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Review

Roles of sex and gonadal steroids in mammalian pheromonal communication

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ABSTRACT

A brain circuit (the accessory olfactory system) that originates in the vomeronasal organ (VNO) and includes the accessory olfactory bulb (AOB) plus additional forebrain regions mediates many of the effects of pheromones, typically comprised of a variety of non-volatile and volatile compounds, on aspects of social behavior. A second, parallel circuit (the main olfactory system) that originates in the main olfactory epithelium (MOE) and includes the main olfactory bulb (MOB) has also been shown to detect volatile pheromones from conspecifics. Studies are reviewed that point to specific roles of several different steroids and their water-soluble metabolites as putative pheromones. Other studies are reviewed that establish an adult, 'activational' role of circulating sex hormones along with sex differences in the detection and/or processing of non-steroidal pheromones by these two olfactory circuits. Persisting questions about the role of sex steroids in pheromonal processing are posed for future investigation.

1. Introduction

Pheromones are compounds of varying chemical structure that are excreted in bodily fluids (e.g., urine, feces, tears, or sweat) from individuals of a species which are detected by the olfactory nervous system of a conspecific so as to influence aspects of its neuroendocrine and/or behavioral function (Karlson and Luscher, 1959; Meredith, 2001). Some authors (McClintock, 2002) have subdivided mammalian pheromones into 4 groups according to functions that include 'release' of some stereotyped behavior, 'priming' of some neuroendocrine response, 'signaling' a social status, or 'modulating' some ongoing behavior or psychological process. We will make no explicit distinction among any of these types of function in our use of the term 'pheromone'. We also note that some authors (Petrulis, 2013) prefer to avoid use of the term 'pheromone' to refer to the general class of chemical signaling molecules that influence conspecifics' behavior/neuroendocrine functions because relatively few compounds produced in mammals (as opposed to insects) meet all of the rigorous criteria originally used to define a 'pheromone'. Chief among these is the notion that an authentic pheromone is a single compound that elicits a response that is 'hard wired' and unaffected by prior experience. We prefer to retain the use of the word 'pheromone' as a convenient term that refers to any mammalian chemosignal that influences a conspecifics' behavior. Note that we also use the term, 'pheromone' to refer to yet-to-be specified combinations of different 'signature mixtures' of compounds that influence conspecifics' behavior (Wyatt, 2010). We think it is pointless to argue over the strict 'pheromonal' status of each compound that has been/will be identified as exerting an influence on mammalian neuroendocrine or behavioral function.

In rodents and other terrestrial vertebrates the vomeronasal organ (VNO) was previously considered to be the primary, if not the sole, 'pheromone detection system' (Chamero et al., 2012; Tirindelli et al., 2009). VNO receptor neurons located in the roof of the mouth extend axons to glomeruli located in the accessory olfactory bulb (AOB) where they synapse onto the dendrites of AOB mitral cells which extend axons to the medial amygdala (MeA; part of the 'vomeronasal amygdala') (Kevetter and Winans, 1981a). Neurons in the MeA project, in turn, to hypothalamic targets including the bed nucleus of the stria terminalis (BNST), the medial preoptic area (mPOA), and the ventromedial hypothalamus (VMH). Individual VNO sensory neurons express a single receptor protein (encoded by one of 2 separate gene families of ~250 genes) that presumably detect specific pheromones, although specific pheromonal ligands for specific receptor proteins have yet to be identified (Dulac and Axel, 1995). Many investigators believe that VNO sensory neurons respond mainly to non-volatile pheromones (which may be peptides or even larger proteins). In some instances, large proteins (e.g., lipocalins) may bind and deliver smaller pheromonal molecules (e.g., 2-secbutyl-4,5-dihydrothiazole) to the

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VNO neuroepithelium (Novotny, 2003). The relatively heavy, non-volatile compounds (as well as sulfated steroids and perhaps even unconjugated sex hormones; see below) are dissolved in mucus and gain access to the VNO neuroepithelium via a vascular pumping mechanism controlled by the sympathetic innervation of blood vessels in the VNO (Meredith and O'Connell, 1979). The main olfactory epithelium (MOE) is clearly the detection system for all general (non-pheromonal) odorants present in the environment (Xu et al., 2000). Olfactory receptor neurons in the MOE express a single receptor gene from a large family of ~900 different genes (Buck and Axel, 1991). MOE olfactory neurons expressing the same receptor gene extend axons to 1–2 specific glomeruli located on the surface of the main olfactory bulb (MOB) where they synapse with dendrites of mitral cells that project extensively to diffuse target sites in the olfactory tubercle and in the anterior as well as the posterior piriform cortex (Sosulski et al., 2011). An early study (Kevetter and Winans, 1981b) demonstrated that a subset of MOB mitral cells also project to cortical amygdaloid nuclei ('olfactory amygdala'). However, more recent studies (Kang et al., 2009; Pro-Sistiaga et al., 2007; Thompson et al., 2012) showed that there is a subpopulation of MOB mitral cells that also project directly to the MeA ('vomeronasal amygdala'). There is considerable evidence from numerous studies conducted over the past 20 years that several volatile chemicals (including the androgenic steroid, androstenone) function as pheromones that influence aspects of behavior and neuroendocrine function after their detection by a specialized population of receptor neurons in the MOE. A summary of the neuroanatomy of the accessory and main olfactory systems in the mouse, including projection targets to the forebrain, is provided in Fig. 1. Note that there exist at least two, additional, specialized components of the mammalian olfactory nervous system (i.e., the septal organ of Masera and the Grueneberg ganglion) whose possible role in pheromonal processing has yet to be determined (Brennan and Zufall, 2006),

In this review we will first consider evidence pointing to specific steroid molecules that function as pheromones in their own right. Next we will review literature showing that there are both sex differences in pheromone detection and processing as well as adult, activational effects of circulating sex hormones on the neuronal processing of pheromones. In many instances, perinatal sex

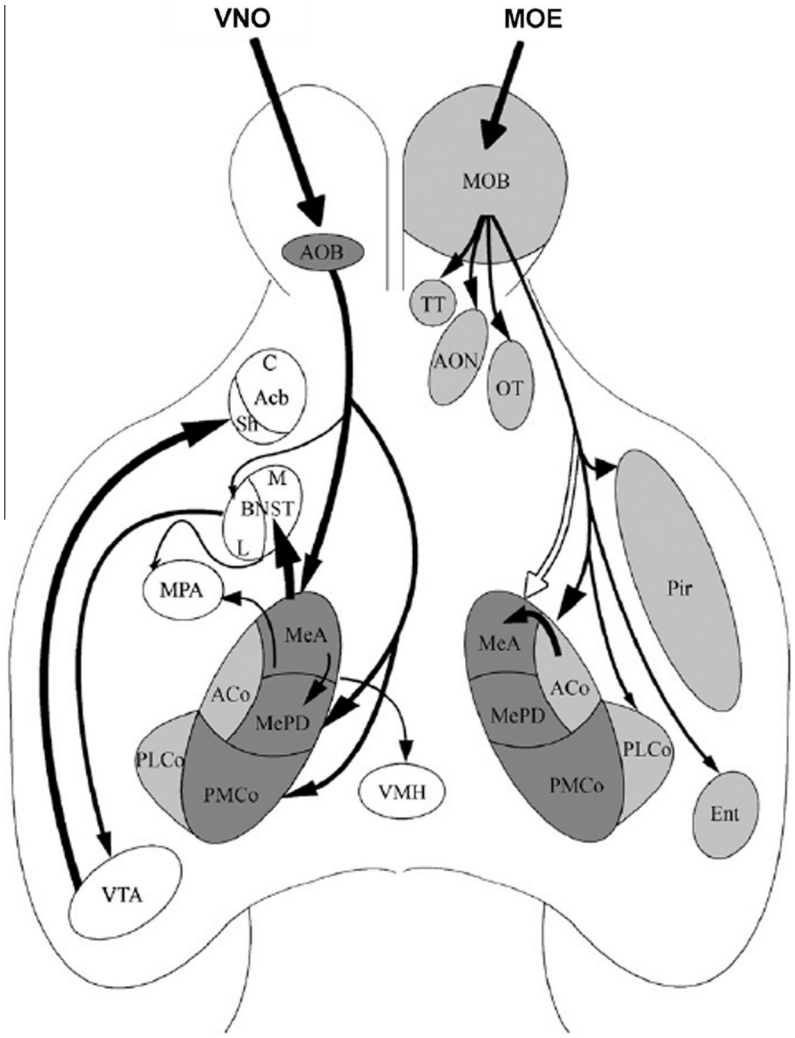

Fig. 1. Cartoon representation of the accessory (left) and main (right) olfactory systems in the mouse. Light shading shows areas that receive direct input from the main olfactory bulb; dark shading shows areas that receive direct input from the accessory olfactory bulb. In the amygdala, light shading indicates the olfactory amygdala and dark shading indicates the vomeronasal amygdala. The open arrow in the main olfactory pathway represents a recently identified direct connection to the medial amygdala from the main olfactory bulb. Abbreviations: VNO, vomeronasal organ; AOB, accessory olfactory bulb; MeA, anterior medial amygdala; MePD, posterodorsal medial amygdala; PMCo, posteromedial cortical amygdala; ACo, anterior cortical amygdala; PLCo posterolateral cortical amygdala; BNST, bed nucleus of the stria terminalis—lateral (L) and medial (M) subdivisions; mPOA, medial preoptic area; VMH, ventromedial hypothalamic nucleus; VTA, ventral tegmental area; Acb, nucleus accumbens—core (C) and shell (S); MOE, main olfactory epithelium; MOB, main olfactory bulb; AON, anterior olfactory nucleus; OT, nucleus of the olfactory tract, Pir, piriform cortex; Ent, entorhinal cortex. Reproduced with permission (Baum, 2009).