tyrosine Hydroxylase (TH), a key enzyme that catalyzes the rate-limiting step in dopamine production; dopamine is highly involved in stimulating the Mesolimbic pathways. The concept behind this test is that if TH is increasing, then dopamine transmission is likely increasing and vis-a-vis. Figure 4 from Vivek's published article in the Journal of Physiology and Behavior, "Roid rage in rats? Testosterone effects on aggressive motivation, impulsivity, and tyrosine hydroxylase" summarizes the results from this study.

Upon observing the change of this key enzyme in rats, Vivek observed no significant difference except in the region of CPU, a region responsible for inhibition and habit learning. The decrease of TH in the CPU is potentially due to the decreased inhibition of

behavioral response, specifically fighting. The PFC is involved in executive function and thus, is related to cognitive processes like decision making while the Accumbens is responsible for motivation. Hence, lack of change in the Acc and PFC parallels the lack of increase in impulsivity and motivation for aggression, respectively.

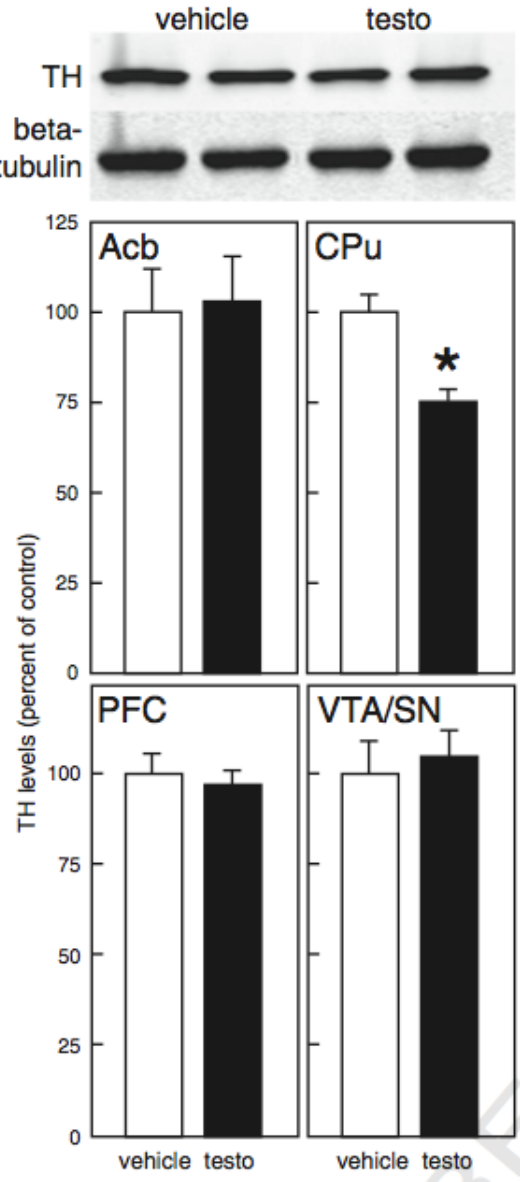

Figure 4. Top: Western blot assays of tyrosine hydroxylase (TH) and beta-tubulin in caudate-putamen from representative Long-Evans male rats (n=2 each) treated chronically with vehicle (left) or testosterone (right). Bottom: Levels of TH in microdissected brain regions from testosterone (closed bars) or vehicle-treated rats (open bars). ACB: nucleus accumbens, CPu: caudate putamen, PFC: medial prefrontal cortex, VTA/SN: ventral tegmental area/substantia nigra. *Asteriks* indicate significant differences between treatment groups.
(Wood *et al., 2012)*

Research on Huntington's Disease

Vivek's other research project with Daniel Stefanko, a graduate student at the lab, focuses on studying the effect of exercise on Huntington's Disease, a neurogenerative genetic disorder that affects muscle coordination and leads to cognitive decline and psychiatric problems. Vivek's role in this project was to prepare samples and calculate the protein concentration for a technique called HPLC, High Pressure Liquid Chromatography. The method allows him to quantify concentrations of dopamine and its metabolites or breakdown products in several regions of the brain potentially affected by Huntington's Disease; these include the cortex, pre-frontal cortex, dorsal striatum, and ventral striatum.

Further, Vivek is interested in studying the modulation of certain proteins in the Huntington's Disease model that may occur as a result of exercise by using a method called Western Immunoblotting. Huntington's Disease is caused by a mutation in chromosome 4, which produces an aggregate of a protein called *Huntingtin*. This protein is responsible for neuronal cell death and Vivek seeks to determine the compensatory effect of exercise. More specifically, he seeks to determine whether there will be a compensation with exercise via an increase in D2R (a dopamine receptor in the indirect pathway) as well as a decrease in the cytotoxicity of NR2B. He and his group do not expect to see any changes in dopamine levels.

Vivek is currently focusing his research upon the protein D2R, which is a known to help with adaptation and learning. Past research with Parkinson's Disease indicates that exercise will increase D2R levels and therefore improve adaptation and learning.

He also studied the glutamate receptor, NR2, a subunit of the NMDA receptor. The NMDA receptor is often a homodimer composed of two parts: NR1 and NR2B or NR2A. An NR2B component, which is sometimes present in neurons' NMDA receptors that are affected by HD, is cytotoxic due to its greater calcium permeability. Vivek's focus lies in investigating the effect of exercise on the cytotoxicity of NR2B; with exercise, the cytotoxicity is expected to decrease.

Significance

Vivek's research holds great significance for future research. It will not only shed light on the molecular mechanism of Parkinson's and Huntington's disease, but also possibly provide a target of treatment. Vivek's research will also further investigate the beneficial effects of exercise and its role as a potential therapeutic agent in two debilitating diseases.