Neuroscience and Biobehavioral Reviews 50 (2015) 29–40

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Biological complexity and adaptability of simple mammalian olfactory memory systems

P. Brennan [a], E.B. Keverne [b,*]

[a] School of Physiology and Pharmacology, University of Bristol, Bristol, UK
[b] Sub-Department of Animal Behaviour, University of Cambridge, Cambridge, UK

ARTICLE INFO

Article history:
Received 5 March 2014
Received in revised form 20 August 2014
Accepted 22 October 2014
Available online 31 October 2014

Keywords:
Olfactory
Vomeronasal
Learning
Memory
Receptors
Neurogenesis

ABSTRACT

Chemosensory systems play vital roles in the lives of most mammals, including the detection and identification of predators, as well as sex and reproductive status and the identification of individual conspecifics. All of these capabilities require a process of recognition involving a combination of innate (kairomonal/pheromonal) and learned responses. Across very different phylogenies, the mechanisms for pheromonal and odour learning have much in common. They are frequently associated with plasticity of GABA-ergic feedback at the initial level of processing the chemosensory information, which enhances its pattern separation capability. Association of odourant features into an odour object primarily involves anterior piriform cortex for non-social odours. However, the medial amygdala appears to be involved in both the recognition of social odours and their association with chemosensory information sensed by the vomeronasal system. Unusually not only the sensory neurons themselves, but also the GABA-ergic interneurons in the olfactory bulb are continually being replaced, with implications for the induction and maintenance of learned chemosensory responses.

Contents

1. Introduction

The chemosensory systems are well established in small brain mammals providing information on predators, gender, offspring and sexual status. All of these features require a process of recognition based on learning and memory. Across very different phylogenies the mechanisms for pheromonal and olfactory learning have much in common. They all engage important and necessary processing at the first relay (accessory olfactory and main olfactory bulb) where intrinsic GABA-ergic neurons are integral to the synchronisation of the output from projection neurons which also play an integral role in the recognition process by these trilaminar circuits (Brennan and Keverne, 1997).

The mammalian vomeronasal chemosensory system (VNO) connects primarily with the amygdala and hypothalamus, regions of

* Corresponding author at: Sub-Department of Animal Behaviour, University of Cambridge, High Street, Madingley, Cambridge CB23 8AA, UK.
Tel.: +44 01223 741816; fax: +44 01223 741802.
E-mail address: ebk10@cam.ac.uk (E.B. Keverne).

http://dx.doi.org/10.1016/j.neubiorev.2014.10.020
0149-7634/

the brain concerned with neuroendocrine responses and primary motivated behaviour. These sub-cortical brain regions regulate hormonal changes that are relevant to sexual behaviour, maternal care and fear responding. In these contexts, recognition of mates and offspring are sustained, contributing to reproductive success and offspring survival. The first relay from the VNO receptors is the accessory olfactory bulb (AOB) which, in the context of pregnancy block, has itself the capacity to form and retain long term memories (Brennan et al., 1990).

Chemosensory neurons are exposed to the vagaries of the external environment and have a relatively short lifespan. Consequently, these receptor neurons undergo regenerative turnover, which continues throughout life. Turnover of receptor neurons can provide adaptability to new environments by selection for different receptor types and the formation of new memories (Nissant and Pallatto, 2011). This raises the question as to how the balance between retaining "old" memories and prioritising new memories occurs. Integral to this is the added complication of adult regeneration of intrinsic bulbar GABA-ergic neurons arriving to this front-line processing circuitry from the sub-ventricular rostral flow of neural progenitor cells.

Mammalian chemosensory neurons are characterised by a large number of genes coding for the receptors that respond to chemical cues and pheromones. This is illustrated by 1400–1700 olfactory receptors, 300-170 vomeronasal class 1 receptors (V1Rs) and 280-220 vomeronasal class 2 receptors (V2Rs) in the mouse and rat (Ibarra-Soria et al., 2014). In Old world primates and apes (including humans) the vomeronasal receptors are virtually all non-coding pseudogenes, while the main olfactory receptors are reduced to a third of the number found in rodent species (Kambere, 2007). The mammalian evolutionary trend for this diminished representation of VNO chemoreception in particular has paralleled the increase in mammalian neocortical size and the switch from nocturnal to diurnal lifestyles (Nei et al., 2008). Nevertheless, the basic principles for coding and initial processing of chemosensory cues and pheromones have much in common across the vomeronasal and main olfactory systems.

The vomeronasal system has a vital and complementary role to the main olfactory system. In mammals vomeronasal receptors are located in the vomeronasal organ, a blind-ended tubular structure in the nasal septum that is connected to the nasal and/or oral cavities (Døving and Trotier, 1998). The main distinction between the function of the two systems appears to be that the main olfactory system is adapted to detect airborne odourants, whereas stimulus access to the vomeronasal organ depends on pumping relatively involatile stimuli such as peptides and proteins into the vomeronasal organ following physical contact with the stimulus source (Meredith and O'Connell, 1979). The mammalian vomeronasal system connects primarily with the amygdala and indirectly to the hypothalamus, regions of the brain concerned with neuroendocrine responses and primary motivated behaviour. These sub-neocortical brain regions regulate coordinated behavioural, autonomic and hormonal responses in contexts such as sexual behaviour, parental care and aggressive/defensive behaviour. The main olfactory and vomeronasal systems play complementary roles in both innate and learned responses to chemosensory signals. This review aims to highlight the different neural mechanisms involved in learning social and non-social olfactory cues and the enhanced plasticity provided by neurogenesis in olfactory systems.

2. Stereotyped versus learned olfactory responses

It used to be thought that the main olfactory system mediated a flexible, learned response to odours, whereas the vomeronasal system mediated relatively stereotyped innate responses to pheromones, However, this has given way to a more complex picture in which both the main olfactory and vomeronasal systems can mediate sterotyped responses to chemosignals, and the responses via both systems can be influenced by learning. The two systems have interrelated functions often providing complementary information about the same stimulus source. For instance, both the main and vomeronasal systems can mediate an avoidance response and freezing behaviour in mice. Predators produce involatile urinary chemosignals belonging to the major urinary protein (MUP) family, which stimulate the V2r receptor class of vomeronasal receptor to elicit freezing and avoidance behaviour in mice (Papes et al., 2010). Different predators produce different MUP variants in their urine potentially enabling mice to discriminate chemosignals from different species of predator (Ben-Shaul et al., 2010).

The main olfactory system can also mediate responses to predator chemosignals, such as the volatile odourant trimethlytoluine (TMT), which is a component of fox faeces. Class I olfactory receptor proteins are expressed by olfactory sensory neurons (OSNs) in the dorsal zone of the olfactory epithelium and project to glomeruli in the D_1 region of the main olfactory bulb (MOB). OSNs expressing Class II olfactory receptor proteins are located in the ventral zone of the olfactory epithelium and project to the D_2 region and to the ventral region of the MOB (Kobayakawa et al., 2007). Wildtype lab mice have an aversion to TMT, which is lost in mice with a large-scale genetic deletion of OSNs expressing class II olfactory receptors that project to the D_2 domain of the MOB. This loss of stereotyped aversion to TMT odour was not due to the inability to detect TMT, as the mice could still learn to either approach or avoid TMT in appetitive and aversive conditioning paradigms via class II-expressing OSNs that projected to the ventral region of the MOB (Kobayakawa et al., 2007). These findings demonstrate that there are populations of mitral cells in D_2 domain of the MOB that are "hardwired" to regions that generate aversive responses to predator odours. The activation of the medial aspect of the bed nucleus of the stria terminalis (BNST) by TMT in wild-type but not D_2 deleted mice identifies this pathway as mediating innate responses to predator chemosignals (Kobayakawa et al., 2007). Interestingly, mice also show innate avoidance responses to odours that are typical of spoiled foods, such as 2-methylbutyric acid and isoamylamine, which appear to be mediated by the D_1 region of the MOB (Kobayakawa et al., 2007) but do not activate the medial aspect of the BNST. These findings suggest that different sub-regions of the MOB mediate innate responses in different behavioural contexts and that these differ from the MOB subregions that convey learned odour responses (Fig. 1).

Both the main olfactory system and the vomeronasal system also mediate pheromonal responses to chemosignals from members of the same species. For instance, the main olfactory system of rabbits mediates the response to the rabbit mammary pheromone 2-methylbut-2-enal (Schaal et al., 2003). This airborne pheromone is produced by the skin surrounding the doe's nipples and induces robust arousal and stereotyped nipple search behaviour in rabbit pups that enables successful nipple location, attachment and suckling (Distel and Hudson, 1985). The vomeronasal system mediates the pheromonal effects such as those of exocrine secretory peptide 1 (ESP-1). This is a peptide pheromone produced in male mouse tear secretions that is sensed by the V2Rp5 vomeronasal receptor and increases the proportion of females showing lordosis in response to mounting attempts by males, via a sexually dimorphic pathway to the ventromedial hypothalamus (Haga et al., 2010). Another exocrine secreting peptide found in mouse tear secretions, ESP-22, is only produced by juvenile mice inhibits mounting attempts by males (Ferrero et al., 2013). Interestingly MUPs from male mice that are from the same family as predator MUPs are sensed by V2Rs to