A Pharmacological Approach for Studying Alcohol Use Disorder: Using Calcium Imaging on hiPSC-Derived Glutamatergic Neurons to Dissect the Glutamate Response in the Context of Chronic Ethanol Treatment

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Alcohol use disorder (AUD) affects over ten million people in the U.S. yet less than 4% of people diagnosed were prescribed a medication approved by the FDA. In fact, the few medications approved have exhibited inconsistent effects across broad patient populations. And because the characteristic compulsive drinking is associated with functional alterations of neuronal reward circuits, it's pertinent to develop a complete understanding of how heavy drinking alters neuronal networks at the molecular and cellular level. Since Glutamate (Glu) neurotransmission plays an important role in the reward circuit, this study provides a vital stepping stone for this goal using hiPSC-derived glutamatergic neurons. Calcium imaging was employed together with a pharmacological approach as a means to dissect the glutamate response into relative contributions by different Glu receptors, specifically the AMPA and NMDA receptors. To investigate how these components of Glu-mediated neuronal activity were affected by ethanol, a portion of the neurons were subjected to chronic ethanol treatment following a scheme to mimic a human drinking pattern. It was shown that chronic alcohol treatment decreases the spontaneous firing and NMDA-mediated contribution to the Glu response. Ethanol also increased the AMPA-R/NMDA-R ratio which may have negative effects on long-term potentiation, an important synaptic phenomena for learning and memory formation. Finally, it was demonstrated that this experimental model of Ngn2 glutamatergic neurons presents an effective, high throughput strategy for studying the functional consequences of ethanol on human brain circuitry and eventually in developing therapeutics to modulate AUD and other diseased states.

Awards Won:

National Anti-Vivisection Society: Second Award of $5,000