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Neuron

A Labeled-Line Neural Circuit for Pheromone-Mediated Sexual Behaviors in Mice

Highlights

- Sex pheromone information is sorted by the amygdala in a sexually dimorphic manner
- A novel pathway from the hypothalamus to midbrain modulates female sexual behavior
- Sex pheromone and predator cue signals are represented by mostly distinct neurons

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In Brief

Ishii et al. show a labeled-line neural circuitry for a sex pheromone, ESP1, that controls sexual receptivity of female mice. This circuit relays information in a sexually dimorphic manner, which is in line with the sex-dependent effects of ESP1.

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A Labeled-Line Neural Circuit for Pheromone-Mediated Sexual Behaviors in Mice

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SUMMARY

In mice, various instinctive behaviors can be triggered by olfactory input. Despite growing knowledge of the brain regions involved in such behaviors, the organization of the neural circuits that convert olfactory input into stereotyped behavioral output remains poorly understood. Here, we mapped the neural circuit responsible for enhancing sexual receptivity of female mice by a male pheromone, exocrine gland-secreting peptide 1 (ESP1). We revealed specific neural types and pathways by which ESP1 information is conveyed from the peripheral receptive organ to the motor-regulating midbrain via the amygdala-hypothalamus axis. In the medial amygdala, a specific type of projection neurons gated ESP1 signals to the ventromedial hypothalamus (VMH) in a sex-dependent manner. In the dorsal VMH, which has been associated with defensive behaviors, a selective neural subpopulation discriminately mediated ESP1 information from a predator cue. Together, our data illuminate a labeled-line organization for controlling pheromone-mediated sexual behavioral output in female mice.

INTRODUCTION

Animals detect diverse environmental signals to adjust their behaviors. In most cases, this process requires learning, and the animal gradually acquires a proper response to a sensory input by utilizing a plastic neural circuit. On the contrary, some sensory signals innately instruct a stereotyped behavioral response, even on first contact. These include various instinctive behaviors such as mating, aggression, and defensive behaviors, which can be robustly evoked by signals from a partner, competitor, or predator, respectively. However, little is known about the neural basis that allows the animal to select the appropriate behavioral output for a particular sensory input. The key to solving this question is identifying the exact neural circuit that conveys information about a sensory signal with a behavioral impact, from the periphery to the behavioral centers in the brain.

For many animals, including mice, the vomeronasal system is critical for detecting chemical signals that control instinctive behaviors (Touhara and Vosshall, 2009). In this system, the vomeronasal receptors expressed in vomeronasal sensory neurons (VSNs) detect chemical and protein cues. This information is first relayed to the accessory olfactory bulb (AOB) and then to the third-order neurons in the medial amygdala (MeA), posteromedial cortical amygdala (PMCo), and bed nucleus of the stria terminalis (BNST) (Dulac and Wagner, 2006). These neurons then send their axonal projections to broad hypothalamic areas where various instinctive behaviors are thought to be controlled. For instance, in mice, the dorsal part of ventromedial hypothalamus (VMHd) regulates defensive behaviors against predators (Canteras, 2002; Kunwar et al., 2015; Silva et al., 2013; Wang et al., 2015), whereas the ventrolateral VMH (VMHvl) is critical for aggression and sexual behaviors in male mice (Lee et al., 2014; Lin et al., 2011; Yang et al., 2013). The VMHvl is also crucial for female sexual behaviors, especially lordosis response, a typical male-receptive posture (Pfaff and Sakuma, 1979; Yang et al., 2013). Additionally, another hypothalamic area, the medial preoptic area (MPA), is related to pup-directed aggression, parenting, and mating behaviors in male mice and maternal behaviors in female mice (Lonstein and Gammie, 2002; Tsuneoka et al., 2015; Wu et al., 2014).

Despite the emerging understanding of the sensory signals and brain areas that control instinctive behaviors, an important unresolved question is the neural organization that converts sensory input into an appropriate behavioral output. The major obstacle to answering this question is the complexity of the signals; physiologically relevant signals often consist of multiple chemicals, which are received by many receptors and therefore may be processed by diverse brain regions. In contrast, in our previous studies, we established a simpler model. Exocrine gland-secreting peptide 1 (ESP1), which is purified from the lacrimal gland of male mice (Kimoto et al., 2005), is detected by a single member of vomeronasal receptor type 2 family, V2Rp5 (also known as Vmn2r116) and enhances female lordosis behavior (Haga et al., 2010). This makes ESP1 a powerful model