THE ROLE OF THE DOPAMINE/ECDYSTEROID RECEPTOR DOPECR IN ETHANOL INDUCED BEHAVIORAL DISINHIBITION

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To my flies.

Without them, none of this would've been possible.

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by

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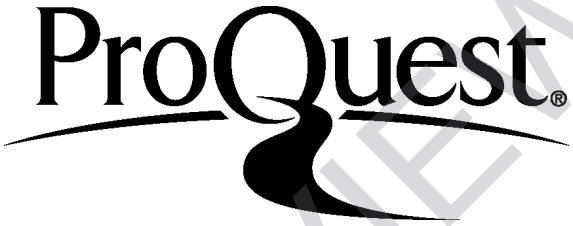

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ABSTRACT

Ethanol, a main active ingredient of alcoholic beverages, exerts numerous effects on behavior through its interaction with diverse membrane and signaling molecules and effector cells. The effects include lack of motor control, behavioral disinhibition, tolerance, sensitization and addiction. In particular, behavioral disinhibition is typically associated with heavy drinking and can lead to detrimental consequences such as car accidents, violent rages, risky sexual behavior and illegal substance abuse. This research aimed to clarify the neural elements and cellular mechanisms underlying behavioral disinhibition induced by ethanol. The neurotransmitter dopamine (DA) is implicated in ethanol-induced behavioral disinhibition (Van Gaalen et al., 2006). To better understand the mechanism that DA regulates ethanol-associated behavioral disinhibition, my study focused on the D1-like receptor DopEcR, an insect G-protein coupled receptor that binds to both DA and steroid hormone ecdysone, in the fruit fly *Drosophila melanogaster*. *Drosophila melanogaster* is a useful model organism to study the genetic and neural mechanisms underlying ethanol consumption, abuse and addiction (Kaun et al., 2011). The fly brain is anatomically simple yet mediates many of the same behaviors observed in intoxicated humans (Kong et al., 2010). Wild type flies show disinhibited inter-male courtship, a type of cognitive behavioral disinhibition, under the influence of ethanol and behavioral sensitization to this behavior with recurring ethanol exposures (Lee et al., 2008). We found that DopEcR deficient (*der*) male flies show abnormal disinhibited courtship and sensitization as well as altered synaptic molecule expression upon recurrent ethanol exposures. The *der* mutant's courtship phenotype was fully restored by expressing DopEcR during adulthood. This indicates a physiological (DopEcR functions at the time of ethanol exposure), rather than developmental, role of DopEcR for courtship disinhibition and sensitization. In addition, the *der* mutant's

abnormal courtship disinhibition was fully rescued by reinstating DopEcR expression in the mushroom body (MB) neurons, indicating the important role of the MB DopEcR in ethanol induced behavioral plasticity. Our study uncovers a key *in vivo* function for the novel G-Protein coupled DA/ecdysone receptor in ethanol-associated behaviors.

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INTRODUCTION

1.1 Overview

Drug abuse and addiction cause profound medical and social issues thus are major concerns worldwide. Specifically, ethanol abuse represents a serious problem since it can lead to tolerance development and ultimately addiction. In the US alone, alcohol use disorders represent a serious economic burden, costing 249 billion dollars, affecting approximately 16.3 million adults. Moderate to heavy drinking is a major cause of disinhibited sexual behavior and aggression, which are reinforced with continuous ethanol abuse, and chronic consumption leads to cognitive and motor impairments such as attention, learning and memory (Robinson et al., 2012; Söderpalm et al., 2009). Ethanol induces similar behavioral responses in rodents and flies. For example, ethanol intake in male rodents is associated with increased sexual motivation and arousal (Harrison and Nobrega, 2009) while male flies exhibit disinhibited behaviors upon repeated ethanol exposure (Lee et al., 2008) . These observations suggest that ethanol acts on the neural system that is highly conserved between humans, rodents and flies to induce behavioral disinhibition and such effect is reinforced with chronic consumption. Determining the mechanisms underlying ethanol-induced behavioral plasticity, such as the direct and indirect neuronal pathways that are affected, is central to understand alcohol abuse.

1.2 Ethanol-induced behaviors

Ethanol is the major intoxicating agent found in intoxicating alcoholic beverages. Unlike other drugs of abuse, it has non-specific neuronal targets. Ethanol affects many neural components yet leads to distinct behavioral responses (such as hyperactive locomotion and

sedation) . The acute effects of ethanol are biphasic (Kaun et al., 2011). At low or medium doses, ethanol acts as a stimulant, where it enhances locomotor activity, mood and disinhibited behavior in male flies. However, at high doses it acts as a depressant, where it leads to lack of motor coordination and sedation (Kong et al., 2010). Increased feelings of pleasure, arousal and dominance that lead to assertive behavior are often associated with binge drinking and enhanced sexual behavior. These behaviors in combination with the disinhibition effect of ethanol consumption may lead to violence, assault and risky sexual practice (Room and Collins, 1983). Chronic ethanol effects, on the other hand, are mediated by adaptive changes in brain activity. Such changes include tolerance to the depressant or sedative effect of ethanol, and behavioral sensitization, in particular enhancement of the euphoric effect of ethanol. Behavioral sensitization is a key behavioral plasticity associated with addiction due to the long lasting effects which extend to the withdrawal period (Iacono et al., 2008). A better understanding of the physiological processes behind behavioral sensitization may contribute to the development of novel treatments against alcohol addiction.

1.3 Behavioral disinhibition

Behavioral disinhibition refers to the loss of restraint over any form of behaviors and is associated with substance use disorders (Iacono et al., 2008). Behavioral disinhibition might result from frontal lobe damage or genetic influences, or as a consequence of alcohol consumption and other types of drugs (Chelune et al., 1986). It is commonly seen in our culture that alcoholic beverage consumption not only make a person feel different, but also removes social constraints, leading to unpredictable and sometimes harmful behavior. Often ethanol-induced behavioral disinhibition is overlooked and underestimated by our society; however, this