

Department of Biological Sciences Seminar Blog

Seminar Date: 03/16/2018

Speaker: Dr. Antoinette M. Maldonado-Devincci, North Carolina Agricultural and Technical State University, Department of Psychology

Title: *“Alcohol and Stress Regulation of Neuroactive Steroids.”*

INVESTIGATION INTO NEUROACTIVE STEROIDS ROLE IN THE CHRONIC ALCOHOL DRINKER’S BRAIN

By: Brooke Deal (Biology PhD Student)

Dr. Antoinette M. Maldonado-Devincci was welcomed to Duquesne University as a guest speaker on behalf of one of our faculty, Dr. Allyson O’Donnell. Dr. Maldonado-Devincci received her bachelors (Psychology), masters (Psychology), and doctorate (Biopsychology) all from the University of South Florida; she then did two postdoctoral fellowships at the University of North Carolina at Chapel Hill. Dr. Maldonado-Devincci is now an Assistant Professor in the Psychology Department at North Carolina Agricultural and Technical State University.

Throughout her entire research career, she has been involved with studying alcohol’s effects on the brain. Today, her lab focuses on how alcohol dependence effects the release of cholesterol-derived neuroactive steroids. Neuroactive steroids are thought to be locally produced in the cell of action and function by increasing or decreasing neuronal excitability through the interaction with ion channels. Her lab’s neuroactive steroid of interest is (3 α , 5 α) 3-hydroxypregnan-20-one (also known as 3 α , 5 α -THP, or allopregnanolone). 3 α , 5 α -THP enhances GABAergic transmission; this means that 3 α , 5 α -THP binds to the GABA receptor which opens the ion channel and floods the neuron with chloride. Inward chloride movement hyperpolarizes the cell causing an overall decrease in neuronal excitability. Increased GABAergic transmission has been shown to have both positive and negative pharmacological effects such as neuroprotection, anticonvulsant, anti-depressant, cognitive impairment, anesthetic, and

sedative-hypnotic. These differences in function are a result, in part, on the site of activity in the brain. She hopes that her research can lead to a new therapeutic drug or technique to ease alcoholics' withdrawal and help keep them from relapsing.

The Maldonado-Devincci Lab has done the majority of their research in rat models. Through this they have found that during occasional ethanol consumption, GABAergic neuroactive steroid production was slightly increased which caused an increase in ethanol sensitivity as ethanol also potentiates GABAergic tone. This increased ethanol sensitivity then often leads to a behavioral decrease in drinking. In contrast, they found that chronic ethanol consumption blunted the effect of ethanol on neuroactive steroids; therefore, decreasing ethanol sensitivity. This decreased sensitivity increased the risk of excessive drinking (to gain the same "buzz") ultimately leading to alcohol use disorders. They hypothesize that if they were able to restore the behavioral sensitivity in chronic ethanol drinkers that it could restore the physical and sensory cues to reduce consumption.

To evaluate this therapeutic strategy, the Maldonado-Devincci Lab needed to first identify the regions of the brain being affected by chronic alcohol exposure. They also need to identify what changes are occurring in which areas due to the neuroactive steroids. Understanding these two key findings would allow for the development of an effective therapy.

The Maldonado-Devincci Lab uses a vapor inhalation model to ensure that the rats become intoxicated. This is done because rodents do not voluntarily drink until intoxication. Rats were left in the chamber for 16 hours a day for 4 consecutive days. The rats were then removed from the chamber for 3 days and then their brains were processed for immunohistochemistry (IHC). Through comparing the change in GABAergic neuroactive steroid levels in the brain of air exposed rats to ethanol exposed rats, the Maldonado-Devincci Lab found that the regions of the brain being affected were the same as those that mediate anxiety, stress, and reinforce ethanol dependence. It was found when 3α , 5α -THP production decreased that the production of corticosterone increased. This switch in neuroactive steroid production from 3α , 5α -THP to corticosterone

is a compensatory switch in the steroid biosynthesis. These findings are still under investigation.

There are only three FDA-approved drugs used to treat alcoholism available currently. In the future, the Maldonado-Devincci Lab plans to investigate pregnenolone in a long-term study to evaluate its efficiency in regulating neuroactive steroids during adolescence. They would like to see if the effects from chronic ethanol exposure can be reversed if pregnenolone is delivered during this time of development. If so, pregnenolone could be another future therapeutic for suffering alcoholics. Overall, Dr. Maldonado-Devincci's Lab is making headway in being one of the first to characterize chronic intermittent ethanol exposure and withdrawal in the areas of brain of C58BL/6J mice. This novel science will help propel science forward in being better able to treat alcoholics going through withdrawal and keeping them in remission.