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Review

Chemosignals, hormones and mammalian reproduction

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ABSTRACT

Many mammalian species use chemosignals to coordinate reproduction by altering the physiology and behavior of both sexes. Chemosignals prime reproductive physiology so that individuals become sexually mature and active at times when mating is most probable and suppress it when it is not. Once in reproductive condition, odors produced and deposited by both males and females are used to find and select individuals for mating. The production, dissemination and appropriate responses to these cues are modulated heavily by organizational and activational effects of gonadal sex steroids and thereby intrinsically link chemical communication to the broader reproductive context. Many compounds have been identified as "pheromones" but very few have met the expectations of that term: a unitary, species-typical substance that is both necessary and sufficient for an experience-independent behavioral or physiological response. In contrast, most responses to chemosignals are dependent or heavily modulated by experience, either in adulthood or during development. Mechanistically, chemosignals are perceived by both main and accessory (vomeronasal) olfactory systems with the importance of each system tied strongly to the nature of the stimulus rather than to the response. In the central nervous system, the vast majority of responses to chemosignals are mediated by cortical and medial amygdala connections with hypothalamic and other forebrain structures. Despite the importance of chemosignals in mammals, many details of chemical communication differ even among closely related species and defy clear categorization. Although generating much research and public interest, strong evidence for the existence of a robust chemical communication among humans is lacking.

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Introduction

Chemical signals or chemosignals, often termed "pheromones", are an important and often critical means of communication for most mammalian species. Most mammals make, distribute and respond to chemosignals in many contexts, including those surrounding reproduction, parent–offspring interactions and territorial/dominance relationships (Brown and Macdonald, 1985). This review focuses on the direct links between social odors and reproduction, that is, the effects of chemosignals on reproductive physiology and behavior in male and female mammals. The voluminous literature on chemosignals and reproduction precludes discussion of chemosignal-influenced behaviors or physiological processes that are further removed from copulation. So, while territorial acquisition and defense (Gosling et al., 2001; Hurst and Beynon, 2004) and maternal behavior (Kendrick et al., 1997) are critical for reproductive success and involve chemosignals, research in these areas will not be covered. Also, a comprehensive review that covers each mammalian order is not possible here and so this review will focus on species for which there is the most information. Unfortunately, this will generally limit discussion to farm and laboratory species; the interested reader is directed to several sources that provide a more comprehensive treatment of odor-communication in mammals (Brown and Macdonald (1985) and relevant sections in Hurst et al. (2008); Mason et al. (2005); and Wyatt (2003)).

Chemosignals and pheromones

Before asking what role chemosignals play in mammalian reproduction, one must explain why the term "pheromone" is not used throughout this review. "Pheromone" was used initially to describe the conspecific chemosignals that elicit behavioral and physiological responses of insects and was defined as "substances which are secreted to the outside by an individual and received by a second individual of the same species, in which they release a specific reaction, for example, a definite behavior or a developmental process" (Karlson and Luscher, 1959; Wyatt, 2009). This idea, roughly analogous to an external hormone, was a logical extension of the classic ethological idea of a species-specific "sign stimulus" that released a biologically important, unlearned (or "innate") and stereotyped behaviors described as "fixed action patterns" (Tinbergen, 1951). The early observations that one or, at most, a handful of chemical compounds were necessary and sufficient for eliciting various behaviors in insects suggested to researchers that similar effects would be observed in mammals (Wyatt, 2003), and that these pheromones could be divided into "releaser pheromones" that affected behavior, and "primer pheromones" that affected developmental/physiological processes.

The problems with extending the term "pheromone" to mammalian biology were recognized early by researchers who noted that mammalian reproductive behavior and physiology are not rigid but are, instead, flexible, context-dependent and modifiable by experience (Doty, 1986, 2010; McClintock, 2002), and whose characteristics are quite different from the typical conception of "pheromone". Despite some successes in isolating specific and behaviorally active compounds (primarily in rodents), these individual substances have rarely been as effective as the full odor and, in several cases, are not species-specific (Gelez and Fabre-Nys, 2004; Ingersoll and Launay, 1986; Rasmussen et al., 1996; Zhang et al., 2008b). Indeed, many identified compounds in social odors have multiple behavioral and physiological functions (Novotny, 2003), suggesting that the releaser vs. primer pheromone distinction is not meaningful at the stimulus level. Moreover, fine distinctions made by animals on the basis of social odors (such as individuality, familiarity, kin) are unlikely to be mediated by the presence or absence of one or a very small number of unique compounds and may, instead, require processing of an odor mosaic or blend (Johnston, 2008). Consequently, in this review, the use of the term "pheromone" will be mostly avoided and the more neutral terms "chemosignal" or "scent" or "odor" will be used in its place.

Chemosensory systems

The basic anatomy and physiology of chemosignal-processing circuits are well defined and consist primarily of the main olfactory system (MOS) and the accessory olfactory system (AOS) and is reviewed in detail elsewhere (Chamero et al., 2012; Halpern and Martinez-Marcos, 2003; Zufall and Leinders-Zufall, 2007). These two systems are largely separate, having both separate sensory neuron populations in the nasal cavity (MOS: main olfactory epithelium (MOE); AOS: vomeronasal organ (VNO)), segregated representations in the nervous system (Fig. 1) and responsiveness to different types of chemosignals: primarily volatile chemicals for the MOS and primarily non-volatiles molecules for the AOS. Nevertheless, complex interactions can occur between these two systems as evidenced by increased accessory olfactory bulb (AOB) activity to volatile chemosignals, an effect dependent on the integrity of the MOS and not on the VNO, (Martel and Baum, 2007) and is likely due to the main olfactory bulb (MOB)-recipient zone in MA projecting back to the AOB (Martel and Baum, 2009b).

The separation of the central AOS/MOS components is not complete as the anterior medial amygdala (MA) receives both direct AOB and MOB information (Fan and Luo, 2009; Kang et al., 2009; Mohedano-Moriano et al., 2012). Interconnections between the two systems also occur within the cortical and MA (Maras and Petrulis, 2010a; Martinez-Marcos, 2009) as well as within downstream structures (Newman, 1999). The MA and connected areas also contain many neurons that are responsive to gonadal steroids (Wood, 1997). Detailed connectional analysis of the MA, bed nucleus of the stria terminalis (posterior) (BNST), medial preoptic area (MPOA) and ventromedial hypothalamus (VMH) has revealed that within each structure, the region that receives the majority of chemosensory information is separate from the area that contains the greatest concentration of androgen (AR) and estrogen (ER) receptors, thus suggesting that steroid and chemosensory information are represented by separate and parallel systems (Newman, 1999; Wood, 1997). For example, the MA can be divided into the chemoreceptive zone that includes the anterior medial amygdala (MAa) and the hormone-sensitive posterodorsal medial amygdala (MApd). Indeed, neural activity in responses to odors in MAa and MApd appear to be different, with greater selectivity for social odors evident in MApd than in MAa (Meredith and Westberry, 2004; Samuelsen and Meredith, 2009) and that the chemosensory-induced immediate-early gene (IEG) response in MApd, BNST and MPOA requires an intact MAa, but not MApd (Maras and Petrulis, 2010b). Likewise, the BNST can be divided into a chemosensory region, the posterior