Title:	Understanding the role of DOP-2, a dopamine autoreceptor, in ethanol dependent locomotion of Caenorhabditis elegans
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Abstract:	Animals tend to respond to a variety of external stimuli by generating appropriate behavioral responses brought about by the modulation of their neuronal circuitry. Our study uses alcohol (ethanol), one of today's most widely abused drug. Although a lot of studies have focused on unravelling the mode of action to allow for addiction to alcohol, not much is known about how it functions to modulate behaviors such as locomotion. In my thesis, I have focused on understanding the neuronal circuitry that could play a role in regulating locomotory behavior under the influence of ethanol. This study uses the model organism C. elegans. Previous work using C. elegans shows that this organism can be modelled for studying important aspects of ethanol abuse, such as dose dependent decline in locomotor activity upon acute exposure to alcohol similar to the depressive effect of ethanol in other animal systems. Ethanol has been shown to mediate its action through diverse pathways, one of which is the dopaminergic pathway. The dopamine (DA) system in C. elegans is involved in the animals feeding, movement and learning and memory and functions through two types of receptor subfamilies D1-like and D2-like receptors. DOP-2, a D2-like family autoreceptor was found to have minimal role if any when studied for DA dependent behaviors and the functions of this receptor are still largely unknown. My work elaborates on how dopaminergic autoreceptor, DOP-2, regulates locomotion in the presence of ethanol. This study provides important insights into DOP-2 function, as it is difficult to assign specific roles to neuromodulators such as DOP-2, as they have roles in wide arrays of behaviors that can be very transient and subtle. In this study, we have used an ethanol (EtOH) based assay to screen the dopaminergic (DAergic) pathway mutants. We found that the DOP-2 autoreceptor mutant showed an ethanol induced sedative behavior (EIS), the animal moves in circles with decrease in body bends and amplitude. This behavior is DOP-2 dependent as we were able to rescue the behavior putting back DOP-2 in the mutant animals and observed that they were behaving like Wild Type (WT) animals, thus this behavior is DOP-2 specific. The mechanism of how the DOP-2 autoreceptor functions in C. elegans is still largely unknown, although in the mammalian system the D2 autoreceptor functions in feedback inhibition on activation to regulate the levels of DA by regulating its synthesis, release and reuptake at the NMJ. On exposure to exogenous DA in EtOH assay conditions, WT animals behaves like dop-2 mutant animals, while the cat-2 (synthesis pathway) mutants with low or negligible levels of DA, showed a behavior similar to WT animal on EtOH exposure. Our FRAP analysis also strengthens the statement as we observed significantly faster recovery of DA in dop-2 mutants compared to WT animals. Thus, the DOP-2 dependent EIS behavior is regulated by increase in synaptic DA concentrations. Further in our study, the role of D2 like autoreceptor DOP-2 in regulating a EtOH induced sedative behavior (EIS), we use this EtOH assay to delineate the neuronal circuitry that is involved in regulating the EIS behavior. The posterior part of the worm seemed to more severely affected than the anterior region, and our results validate this, as we observe partial rescue from the behavior on expressing DOP-2 in posterior neuron but not in the anterior dopaminergic (DAergic) neuron. We go on to show through our ablation studies that the DOP-2 autoreceptor functions on PDE, a posterior DAergic neuron to regulate the levels of dopamine (DA) at the synapse. PDE forms unidirectional synapses on a mechanosensory neuron DVA. We further show that increased DA at the synapse in dop-2 mutant mediate its action by activating the downstream circuitry, by binding to D1 like receptor DOP-1 expressed on DVA neuron. Activation of DVA through the DOP-1 receptor leads to enhanced release of a DVA specific neuropeptide NLP-12, that binds to its cholecystokinin like receptor CKR-2 present on cholinergic motor neuron, thus modulating, here leading to increase in the release of a neurotransmitter acetylcholine (ACh), that leads to muscle excitation and hypercontraction, leading to the EIS behavior.
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