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Genetic Isolation of Hypothalamic Neurons that Regulate Context-Specific Male Social Behavior

Graphical Abstract

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In Brief

Soden et al. characterize a population of neurons in the ventral premammillary nucleus of the hypothalamus that are genetically defined as dopaminergic but that do not release detectable dopamine. These neurons are activated in specific social contexts and function via glutamate release to regulate male same-sex social interactions.

Highlights

- A group of neurons in the ventral premammillary nucleus express dopamine markers
- These neurons are activated in male intruder, but not resident, mice
- These neurons regulate same-sex social behavior in specific contexts
- These neurons function via glutamate release, but do not release detectable dopamine

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Genetic Isolation of Hypothalamic Neurons that Regulate Context-Specific Male Social Behavior

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SUMMARY

Nearly all animals engage in a complex assortment of social behaviors that are essential for the survival of the species. In mammals, these behaviors are regulated by sub-nuclei within the hypothalamus, but the specific cell types within these nuclei responsible for coordinating behavior in distinct contexts are only beginning to be resolved. Here, we identify a population of neurons in the ventral premammillary nucleus of the hypothalamus (PM_V) that are strongly activated in male intruder mice in response to a larger resident male but that are not responsive to females. Using a combination of molecular and genetic approaches, we demonstrate that these PM_V neurons regulate intruder-specific male social behavior and social novelty recognition in a manner dependent on synaptic release of the excitatory neurotransmitter glutamate. These data provide direct evidence for a unique population of neurons that regulate social behaviors in specific contexts.

INTRODUCTION

In rodents, olfactory information is a major modality for social communication. Inputs from the main olfactory bulb and accessory olfactory bulb directly innervate sub-nuclei of the medial amygdala that transmit this information to the hypothalamus (Scalia and Winans, 1975; Kevetter and Winans, 1981; Choi et al., 2005; Sosulski et al., 2011). The hypothalamus also receives direct olfactory information relevant to social cues (Yoon et al., 2005). Hypothalamic sub-populations have been identified within the ventrolateral ventromedial hypothalamus (VMH_{VL}) that regulate key social behaviors, including aggressive responses to conspecific threats and mating (Lin et al., 2011; Lee et al., 2014). Neurons within the medial pre-optic area (MPO) of the hypothalamus have also been isolated in mice and shown to regulate parental care or agression toward pups, depending on the animals' sexual experience (Wu et al., 2014). Numerous other sub-nuclei within the hypothalamus have been implicated in the regulation of social behaviors (Swanson, 2000), but virtually nothing is known about the cell types within these regions that contribute to these behaviors.

The ventral premammillary nucleus of the hypothalamus (PM_V) is highly connected with the brain's social networks (Canteras et al., 1992; Swanson, 2000; Cavalcante et al., 2014), and mapping studies using the immediate early gene *Fos* demonstrated that PM_V neurons are activated in multiple social contexts (Cavalcante et al., 2006; Borelli et al., 2009; Motta et al., 2009; Donato et al., 2010, 2013). Early analysis of the catecholamine-producing neurons of the brain identified a non-canonical dopamine neuron population within the PM_V (Hedreen, 1978; Meister and Elde, 1993; Zoli et al., 1993), but whether these neurons regulate social behavior and whether they use dopamine as a neurotransmitter is not known. Based on previous evidence that neurons in the PM_V express mRNA for the dopamine transporter (DAT; Meister and Elde, 1993), we used DAT as a genetic marker to isolate this population. We demonstrate that PM_V-DAT neurons are connected to brain regions implicated in conspecific social behavior and are principally glutamatergic, but do not release detectable dopamine. We show that PM_V-DAT neurons are most highly activated when male mice are intruders into the residence of a larger male. Chemogenetic inhibition of PM_V-DAT neurons specifically reduces exploratory social behavior in intruder males and impairs social novelty recognition. Activation of PM_V-DAT neurons increases exploratory social investigation of familiar mice in a manner dependent on synaptic glutamate release. Our genetic isolation and characterization of this unique neuronal population provides direct evidence for a hypothalamic cell type that regulates male intruder behavior and social novelty in specific contexts.

RESULTS

Genetic Isolation of PM_V-DAT Neurons

Given the previous identification of neurons in the PM_V that express DAT (Hedreen, 1978; Meister and Elde, 1993), we sought to determine the function of these neurons within social contexts. To confirm the presence of these neurons, we performed a differential search of the Allen Institute for Brain Science Mouse Brain Atlas in situ hybridization data (Lein et al., 2007). Three of