Changes in Ih current channel's subunits 2 & 4 during the expression of cocaine sensitization

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Cocaine abuse can induce neurobiological adaptations in the Mesocorticolimbic (MCL) system. These can include changes in the excitability of neurons, which can contribute to the development and expression of cocaine sensitization. The Hyperpolarization-Activated Cyclic-Nucleotide Current (Ih), is a ubiquitous voltage dependent current generated by non-selective cation channels HCN. The potential regulatory role of Ih current in neuronal excitability is subjected to the expression of Hyperpolarization-Activated Cyclic-Nucleotide gated channel (HCN) subunits. Immunohistochemical studies have shown that HCN_1 and HCN_2 are the most abundant subunits in the MCL system, with HCN2 being the most expressed in the ventral tegmental area (VTA). In addition, HCN_1 and HCN_2 subunits differ in steady-state voltage dependence, kinetics of activation, and response to cAMP. It has been reported that dopamine neuron excitability is altered after cocaine administration, which leads us to suggest that such changes could be due to modifications in Ih current and/or changes in the expression profile of HCN_1 and HCN_2 subunits after cocaine exposure. Electrophysiological measurements in our laboratory have shown that Ih current and dopaminergic cell size are decreased in the VTA of cocaine sensitized animals. Additionally, molecular experiments have shown that there is a total protein increase in HCN2 subunit in the VTA, yet the subunit remains intracellularly. In order to further characterize the role of HCN channels in the VTA during cocaine sensitization, we need to determine HCN channel localization in the neurons. For this, we will use the Golgi-Cox Immunofluorescence technique to have additional evidence supporting our electrophysiology experiments. We hypothesize that HCN channels in the VTA are located in the soma of neurons, where they would be able to promote cell excitability. In cocaine treated animals, the decrease in HCN2 subunit expression would serve as a compensation to increased cell excitability after cocaine sensitization.