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Review

Roles for learning in mammalian chemosensory responses

Philip R. Griffiths, Peter A. Brennan *

School of Physiology and Pharmacology, University of Bristol, Medical Sciences, University Walk, Bristol BS8 1TD, UK

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ABSTRACT

This article is part of a Special Issue "Chemosignals and Reproduction".

A rich variety of chemosignals have been identified that influence mammalian behaviour, including peptides, proteins and volatiles. Many of these elicit innate effects acting either as pheromones within species or allelochemicals between species. However, even innate pheromonal responses in mammals are not as hard-wired as the original definition of the term would suggest. Many, if not most mammalian pheromonal responses are only elicited in certain behavioural or physiological contexts. Furthermore, certain pheromones are themselves rewarding and act as unconditioned stimuli to link non-pheromonal stimuli to the pheromonal response, via associative learning. The medial amygdala, has emerged as a potential site for this convergence by which learned chemosensory input is able to gain control over innately-driven output circuits. The medial amygdala is also an important site for associating social chemosensory information that enables recognition of conspecifics and heterospecifics by association of their complex chemosensory signatures both within and across olfactory chemosensory systems. Learning can also influence pheromonal responses more directly to adapt them to changing physiological and behavioural context. Neuromodulators such as noradrenaline and oxytocin can plasticise neural circuits to gate transmission of chemosensory information. More recent evidence points to a role for neurogenesis in this adaptation, both at the peripheral level of the sensory neurons and via the incorporation of new neurons into existing olfactory bulb circuits. The emerging picture is of integrated and flexible responses to chemosignals that adapt them to the environmental and physiological context in which they occur.

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Introduction: what are pheromones?

Pheromones were first defined by Karlson and Lüscher over 50 years ago as "substances secreted to the outside of an individual and received by a second individual of the same species in which they release a specific reaction, for example a definite behaviour or developmental process" (Karlson and Lüscher, 1959). First identified in silk moths (Butenandt et al., 1959), many examples have since been identified in insects and have important practical applications in pest control. However, our knowledge and understanding of vertebrate and mammalian pheromones, which are the focus of this review, has lagged appreciably behind

* Corresponding author.
E-mail address: p.brennan@bristol.ac.uk (P.A. Brennan).

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that of insects. Indeed some have questioned whether mammalian pheromones really exist (Doty, 2010). However, the ever-growing number of examples of substances that meet the original definition of a pheromone provides convincing evidence that pheromonal effects do occur across a range of mammalian species. However, the evidence for pheromonal effects is less strong in apes and humans in which the importance of visual and verbal modes of communication has led to the evolutionary decline in olfactory capability in general (Kambere and Lane, 2007).

When Karlson and Lüscher first proposed their definition of a pheromone they envisaged that their definition would be redefined and updated over time (Karlson and Lüscher, 1959). Yet it still forms the core of most accepted definitions, such as the recent, slightly modified definition by Wyatt, "molecules that are evolved signals, in defined ratios in the case of multiple component pheromones, which are emitted by an individual and received by a second individual of the same species, in which they cause a specific reaction, for example, a stereotyped behavior or developmental process." (Wyatt, 2014). Others have added their own additional requirements such as that a pheromone must be airborne (Stern and McClintock, 1998). But there are whole classes of involatile substances that have pheromonal effects following direct physical contact, so this is definitely not a requirement for a pheromone (Brennan and Zufall, 2006). It has also been suggested that pheromones should not be consciously perceived. But the majority of pheromones will stimulate main olfactory receptors and therefore will have a perceptible odour so it would be more appropriate to state that pheromones do not have to be consciously perceived to have a pheromonal effect, as pheromonal receptors are typically several orders of magnitude more sensitive than canonical olfactory sensory neurons (Leinders-Zufall et al., 2000). One of the most useful refinements to the original definition of the term pheromone is the requirement for there to be mutual benefit to sender and receiver (Meredith, 1998), although this can be difficult to establish in practice. Built into this definition is the assumption that evolutionary selection has led to the co-evolution of the pheromonal signal and the pheromonal sensing system, with specialised receptors hard-wired to neural pathways eliciting an innate response. However, this does leave out a whole class of signals, such as individuality chemosignals that have evolved to transmit information about individual identity but that do not necessarily elicit an innate response and need to be learnt (Brennan and Kendrick, 2006). This requirement for learning means that they do not fit in the classical definition and they have been termed signature cues (Wyatt, in press).

Innate vs learned chemosensory responses

The original definition of pheromonal action does not specify that responses need to be innate only that the responses should be "definite". However, there are many general odour cues that have not evolved as specific signals that can be sensed and learned by the main olfactory system and it would not be useful to regard these as having pheromonal effects. Therefore, pheromonal signals are best regarded as mediating innate responses, i.e. they do not have to be learnt. Not all innate chemosensory responses are classified as pheromonal. Pheromone is the term given to a cue acting within species. Cues acting between species, such as predator or prey cues are classed as allelochemicals (Wyatt, 2003), but may share similar sensory and neural pathways to pheromones. Examples of pheromonal responses in which the sensory receptors and neural pathways are most completely understood are those mediated by exocrine secretory peptides (ESPs) in mice. These are a multigene family with around 20 members in mice encoding related 7 kDa peptides that are sensed by the peptide/protein-sensing V2r class of vomeronasal receptors (Kimoto et al., 2005). Analysis of tissue expression levels of ESPS has identified two that are expressed in tear glands and sensed by the vomeronasal system following direct contact with the head region of the producer. The sex pheromone ESP1 is only produced by male mice, and constitutive knockout of the V2Rp5 receptor that mediates ESP1 action reduces lordosis quotient in female mice from 40% to 10% (Haga et al., 2010). ESP22 is produced by juveniles of both sexes and reduces sexual behaviour directed towards the juveniles by sexually mature males (Ferrero et al., 2013). Interestingly, lack of selective pressure on reproduction has led to significant differences in the pheromonal signals produced by different inbred strains of mice. For example males of the C57BL/6 strain lack production of ESP1 (Haga et al., 2010) and juveniles of the CBA strain produce very low levels of ESP22 (Ferrero et al., 2013). These differences between inbred strains are useful experimentally as they are effectively naturally occurring knockouts for these particular pheromones, but this also suggests that care needs to be exercised when investigating social behaviour using inbred strains of mice.

Another example of innate responses mediated by mammalian pheromones are the testosterone-dependent chemosignals present in urine from adult male mice that elicit aggression from other males and from lactating females. This aggression is elicited by both volatile and non-volatile constituents of male urine sensed by the vomeronasal organ (Chamero et al., 2007). The non-volatile constituents have been identified as major urinary proteins (MUPs). MUPs are lipocalins that bind small volatile ligands including brevicomin and thiazole, a mixture of which has also been found to elicit aggression, but only when added to the urine of castrated males (Novotny et al., 1985). This suggests that the brevocomin–thiazole mixture alone is insufficient to elicit aggression and needs to be sensed in the context of other, testosterone-independent urinary constituents to be effective. The context-dependence of this pheromonal effect is also evident in the requirement for a suitable conspecific that is associated with the cues to act as a target for the aggression. When males sense the same urinary cues in the context of an unfamiliar urine mark encountered in their territory, countermarking behaviour is elicited rather than aggression (Humphries et al., 1999). Moreover, despite the fact that their own urine marks contain a similar mix of volatile and involatile chemosignals, they do not elicit countermarking behaviour presumably because they have been learned as being familiar (Hurst et al., 2001). Thus even though there are likely to be relatively direct and hard-wired pathways from pheromonal input to behavioural output, these pheromonal effects are modulated by contextual cues and learning in mammals, as they are in invertebrates (Wyatt, 2014).

The aggression promoting effects of male urinary chemosignals are abolished by surgical ablation of the vomeronasal system (Clancy et al., 1984; Maruniak et al., 1986). The involvement of the vomeronasal system is further supported by the lack of aggression elicited by mature male intruders in the TRPC2 line of males and lactating females in which the gene for the vomeronasal transduction channel TRPC2 has been constitutively knocked out (Leypold et al., 2002; Stowers et al., 2002). This genetic manipulation produces a complex phenotype involving increases in inappropriately directed mounting behaviour in both males and females (Kimchi et al., 2007; Stowers et al., 2002). However, as was apparent from the earliest publications, TRPC2 knockout does not abolish all vomeronasal transduction (Kelliher et al., 2006; Leypold et al., 2002). TRPC2 is activated by the diacylglycerol branch of the phosphatidyl inositol bisphosphate signalling pathway. However, responses can still be generated by VSNs in TRPC2 knockout mice, by the release of intercellular Ca^{2+} via inositol trisphosphate signalling (Chamero et al., 2012) and subsequent activation of Ca^{2+}-dependent K^+ and Cl^- channels (Dibattista et al., 2012; Kim et al., 2012). Different vomeronasal stimuli acting at different G-protein coupled vomeronasal receptors might differentially activate these two branches of the transduction pathway, leading to a selective deficit of specific vomeronasal stimuli in TRPC2 mice, whilst responses to other vomeronasal stimuli, such as MHC peptides is unimpaired (Kelliher et al., 2006). This can explain the various discrepancies reported between the effects of vomeronasal ablation and TRPC2 knockout (Keller et al., 2014; Martel and Baum, 2009). Overall a picture is beginning to emerge that pheromones not only can induce a specific behavioural reaction according to the original definition, but also that some pheromonal effects can