



## Review

# From sexual attraction to maternal aggression: When pheromones change their behavioural significance



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## ARTICLE INFO

Available online 23 August 2014

## Keywords:

Mouse  
Major urinary proteins  
Darcin  
Socio-sexual behaviour  
Vomeranasa  
Olfactory

## ABSTRACT

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

This paper reviews the role of chemosignals in the socio-sexual interactions of female mice, and reports two experiments testing the role of pup-derived chemosignals and the male sexual pheromone darcin in inducing and promoting maternal aggression. Female mice are attracted to urine-borne male pheromones. Volatile and non-volatile urine fractions have been proposed to contain olfactory and vomeronasal pheromones. In particular, the male-specific major urinary protein (MUP) MUP20, darcin, has been shown to be rewarding and attractive to females. Non-urinary male chemosignals, such as the lacrimal protein ESP1, promote lordosis in female mice, but its attractive properties are still to be tested. There is evidence indicating that ESP1 and MUPs are detected by vomeronasal type 2 receptors (V2R).

When a female mouse becomes pregnant, she undergoes dramatic changes in her physiology and behaviour. She builds a nest for her pups and takes care of them. Dams also defend the nest against conspecific intruders, attacking especially gonadally intact males. Maternal behaviour is dependent on a functional olfactory system, thus suggesting a role of chemosignals in the development of maternal behaviour. Our first experiment demonstrates, however, that pup chemosignals are not sufficient to induce maternal aggression in virgin females. In addition, it is known that vomeronasal stimuli are needed for maternal aggression. Since MUPs (and other molecules) are able to promote intermale aggression, in our second experiment we test if the attractive MUP darcin also promotes attacks on castrated male intruders by lactating dams. Our findings demonstrate that the same chemosignal, darcin, promotes attraction or aggression according to female reproductive state.

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## Introduction

Rodents, and specifically mice (*Mus musculus domesticus*), constitute useful models to understand the neural and endocrine basis of social behaviours. Like in most other mammals, rodent social behaviours include sexual interactions (intersexual attraction and mating), agonistic encounters in which competitors fight for a territory and for mates, and parental care and other behaviours that increase the likelihood of offspring survival, e.g. nest building and pup defence. Being macrosmatic animals with highly developed olfactory and vomeronasal epithelia (plus other minor sensory organs such as the septal organ of Maserà and the ganglion of Grueneberg; see Fortes-Marco et al., 2013), rodents mainly use chemosignals for intraspecies communication. Combined lesions of the main and accessory olfactory systems have devastating effects on their social interactions (see Pfeiffer and Johnston, 1994). This is because rodents emit a myriad of pheromones, e.g. chemosignals that trigger specific social behaviours and/or neuroendocrine responses in conspecifics (Karlson and Luscher, 1959).

Females of laboratory mice (and of other rodents) constitute an especially interesting model to analyse how chemosignals are processed for the control of behaviour. In contrast to males, laboratory female mice do not attack intruders to defend their territory or to get access to possible mates, but they are usually engaged in affiliative interactions with conspecifics (although interfemale aggression is present in some wild-stock mice, Stockley et al., 2013). However, for the first 10 days after parturition, dams not only show pup-directed maternal behaviour (arched back posture, lactation, pup grooming and licking), but also attack conspecifics approaching the nest. Since pup killing is pervasive among wild rodents, attacks against intruders are usually interpreted as a defence of the pups, thus being called maternal aggression (Lonstein and Gammie, 2002).

Analysis of the changes that occur in female social behaviour after parturition and their physiological substrates constitutes an interesting issue that could prove very helpful for understanding the neuroendocrinology of social interactions. A first question in this respect is whether pheromone sensing is equally involved in female-to-male reactions throughout the life of the female. Two alternative, but not necessarily exclusive possibilities exist. On the one hand, changes in female physiology (e.g. endocrine state) and/or behavioural stimulation (e.g. interaction with pups) occurring through pregnancy, parturition and lactation might alter the pattern of receptor expression in the vomeronasal and/or olfactory epithelia (e.g. Alekseyenko et al., 2006), or the responsiveness of olfactory and/or vomeronasal sensory neurons to their ligands (Stowers and Dey, 2014). A similar phenomenon has been suggested for the vomeronasal system of males in relation to their paternal vs infanticide behaviour (Tachikawa et al., 2013). As a consequence, lactating dams might detect new chemosignals derived from conspecifics or, alternatively, they might fail to detect chemosignals that they detected before. This would result in a change in social behaviour. Alternatively, females might detect the same male pheromones throughout their lives, but changes in the central nervous system during pregnancy, parturition and lactation would alter the response to these chemosignals thus modifying the social behaviour of females.

In this essay we assess these hypotheses concerning changes in the response of female mice to male chemosignals. Male-derived chemicals attract females during most of their life but, during a specific period after parturition, lactating dams fiercely attack male intruders. We first review evidence that these responses, attraction to males and attacks towards male intruders, are mediated by chemosignals detected

by the olfactory and/or vomeronasal epithelia. As we will see, it seems that vomeronasal stimuli are needed for both sexual attraction and attacks on intruders, but olfactory inputs also are likely to be involved. Chemosignals promoting aggressiveness against intruders might arise from the female's pups, thus corresponding with experimental evidence that mother–pup interactions are needed to maintain maternal aggression (Gandelman, 1972). On the other hand, intruder-derived chemosignals could be the key stimuli for maternal aggression, thus explaining differential attack intensity towards different types of intruders reported in the literature (Gandelman, 1972; Rosenson and Asheroff, 1975; Bean and Wysocki, 1989).

Finally we will describe and discuss the results of two experiments that demonstrate that: a) attacks on male intruders by lactating females are promoted by a testosterone-dependent factor expressed by intruders; b) contact with the pups is necessary but not sufficient for developing nest defence; and c) the recombinant sexually attractive male pheromone darcin, when sprayed onto castrated males used as intruders, is able to promote aggression from lactating female mice.

## Role of chemosignals in intersexual attraction in mice

In most animals, intersexual attraction involves emission of signals by males (songs, odours, displays) that attract females. Male mice mainly use ultrasonic vocalisations (Nyby et al., 1981; Holy and Guo, 2005) in the range of 30–110 kHz, and chemical signals that they release in their territory by means of urine marking behaviour (Hurst, 1987). Chemical cues are, however, preeminent since male mice sing ultrasonic courtship vocalisations in response to conspecific urinary odours (Guo and Holy, 2007).

In agreement with their role in intersexual attraction, male-derived chemosignals are attractive to adult but not to pre-pubertal female mice that, in fact, avoid them (Drickamer, 1989; Mucignat-Caretta et al., 1998). This can be observed using simple two-choice tests in the laboratory, in which females are left to freely explore two sources of chemosignals. Adult females prefer male- to female-derived chemosignals whether presented as an entire anaesthetised animal, a drop of urine or soiled-bedding. Similarly, adult females also prefer intact to castrated male-derived odours (Martinez-Ricos et al., 2007; DiBenedictis et al., 2012). This indicates that males produce a testosterone-dependent chemosignal that is attractive to adult females, but aversive to pre-pubertal females. Moncho-Bogani et al. (2002) tested this attractiveness in females that had been reared in the absence of adult male chemosignals. These so-called “chemically naïve” adult females already preferred male-soiled bedding to the more familiar female-soiled bedding even during their first experience with male chemosignals. Therefore, these chemosignals comply with the original definition of pheromones (Karlson and Luscher, 1959), as they trigger stereotyped, hardwired or non-learned responses in conspecific females.

## Volatile male sexual pheromones: chemical species and their detection

The identity of the attractive male pheromone(s) has been a controversial issue. There is an open debate about the volatile and/or non-volatile nature of these male sexual pheromones, as well as about the sensory organ responsible for their detection, namely the olfactory epithelium or the vomeronasal organ. Consequently, it is also unclear what kind of olfactory or vomeronasal receptors can detect the attractive male-derived chemosignals. As discussed by Fortes-Marco et al. (2013), these hardwired responses require highly specific receptors. This excludes the canonical, generalist olfactory receptors. Instead,

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