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CHEMOSENSORY SIGNALS AND THEIR RECEPTORS IN THE OLFACTORY NEURAL SYSTEM

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Abstract—Chemical communication is widely used among various organisms to obtain essential information from their environment required for life. Although a large variety of molecules have been shown to act as chemical cues, the molecular and neural basis underlying the behaviors elicited by these molecules has been revealed for only a limited number of molecules. Here, we review the current knowledge regarding the signaling molecules whose flow from receptor to specific behavior has been characterized. Discussing the molecules utilized by mice, insects, and the worm, we focus on how each organism has optimized its reception system to suit its living style. We also highlight how the production of these signaling molecules is regulated, an area in which considerable progress has been recently made.

Key words: olfactory, pheromone, odorant, receptor.

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INTRODUCTION

All organisms are required to make appropriate decisions depending on their situation in their living environment in order to maintain their life and conserve their species. They achieve these needs by obtaining various information about food, predators, poisons, potential mates and competitors from the external world, and respond to them appropriately. In most animals whose auditory and visual systems are not developed, such information is provided by chemicals that are sensed by the olfactory system. As there are a large variety of

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Abbreviations: ACTH, adrenocorticotropic hormone; BT, 2-*sec*-butyl dihydrothiazole; CAII, carbonic anhydrase II; CO_2, carbon dioxide; CS_2, carbon disulfide; cVA, 11-*cis*-vaccenyl acetate; DB, dehydro-*exo*-brevicomin; GC-D, guanylyl cyclase D; ELG, extraorbital lacrimal gland; ESP1, exocrine gland-secreting peptide 1; GPCR, G-protein-coupled receptor; GR, gustatory receptor; fMLF, N-formylmethionine-leucine-phenylalanine; FPR, formyl peptide receptor; HEK293, human embryonic kidney 293; IR, ionotropic receptor; MHC, major histocompatibility complex; MOE, main olfactory epithelium; MTMT, (methylthio)methanethiol; MUP, major urinary protein; OBP, odorant binding protein; OR, odorant receptor; OSN, olfactory sensory neuron; PBAN, pheromone biosynthesis activating peptide; PG, pheromone gland; STFP, socially transmitted food preference; SNMP, sensory neuron membrane protein; TAARs, trace amine-associated receptors; TGF-β, transforming growth factor beta; TMT, 2,5-dihydro-2, 4, 5-trimethylthiazole; V1R, vomeronasal receptor type 1; V2R, vomeronasal receptor type 2; VNO, vomeronasal organ; Z5-14:OH, (*Z*)-5-tetradecen-1-ol.

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chemicals and molecules present in the natural environment, how specific chemicals are discriminated and how an appropriate behavior is elicited in response to these chemicals are important issues. Following the discovery of the olfactory receptor superfamily (Buck and Axel, 1991), a variety of chemosensory receptors required for specific chemical cues have been identified, providing a molecular basis for detection of these cues. Recent studies combining genetics with imaging and behavioral analyses have significantly advanced our understanding of the mechanisms underlying the perception of chemical cues and the subsequent behavioral responses elicited.

In this review, we summarize the current knowledge of signaling molecules that act as chemical cues and that in turn elicit specific behaviors, focusing on those whose receptors have been identified, and describe the mechanisms underlying how the chemosensory systems convey the signals that regulate specific behaviors through these receptors at a neural level. To further our understanding of various chemosensory systems in which the individual species respond to a specific cue depending on their living environment, we outline the current knowledge in the mouse, various insect species and the worm. In Section ''Chemical cues'', we begin by describing the signaling molecules that act in various physiological contexts with an emphasis on the recent progress made in the study of the regulation of their production, especially in the mouse and worm. In Section ''Receptors'', we review the molecular mechanisms underlying the linkage from signaling molecules to behaviors, focusing on the current understanding of the signaling flow from receptor to final output behavior, an area in which considerable progress has been made in the mouse and insect species.

CHEMICAL CUES

In this section, we review the current understanding of the signaling molecules that provide chemical cues in various physiological contexts, focusing on their action in recipients. In addition, we also discuss how the production of these molecules is regulated. The numbers cited for the compounds correspond to those outlined in Table 1.

Mouse

Food choice. Animals are continuously faced with the problem of selecting appropriate foods. The major odorants emitted from spoiled foods include alkylamines, aliphatic acid and aliphatic aldehydes. These molecules are known to be derived from an amino acid or fatty acid and produced via bacterial decarboxylation or lipid oxidation. For example, lipid oxidation of meat and dairy products results in the production of hexanal (**1**) and n-hexanoic acid (**2**) (St Angelo, 1996; Takahashi et al., 2004). Decarboxylation of leucine produces isoamylamine (**3**), an odor produced by decaying meats (Dielenberg and McGregor, 2001; Takahashi et al., 2004). These compounds produce a rancid flavor that induces aversive behavior in rodents.

Rodents may also use other con-specifics as a poison tester. Individuals that have eaten a safe food emit two kinds of volatile cues known as food-derived odorants and carbon disulfide (CS_2: **4**) via their breath. These volatiles in turn provide information about food safeness to other individuals. When mice detect CS_2 and food-derived odorant(s), they exhibit an enhanced preference for the food (Munger et al., 2010). This specific olfactory response is termed the socially transmitted food preference (STFP).

Recently, it has been shown that feces of mice that have eaten a food also promote a preference for that food in mice exposed to the feces (Arakawa et al., 2013). Acquisition of this STFP is likely mediated by a pair of food-derived odorant(s) and a natriuretic peptide, uroguanylin (**5**). Uroguanylin is known as a peptide hormone produced in the intestine, where it regulates fluid and electrolyte balance, and may be excreted into feces (Forte, 2004).

Individual recognition and successful courtship via volatile chemosignals. Chemical communication via the recognition of both volatile and non-volatile cues contributes to successful mating in rodents. When a mouse encounters con-specifics of the opposite sex, volatile signals are first utilized to recognize that the mice are actually of the opposite sex. Males emit several volatiles in their urine in a testosterone-dependent manner that attracts the female mice. These testosterone-dependent chemosignals advertise the presence of a reproductively active and socially dominant male. The compounds emitted include 2-*sec*-butyl dihydrothiazole (BT, **6**), dehydro-*exo*-brevicomin (DB, **7**), α- and β-farnesene (**8**), (methylthio) methanethiol (MTMT, **9**) and (*Z*)-5-tetradecen-1-ol (*Z*5-14:OH, **10**) (Jemiolo et al., 1991; Lin et al., 2005; Tirindelli et al., 2009; Yoshikawa et al., 2013).

Novotny and co-workers identified BT, DB and two farnesene compounds based on the assumption that male-specific and socially dominant urinary constituents were responsible for the attractiveness to females (Novotny et al., 1984; Harvey et al., 1989). Firstly, these studies demonstrated that BT and DB were major urinary constituents that were reduced upon castration in male mice. They then showed that adding BT and DB to the urine obtained from the castrated mice resulted in the restoration of the castrated male mice urine ability to attract female mice (Jemiolo et al., 1991). They also isolated two farnesene compounds from the preputial gland, a male-specific exocrine gland, which excretes compounds into urine (Harvey et al., 1989; Novotny et al., 1990). It had been previously suggested that a number of the male urinary attractants were excreted from this gland (Bronson and Caroom, 1971). These farnesene compounds were subsequently shown to function as attractants for female mice (Jemiolo et al., 1991). Interestingly, BT, DB and farnesene compounds may also be capable of inducing puberty acceleration in pre-pubertal female mice, as is the opposite case with