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The Combined Role of the Main Olfactory and Vomeronasal Systems in Social Communication in Mammals

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Abstract

The main olfactory and the vomeronasal systems are the two systems by which most vertebrates detect chemosensory cues that mediate social behavior. Much research has focused on how one system or the other is critical for particular behaviors. This has led to a vision of two distinct and complexly autonomous olfactory systems. A closer look at research over the past 30 years reveals a different picture however. These two seemingly distinct systems are much more integrated than previously thought. One novel set of chemosensory cues in particular (MHC Class I peptide ligands) can show us how both systems are capable of detecting the same chemosensory cues, through different mechanisms yet provide the same general information (genetic individuality). Future research will need to now focus on how two seemingly distinct chemosensory systems together detect pheromones and mediate social behaviors. Do these systems work independently, synergistically or competitively in communicating between individuals of the same species?

Introduction

In mice chemosensory cues influence neuroendocrine and behavioral processes important for social behavior. Neuroendocrine responses resulting in puberty acceleration (Vandenbergh, 1973), pregnancy block (Bruce, 1960) and LH secretion (Bronson and Desjardins, 1974) are all stimulated by urinary compounds from opposite sex conspecifics. Social behaviors such as social aggression, sexual attraction and sexual partner selection are also coupled to chemosensory cues from opposite sex conspecifics. (Previously reviewed in Keverne, 1999; Johnston, 1998; Doty, 1986; Vandenbergh, 1983). Ultimately, reproductive success in mice is dependent on the detection and processing of these chemosensory cues. Despite decades of research investigating olfaction and social behavior there are numerous questions unresolved about how chemosensory cues are detected and ultimately influence social behavior.

In 1942 Frank Beach postulated that no one sensory cue is obligatory for sexual partner selection. With very few exceptions, possibly the ferret for instance (Kelliher and Baum, 2002), this is likely true. More to the point one might argue that most social behaviors in vertebrates are much too complicated to be solely controlled by a single mechanism. Instead social behavior requires the integration of multiple sensory cues within the hormonally mediated neural networks of the brain. We can also make the same arguments for behavioral and physiological responses to chemosensory cues. As we see that the chemical senses are much more complicated than previously thought we also find that the “how” and the “where”

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of sensory detection and processing is becoming equally as complicated. We are now beginning to observe that these responses are mediated by multiple chemosensory systems that all work towards influencing social behaviors.

In most mammals chemical cues entering the nasal cavity are detected by either sensory receptors in the main olfactory epithelium, the vomeronasal epithelium or both. Pitting the olfactory system against the vomeronasal system with respect to a particular behavior or for the detection of a set of cues (e.g. pheromones) had become commonplace for researchers and laymen alike. Yet where we once thought a particular olfactory subsystem was obligatory for the detection of a particular cue and or responsible for a specific behavior, we are now beginning to realize these subsystems are much more integrated. Chemosensory systems such as the olfactory epithelium and vomeronasal system can in some instances detect the same chemical cues, many of which have been labeled as pheromones. Piecing together how these systems work together to mediate social behavior has now become increasingly more difficult.

What makes a Pheromone a Pheromone?: The Concept of 'Pheromone'

Whether particular chemical cues should be considered to be pheromones has led to some highly contentious arguments amongst some biologist. The term pheromone was first coined by Karson and Lascher and 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 behavioral or developmental process” (Karlson and Lüscher, 1959). In relation to mammals the definition has changed somewhat out of either necessity or sometimes convenience. In order to define a chemical cue as a pheromone some investigators have often applied artificial criteria such as whether it is detected by the vomeronasal organ, or is a nonvolatile or that it is unconsciously detected. Sometimes justification for such criteria is given but often it is just a matter of historical precedent. With our current knowledge of chemical processing in the main olfactory and vomeronasal systems, it is becoming increasingly obvious that the term pheromone as defined for insects cannot be appropriately applied to vertebrates. Some researchers have argued that the term as applied to mammals isn't even scientifically useful (Beauchamp et al., 1976), while others suggest the definition needs to be refined (Meredith, 2001). The term was intended to define special communication between conspecific insects, in which pheromones tend to directly influence an innate behavioral response such as for a sex, alarm or trail pheromone. With few possible exceptions, vertebrates do not display instinctive or reflexive behavior to a single sensory cue. Furthermore in the instances where individual cues have been identified many cues appear to have the same function (Novotny, 2003). Historically pheromonal effects in mammals were identified as responses to urine or other excretions but lacked an identified molecule or set of molecules that could account for these effects. Pheromonal effects were instead attributed to “urinary pheromones” or “vaginal and gland secretions” without any real knowledge of what these pheromones were. For some species, particularly mice, there have been significant advances in identifying molecules that might be involved in pheromonal effects (Novotny, 2003; Luo and Katz, 2004), although there is still some controversy surrounding how these molecules work. It is not known whether these molecules can work alone, as blends or only in context of other cues, thus leaving open the question of whether they can really be described as pheromones.

In insects pheromonal responses had been segregated into two categories, primer and releaser. While these divisions have also been applied to vertebrates additional categories are also often described. McClintock (2002) describes pheromones as falling into four different types of; primer, releaser, signaler and modulator. Primer pheromones have been described as chemical cues that initiate physiological responses which can be long lasting. For instance, pheromones from male urine induce precocious puberty (Vandenbergh, 1969) and synchronize the estrous

cycles of group-housed female mice (Whitten, 1959). These effects are mediated by the hypothalamic-pituitary-gonadal (HPG) axis, although, the exact neuroendocrine mechanisms have yet to be elucidated. Pheromones from female mouse urine induce luteinizing hormone (LH) surges in male mice, thereby promoting testosterone secretion (Johnston and Bronson, 1982; Wysocki et al., 1983). Releaser pheromones activate an immediate response, which is generally behavioral. The two most common examples are the nipple suckling pheromone in rabbits 2-methylbut-2-enal (Schall et al., 2003) and androstenone, which elicits an immobile mating posture in sows (Pearce and Hughes, 1987; Dorries et al., 1997). Signaler pheromones do not necessarily initiate behaviors but instead provide socially relevant information about an individual such as reproductive status, social hierarchy, or even individual identity (Johnston, 1998, 2000). Modulator pheromones have been proposed as cues that modulate affect in humans (Jacob and McIntock, 2000). These would be social cues that influence mood without directly causing a behavior. Whether modulator pheromones can be attributed in other mammals or whether this classification will be more widely recognized still remains to be seen (Wysocki and Preti, 2006). We see that just as the definition of pheromone is (and possibly because it is) in flux, developing a taxonomy for different pheromonal responses in vertebrates is not necessarily possible at this point. A number of responses that were first considered in the releaser category, such as those that elicit attraction between opposite-sex conspecifics (Nyby et al., 1981; Scott and Pfaff, 1970) cross categories having properties of both releaser and signaling pheromones. Even chemically identified pheromones such as α and β farnesenes elicit both primer effects on females, inducing estrous (Ma et al. 1999) and releaser/signaling effects responsible for attraction of females and mediating aggressive displays in males (Jemiolo et al., 1991). The differences may be a matter of context in which they are detected (i.e. when and where the signal is received), however until we understand the neural and physiological mechanisms that these pheromones interact with we are unlikely to fully understand how these cues are influencing social behaviors.

A difficulty with using a broad definition of a pheromone is that one could make an argument for any intraspecific chemical cue as being a pheromone. By contrast, if using a narrow definition of pheromone it is unlikely that any mammalian chemical cues would fit the definition. I would argue that the precise definition of a pheromone is unimportant. Our real scientific interests should be in understanding how chemical cues are detected and processed by the complicated arrangement of olfactory organs and central nervous system circuits. Until we have a better understanding of how these systems work we are not going to fully understand the nature of the cues themselves. I have begun to think of pheromones less as entities and more as concepts. A concept can be assessed based on its usefulness rather than its absolute accuracy (Brain, 1989, in describing the concept of aggression). I see the concept of a pheromone as being a chemical cue that is excreted by an individual while the sole or primary function of this excretion is to communicate with a member of the same species. I strongly feel that the use of the term pheromone as a concept in the literature is justified, provided that it is more informative than distracting.

Pheromones and the dual olfactory hypothesis

There are two main organs of chemical communication in the nasal cavity of most terrestrial vertebrates, the main olfactory epithelium (MOE) and the vomeronasal organ (VNO). Together these two systems are likely to detect all chemosensory cues that pass through the nose. Of course depending on the species there may be as many as six distinct organs or structures in the nasal cavity that can detect chemosensory cues. The gruneburg ganglion complex and nervous terminalis (Breer et al 2006) are two such structures but it is unclear if either serves a primary sensory function. The septal organ (Ma et al., 2003) and trigeminal system (Bryant and Silver, 2000) are known to be primary sensory structures however they are likely to detect some of the same cues as the MOE yet process them differently. Both the MOE and VNO are

well described in structure and physiology (Touhara, 2002; Zufall et al., 2002), yet many of the specifics involving the detection and processing/perception of cues, such as pheromones, still remain unclear. This has allowed for maintained controversy, debate and ultimately research into how pheromones mediate behavior.

There has been a long history of research studying mammalian pheromones and the mammalian VNO, however, the most important research in terms of bringing these two topics together was that of Powers and Winans (1973). Powers and Winans (1973) performed one of the first sets of experiments to show that the vomeronasal organ was intimately involved in social communication. Their study demonstrated that sexually naïve male hamsters that had their vomeronasal organs removed showed significant deficits in mating. Since that seminal study (and further discovery by Meredith et al., 1986) the critical role of the vomeronasal organ in the detection for pheromones had been proposed. Anatomical mapping of the vomeronasal system furthered the notion that the vomeronasal system was a detector of pheromones. Numerous tract tracing studies showed direct connections from the vomeronasal system to limbic structures including the bed nucleus of the stria terminalis and the anterior and posterior medial amygdala each connecting further to hypothalamic nuclei but bypassing olfactory cortex. By contrast the main olfactory system was anatomically separate connecting to a different area of the amygdala and communicating with olfactory (piriform) cortex, orbital frontal cortex and some sparse thalamic connections (Scalia and Winans, 1975; Keverter and Winans, 1981; Shipley et al., 1996 and references within). This anatomical scheme may have propagated the idea that pheromones were unconsciously detected and activated instinctual behaviors or autonomic physiological functions. The main olfactory system connected to brain areas involved in learning and conscious thought while the vomeronasal system bypassed these areas and instead connected to areas involved in reproduction and autonomic function. It has been convenient to believe that there are two separate and distinct olfactory systems, the main olfactory system to act as a molecular analyzer to detect olfactory cues and the accessory olfactory system to detect pheromones (Reviewed in Halpern 1987, updated in Halpern and Martinez-Marcos, 2003; Wysocki, 1979).

For instance it had been thought that the vomeronasal organ might be “the” chemosensory organ for sex discrimination. Clearly, in both male hamsters (Johnston and Rasmussen, 1984) and mice (Wysocki et al., 1982) it has been suggested that the accessory olfactory system may mediate discrimination between male and female cues yet had never be shown to be obligatory. More recently Stowers et al., (2002) and Leyopold et al., (2002) reported that mice lacking a functional TRPc2 protein, have absent or severely impaired vomeronasal responses. Behaviorally these animals show a complete lack of social aggression measured by a resident intruder paradigm. Examples of chemosensory communication influencing social aggression can be found in most every species ever studied. Therefore while there is no question that olfaction plays an important part in social aggression what varies across species is the importance placed on olfactory cues. In rodents social aggression is highly dependent on chemosensory communication and in particular much emphasis had been placed on the role of the vomeronasal organ. In male mice the removal of the vomeronasal organ reduces inter-male aggression (Maruniak et al., 1986). Likewise, maternal aggression is eliminated in lactating female mice after vomeronasal removal (Bean and Wysocki, 1989). Male TRPc2-KO mice completely fail to display aggressive behaviors, such as fighting and biting, in resident intruder paradigms. Female TRPc2-KO mice likewise failed to display maternal aggression towards invading male mice (Leyopold et al., 2002). Instead of fighting male TRPc2-KO mice would commonly mount male intruders and initiate what would appear to be a sexual encounter. Stowers et al., (2002) concluded from this experiment that male TRPc2-KO mice were incapable of discriminating between male and female. Their model suggests that the one role of the VNO is to discriminate between male and female and that this gender discrimination is ultimately responsible for mediating displays of aggression. This makes sense that social

aggression occurs through the perception and identification of the stimuli, however, it isn't clear that removal of vomeronasal input necessarily interferes with perception (i.e. gender discrimination) directly, but may just prevent detection of cues that facilitate social aggression. In fact mice with genetic lesions of the main olfactory epithelium (CNGA2-KO mice) show similar defects in aggression that TRPC2-KOs do (Mandiyan et al., 2005). To the contrary both mice (Pankevich et al., 2004) and ferrets (Woodly et al., 2004) have been found to be perfectly capable of discriminating between males and females after surgical removal of the vomeronasal organ. It is interesting to speculate that some of the behavioral defects of TRPC2-KO maybe a result of motivational changes associated with defects in experience normally provided by the VNO during an animal's development. It is important to also note that aggression defects have been observed in a wide array of different transgenic knock-out models (McCarthy and Auger 2002). In a strain of mouse with a deletion of the vasopressin 1b receptor (VR1b), we have also observed a marked decrease in aggressive behavior as measured by a resident intruder paradigm (Wersinger et al, 2002; Wersinger et al., 2004). The phenotype exhibited marked similarities to the TRPC2 knock-out model. With these mice we were able to conclude, using an operant conditioning paradigm, that the social defects were based on changes in motivation as opposed to an inability to discriminate between male and female mice (Wersinger et al., 2004).

In chemosensory deficient mice defects in social aggression are just as likely to be due to the inability to detect chemosensory cues that directly facilitate aggression regardless of gender recognition. Two odors dehydro-exo-brevicomin and 2-(sec-butyl)-dihydrothiazole, which are found in high quantities in male urine, are known to facilitate aggression in male mice (Novotny et al., 1985). Achiraman and Archunan (2002) identified five different volatile odors in urine of male Swiss mice that are not present in female urine. Three of these compounds (3-amino-s-triazole, 4-ethyl phenol, 2,7-dimethyl octane) induce aggression in male mice much like dehydro-exo-brevicomin. While some of these compounds are known to be detected by the vomeronasal organ (Leinders-Zufall et al. 2000) whether aggression facilitating actions work solely through this system is still unknown.

Years of research, on a variety of different vertebrate species, have in fact shown us that the simple dichotomy of main versus the accessory olfactory systems is not tenable (Restrepo et al. 2004; Shepherd 2006; Spehr et al. 2006b). Numerous studies, in pigs (Dorries et al., 1997), ewes (Cohen-Tannoudji et al., 1989), ferrets (Kelliher et al., 2001), rabbits (Schall et al., 2003) and mice (Lin et al., 2005) have shown that the main olfactory system detects chemical cues that could be considered pheromones. Others have shown the main olfactory system mediates signaling in the amygdala and hypothalamus normally associated with the processing of pheromonal cues in sexually experienced hamsters (Fernandez-Fewell and Meredith, 1998) ferrets (Kelliher et al., 1998; Kelliher et al., 2001) and rats (Swann et al., 2001). Furthermore, sex steroids mediate these signals both peripherally and centrally (Kelliher et al., 1998) which is also thought to be a distinguishing feature of the vomeronasal pathway (Wood, 1998).

The vomeronasal system can also detect a wider variety of chemical cues than just pheromones. Snakes have long been know to use their vomeronasal system to detect prey odors (Halpern and Kubie 1980; Wang et al., 1993; Alving and Kardong, 2004) and VSN from mice have been found to respond to a wide variety of odors some of which could be considered food odors (Sam et al., 2001). Hamsters appear to detect and process odors from different species such as mice, rats and cats (Meredith and Westberry, 2004) and possibly some food odors through the vomeronasal system. Mice with impaired main olfactory function because they lack the gene for adenylyl cyclase 3, may consciously detect odors and form memories as measured by habituation/dishabituation experiments (Trinh and Storm 2003). Trinh and Storm (2003) never showed that these mice couldn't consciously detect odors in the absence of a VNO leaving

open the possibility that another olfactory subsystem such as the GC–D system may be utilized in this case (Lin et al. 2004). The boundaries are even more blurred after an amazing discovery that subsets of olfactory receptors (44 OR genes in all) are expressed in the vomeronasal organ (Levai et al., 2006). Not only are ORs expressed in the VSNs that project to the accessory olfactory bulb but they are simultaneously expressed in OSNs located in the main olfactory epithelium and from there project to the main olfactory bulb. This study suggests that not only can the vomeronasal system detect some of the same odors as the main olfactory system but also that they could use the same receptor mechanism. Together with the evidence that vomeronasal receptors might also be present in the main olfactory epithelium (Rodriguez et al. 2000; Wakabayashi et al., 2002) we may find that the processing and interpretation of these signals centrally is more important than the location of the receptors peripherally.

Unfortunately there is still a propensity for academics and laymen alike to attribute all pheromone activity to the vomeronasal system although we know this distinction to be false. Instead the new question that needs to be proposed and answered is how these seemingly distinct systems together detect pheromones and mediate social behaviors. Do these systems work independently, synergistically or competitively in communicating between individuals of the same species? Our current knowledge of the field, together with advances in molecular technology will allow us to actively pursue these questions.

Pheromones and the HPG Axis

Reproduction and reproductive behavior in vertebrates is ultimately under the control of the neuropeptide GnRH. GnRH is responsible for gonadotropin release and thus gonadal function and steroidogenesis. Thus it is not surprising that many pheromonal effects, which contribute to reproductive success, have been linked to GnRH regulation. Pheromone induced increases in testosterone in male mice and hamsters are associated with increases in LH release (Maruniak and Bronson, 1976;) an effect that appears primarily (or absolutely in the case of hamsters) mediated by vomeronasal organ (Wysocki et al., 1983; Coquelin et al., 1984; Pfeiffer and Johnston, 1994). In addition to mediating gonadal function and steroidogenesis GnRH has been known to directly influence sexual behavior in rodents. Infusing GnRH in to the third ventricle or POA enhances sexual behavior in male and female rodents (Hull et al., 2002; Pfaff et al., 1994) especially if their reproductive capability had been previously compromised (Dorsa and Smith 1980; Gibson et al. 1987). Moreover, direct infusions of GnRH into the ventricular system can rescue sexual behavior in both female and male hamsters and female mice that is disrupted by lesions of the nasopalatine duct (Mackay-Sim and Rose, 1986) or vomeronasal organ (Westberry and Meredith, 2003; Keller et al., 2006). Direct stimulation of the GnRH system from cues detected by the main olfactory system has been shown in other mammals. The “male effect” observed in a number of ungulates and well studied in ewes has linked pheromone present in male hair to changes in GnRH secretion in females. This effect in ewes is primarily mediated by the main olfactory system (reviewed in Gelez and Fabre-Nys, 2004).

Interestingly two recent studies have shown the main olfactory system is more anatomically connected to the GnRH system than previously thought. Genetically inserted transneuronal tracers show both direct and indirect reciprocal connections to GnRH neurons in mice (Boehm et al., 2005; Yoon et al., 2005). Both Boehm et al. (2005) and Yoon et al. (2005) also used markers of neuronal activation to investigate whether pheromones could stimulate GnRH neurons or neurons pre or post-synaptically connected in the pathway. Boehm et al. (2005) found that the male pheromone α -farnesene or pheromones associated with soiled female bedding induced c-fos expression in neurons both pre and post-synaptically connected to GnRH neurons. More surprisingly many of the c-fos positive neurons pre-synaptically connected to GnRH neurons were found in olfactory areas associated with main olfactory function, including

the anterior cortical amygdala and the piriform cortex. The combination of inputs to GnRH neurons from main olfactory cortex and amygdala with that of vomeronasal areas of the amygdala is highly suggestive of a complex integration of these two olfactory systems. What is not known is exactly how they interact, whether it is cooperatively, antagonistically, or if in fact systems still work independently of each other. Yoon et al. (2006) went a step further and suggested that chemosensory inputs to GnRH neurons are limited to main olfactory origins. Psuedorabies injections in to CRE:GnRH recombinant mice visualized retrograde connections to GnRH neurons. In these mice labeled pathways were limited to the main olfactory pathway. Furthermore, MapK, which can be used as a marker of neuronal activation, showed that female odors directly activated GnRH neurons in male mice. Genetically modified mice with defects in the OSNs (CNGA2-KO) eliminated this effect whereas transgenic mice with defects in VSNs (TRPC2-KO) still had a significant increase in GnRH-MAPK double labeling. Therefore, not surprisingly odors working through the main olfactory system may influence GnRH regulation in the hypothalamus. Yet based on numerous studies it is unlikely that the vomeronasal system is not involved in certain aspects of chemosensory mediated effects on GnRH (Wirsig-Wiechmann and Wiechmann, 2001; Wysocki et al., 1983; Coquelin et al., 1984; Meredith and Fewell, 2001; Pfeiffer and Johnston, 1994; Merdith, 1998).

In ferrets, which are reflex ovulators, we had originally hypothesized that pheromones may play a key role in the preovulator LH surge (Wersinger and Baum, 1996; Kelliher et al., 1998). Chemosensory cues alone were insufficient to induce c-fos expression in GnRH neurons (Wersinger and Baum, 1996). Chemosensory induced Fos expression in nuclei that provide excitatory input to GnRH neurons suggested instead that such cues still might be required for the stimulation of GnRH neurons (Wersinger and Baum, 1996; Kelliher et al., 1998). To the contrary, rendering ferrets anosmic failed to alter c-fos expression in GnRH neurons. Instead both anosmic and non-anosmic female ferrets showed significant, and indistinguishable increases in c-fos expression in GnRH neurons (Bakker et al., 2001). Thus it is possible that in this reflex ovulating species somatosensory stimulation significantly overshadows any chemosensory component. There are suggestions that other reflex ovulates may differ in this respect. In musk shrews, a reflex ovulating species, chemosensory cues from a male significantly increase the number of GnRH neurons that can be observed in sexually naïve females. This would suggest a significant increase in the amount of GnRH available for release and observable through immunocytochemistry rather than an actual increase in the number of GnRH neurons. Likewise, removing both main olfactory and vomeronasal input by bulbectomizing musk shrews prevents ovulation (Rissman and Li, 2000).

It is obvious that pheromonal modulation of the HPG axis occurs from multiple chemosensory cues but also by multiple chemosensory systems. While individual chemosensory cues may be detected only by a single system others may work through multiple systems. We are far from unraveling the mechanisms by which these pheromones ultimately mediate reproduction and/or reproductive behaviors.

MHC and genetic individuality

Most models of chemosensory mediated individual recognition involve discussions of the major histocompatibility complex (MHC). Yamazaki et al. (1976) found the first experimental evidence that the same genes responsible for self vs. non-self recognition in the body (the adaptive immune response) are also responsible for inter-individual communication of self and non-self. Since that time evidence of odor based MHC mate preferences have been found in a wide range of vertebrates; mice (Yamazaki et al., 1979), rats (Brown et al., 1987), humans (Eggert et al., 1998), fish (Landry et al., 2001; Reusch et al., 2001), avians (Freeman-Gallant et al., 2003) and reptiles (Olsson et al., 2003). Despite a growing number of experiments linking MHC to mate preferences, the exact nature of the chemosensory cues involved has remained

elusive. A number of models of how MHC genotype translated into “Odortype” had been suggested ranging from the degradation products of MHC molecules to volatile odors produced by microflora specific for a MHC genotype (Penn and Potts, 1998; Beachamp et al., 2003). Recently the laboratories of Zufall and Boehm have identified a novel source of MHC related chemosignals. They found that the peptide ligands of the MHC class I molecules are an ideal mechanism for signaling MHC genotype (Boeham and Zufall 2006; **see Text Box**). The same binding properties of peptide ligands that are important for conveying individual identity in the adaptive immune system could be co-opted by the olfactory system to transmit genetic individuality (Boeham and Zufall, 2006). By contrast there is an equally compelling theory that the adaptive immune system could have co-opted the MHC from the sensory systems (Brown, 1983; Boehm, 2006).

Peptide ligands of MHC class I molecules activate sensory neurons in the vomeronasal epithelium and signal individual recognition in the context of the Bruce Effect (Leinders Zufall et al., 2004). Furthermore these peptide ligands are detected by the VSNs with the same or similar binding mechanism used by MHC class I molecules. MHC class I molecules bind 9–20 amino acid long peptides by recognizing specific binding residues. Thus specific MHC class I molecules will only bind peptides with those particular amino acid residues at the anchor sites (termed anchor residues). As with peptide binding on MHC class I molecules, individual VSNs respond to different peptide ligands provided they had the same anchor residue. By contrast, a similar peptide ligand with changes only in the amino acids at the anchor residue site failed to activate the same VSN (Lienders-Zufall et al., 2005). Thus it is believed that vomeronasal receptors recognize anchor residues in the same way that MHC class I molecules do. Since peptide ligands directly reflect the sequences found in MHC class I molecule binding pockets, vomeronasal detection of the MHC peptide ligands provide an ideal conduit for transmitting genotype recognition from one animal to the next (Zufall and Boehm, 2006).

Although Leinders-Zufall et al. (2005) provided evidence for an individual recognition system working through the vomeronasal system many studies have shown that MHC based individual recognition also occurs through the main olfactory system (Penn and Potts, 1998; Yamazaki et al., 1979; Beauchamp et al., 1985). Until recently conventional wisdom would have precluded that nonvolatile peptides such as MHC peptide ligands would be detected by sensory neurons in the main olfactory system. We recently showed however, that not only are these peptides detected by OSN’s but also that male mice display preferences to peptides specific for a different mouse strains (Spehr et al., 2006a). OSNs of mice detect MHC peptide ligands by the same signal transduction pathway as most odors via the canonical olfactory cAMP signaling pathway and CNG channel. Also, like other odors detected by the OSNs, detection appears to occur in a combinatorial manner. This is an important distinction between detection via the main olfactory and vomeronasal epithelium. Whereas individual VSNs bind specific peptides based on there anchor residues, some OSNs are capable of responding to multiple peptides with different anchor residues. Although peptide ligands are detected by different signaling (and receptor) mechanisms by both the VNO and MOE, mice still appear to recognize peptides as belonging to the same or different MHC haplotype. Male mice show preferences for urine supplemented with peptide from a different MHC haplotype than their own. The observed preference is working through the main olfactory system because mice with vomeronasal lesions still show this preference (Spehr et al., 2006a).

MHC peptide ligands are a novel set of ligands that are signals of genetic individuality. They are detected by the vomeronasal organ and contribute to the pheromonal mediated pregnancy block, but also detected by the main olfactory epithelium and contribute to dissociative urine preferences. Yet in terms of individual recognition and even MHC mediated individual recognition they are unlikely the sole cues. Many previous experiments have attributed MHC mediated individual recognition to volatile chemosensory cues. Experiments using y-mazes

and olfactometers have shown that mice can discriminate between individuals of different MHC genotypes using volatile chemosensory cues (Beauchamp et al., 1985). The most common hypothesis for volatile transmission of MHC related odors is that MHC peptide ligands will be degraded when released from the body resulting in different patterns of volatile metabolites (Singer, 1997). By contrast our experiments with MHC peptide ligands clearly require direct physical contact to be sensed. When same strain mouse urine is supplemented with a different strain MHC peptide ligand and placed behind a barrier mice readily investigated but failed to discriminate between different peptide ligands (Spehr et al., 2006a). The involvement of multiple chemosensory cues or even multiple sensory systems for individual recognition should not be surprising. Behavioral responses to genetically related (or disparate) chemosensory cues are often found to differ depending on the context of detection. Whether cues are utilized for different behaviors, (dissociative mating, maternal or neonatal recognition, familiar recognition for nepotistic reasons), or different social contacts (contact with sent marks, individuals from a distance, direct physical contact), ultimately behaviors are going to require additional sensory cues associated with encounter. Even in respect to the Bruce effect, recognition of MHC peptide ligands is unlikely to be solely responsible for the physiological response. For the Bruce effect to occur a mated female needs to be exposed to urine from a sexually mature strange male (Brennan, 2004) and while we can't yet rule out that a sexually dimorphic gland such as the preputial gland might mediate the availability of MHC peptide ligands it is more likely that additional sex and steroid dependent chemosensory cues in urine are also involved. This cue maybe a sex specific peptide or protein produced solely as a chemosensory cue, similar to the ESP1 protein identified in lacrimal fluid of male mice (Kimoto et al., 2006) or an excreted steroid hormone that has been exploited as a sex specific cue (deCaatanzaro et al., 2001). So while we have identified pheromones of individual recognition, the process of individual recognition requires much more than a single pheromone or even a single chemosensory system.

Conclusions

The main olfactory and vomeronasal systems are two structurally distinct organs of chemical communication however, understanding the functional distinctions between the main olfactory system and the vomeronasal system is becoming significantly more complicated. The broad assertion that one system is specialized to detect a particular type of chemical cue; pheromone or an odor, a volatile or nonvolatile or innately recognizable or learned, fails to be convincing when under close scrutiny. Thus serious questions remain as to how these seemingly distinct systems interact to transmit chemical cues into meaningful social stimuli. Both systems are not only capable of detecting similar classes of chemical cues (pheromones) but in some cases the same exact chemical molecules. The two systems may detect the same chemical molecule using different receptor mechanisms (as presumed with MHC class one ligands, Spehr et al., 2006b) or detection of the same cues may occur by the same receptors in both epithelia (ORs in the vomeronasal organ; Levei et al 2006). MHC peptide ligands have provided us with the first example of an individual chemical cue that can be detected by both the main olfactory epithelium and vomeronasal organ while still providing the same general information to the individual (genetic individuality). Yet while similar in the information communicated the specific meaning of the signal may be different between the two systems. Is a MHC peptide ligand a pheromone though? Broadly defined yes, narrowly defined no, yet certainly they meet the concept of a pheromone. In the end semantics fail to change the importance of these molecules for social behavior. As important as findings of how chemical cues of genetic identity are detected and processed are it is equally important that mice have evolved that ability to detect and discriminate between individuals based on MHC class I peptide ligands using two distinct systems, the MOE and VNO.

One underlying theme of behavioral responses to pheromones is that such behaviors depend on the context of detection. This would suggest that such mammalian pheromones alone are insufficient in eliciting behavioral responses but instead are dependent on input of other sensory signals either chemosensory in nature or not, for the correct response to be elicited. This highlights need for future research into how multiple sensory systems detect and integrate signals important for the reproductive success on mammals. Certainly there is still a lot to be gained by investigating how particular chemosensory systems function independently of each other but it is also going to require concerted efforts in investigating how these systems work together.

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Figure 1. MHC Class I peptide Ligand Hypothesis

Virtually any cell type in the vertebrate organism has the ability create and release MHC class I peptide ligands. Provided they have MHC class I immunity. Both endogenous and foreign proteins are broken down in cells by ubiquitous proteasomes intracellularly. This results in degradation peptides between 4 and 20 amino acids in length. These peptides, which generally cannot pass through membranes, are transported into the endoplasmic reticulum (ER) via a transporter for antigen processing (TAP). In the ER peptides are loaded on to MHC class I molecules. Only peptides, which are compatible with the individual's MHC, class I molecules will be loaded. The specificity of binding is dependent on two specific binding residues of each peptide (anchor residues) fitting in to the binding pocket of the MHC class I molecule. After peptide binding MHC class I molecules are transported to the plasma membrane where they are presented to the immune system. MHC class I molecule-peptide complexes are eventually shed from the cell surface into extracellular space. Fragments of the MHC class I molecules are then found in serum, saliva, sweat and urine. Presumably the peptides bound to the MHC class I molecules will also be released intact however this has yet to be demonstrated empirically. It is thus hypothesized that MHC peptide ligands will be excreted by a variety of mechanisms and that the peptides that are released will be specific for the MHC genotype of the individual. For example an individual with an H2-K^d MHC haplotype will only excrete peptides that are specific for those MHC class I molecules. By contrast an individual with an H2-D^b haplotype will have a different set of peptide ligands excreted.

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