Mechanisms underlying sexual and affiliative behaviors of mice: relation to generalized CNS arousal

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The field of social neuroscience has grown dramatically in recent years and certain social responses have become amenable to mechanistic investigations. Toward that end, there has been remarkable progress in determining mechanisms for a simple sexual behavior, lordosis behavior. This work has proven that specific hormone-dependent biochemical reactions in specific parts of the mammalian brain regulate a biologically important behavior. On one hand, this sex behavior depends on underlying mechanisms of CNS arousal. On the other hand, it serves as a prototypical social behavior. The same sex hormones and the genes that encode their receptors as are involved in lordosis, also affect social recognition. Here we review evidence for a micronet of genes promoting social recognition in mice and discuss their biological roles.

Keywords: CNS arousal; affiliative behavior; oxytocin; lordosis; social recognition

BACKGROUND

Neuroscience, during the 20th century, frequently considered that comprehensive mechanistic explanations of behavior demanded work with lower species such as *Drosophila* or *C. elegans*. Hormone-driven social behaviors exhibited by mammals, however, have proven to be more approachable than anticipated. Mating behaviors are quintessentially social behaviors. In fact, some evolutionary biologists have speculated that sex behavior sets the ‘*bau plan*’, the fundamental organizing principle, for all mammalian social behaviors. Therefore, after briefly summarizing mechanisms for the female quadruped’s primary hormone-dependent sex behavior, lordosis and its underlying mechanisms of CNS arousal, we will discuss genetic and hormonal influences on social recognition in female mice. A brief discussion of future possibilities for this field of work will follow.

MECHANISMS OF SEXUAL BEHAVIOR

Receptors

The development and use of steroid autoradiographic techniques (Pfaff, 1968; Pfaff and Keiner, 1973) permitted the discovery of a limbic-hypothalamic system of sex hormone binding neurons that express genes for the cognate hormone receptors. This limbic-hypothalamic system, discovered in rat brain, turned out to be universal among vertebrates (Morrell and Pfaff, 1978). The subdivision of this

system into nerve cell groups that primarily express estrogen receptors- α and β has been accomplished with immunocytochemical techniques (Shughrue *et al.*, 1997; Laflamme *et al.*, 1998).

Neural circuits

Knowing which forebrain neurons concentrated and retained the steroid sex hormones that promote hormone-dependent sex behaviors was of great help in figuring out the lordotic behavior circuitry. The other two ‘anchors’ constituted the sensory input pathways, signaling cutaneous stimuli from mounting by the male, and the motor pathways for executing the vertebral dorsiflexion of lordosis. The circuit (Figure 1) that features hypothalamic control over a spinal-hindbrain-midbrain-spinal circuit was summarized in *Estrogens and Brain Function* (1980).

Genes

Several genes have the properties that their mRNA levels are increased by estrogen treatment and their products are important for fostering estrogen-dependent lordosis behavior (Figure 2). They include transcription factors, neurotransmitter receptors, neuropeptides and their receptors, and have been summarized in *Drive* (1999). The potential number of such genes may be quite large, according to our recent microarray results. From one microarray came the important role for prostaglandin D synthase (Mong *et al.*, 2003a, b).

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Fig. 1 Lordosis circuit. The neural circuit that produces lordosis behavior, the primary estrogen-dependent sex behavior in female four-footed mammals. The circuit is bilaterally symmetric, but is drawn here on one side only, for visual clarity. The behavior is triggered by cutaneous stimuli, facilitated by estrogenic action in ventromedial hypothalamic neurons, and is manifest in massive contractions of the deep back muscles (bottom). Its neuroanatomic and neurophysiologic features indicated a modular construction (right), which turned out to match embryologic divisions of the neuraxis. (Adapted from Pfaff, 'Drive', MIT Press, 1999).

Implications

Extensive progress in these four lines of work (neuroanatomic, electrophysiologic, genetic and behavioral) was derived from three strategic advantages: the molecular genetics permitted by current knowledge of steroid hormone

action on transcription; simple and discoverable stimuli that trigger lordosis behavior and an extremely simple lordosis behavior motor topography, not even requiring locomotion. Taken together, these four trains of experiments proved for the first time in a mammalian brain that specific biochemical

Fig. 2 Syllogism figure of genes affected by estrogens. This list of genes has two properties: (i) estradiol (E) treatment raises their transcript levels following E binding to estradiol receptor (ER)- α or β ; and (ii) their products facilitate lordosis behavior. A microarray study revealed an exception: Prostaglandin-D Synthase mRNA is *reduced* in the preoptic area, where it *inhibits* lordosis behavior. Their concerted actions currently are conceived as functional genomic modules downstream from hormone action. (Adapted from Pfaff, 'Drive', MIT Press, 1999).

reactions in specific nerve cell groups govern a mammalian behavior. Lordosis behavior is biologically important because it controls reproduction for the species.

Beginning experimentation with a very simple behavior such as lordosis was necessary in order to answer the question: 'Is it possible to discover detailed mechanisms for *any* mammalian behavior?' Having accomplished that, we now face the question: 'Is it possible to address a neuronal function that underlies *all* mammalian behaviors?' Specific sex behaviors depend on sexual arousal. In turn, sexual arousal is one specific manifestation of generalized CNS arousal (Frohlich *et al.*, 1999; Garey *et al.*, 2003; Pfaff, 2006).

GENERALIZED CNS AROUSAL: THEORY AND QUANTITATIVE ASSAY

Responding in an adaptive manner to incoming signals from the external environment and in a manner consistent with the body's physiological requirements is necessary for all animals, including humans, to survive. Indeed, over a lifetime, animals receive constant stimuli from their environment—responding to some stimuli and ignoring others. Considering that the saliency of a stimulus can be transient and be affected by the current environmental or social setting, as well as the animal's complex internal physiological and emotional state, neuroscientists could face a daunting task understanding the CNS mechanism for this responsiveness. How do these external and internal influences wake up the brain? What is the 'energy source' that supports or arouses behavior?

Such a 'generalized arousal' system should be basic to all specific mental and emotional functions and is thought to be supported in the CNS by a primitive brainstem neuronal system which has neuroanatomical neurophysiologic and neurochemical components that are universal to all vertebrate animals (Pfaff, 2006). This complex system must be suited to monitor the animal's constantly changing internal and external environments and then flexibly drive behavioral responses—both instinctive and learned, in a manner that is individual to each animal and situation. Clearly, studying arousal from a mechanical approach, summing factors affecting arousal state and projecting potential responses, is not practical. However, since the initiation and maintenance of behavior is critically dependent on CNS arousal, one way to address the arousal function is to focus on behavioral expression of arousal.

Previous behavioral experiments in our lab indicated the existence of such a generalized arousal function of the CNS in mice. Testing the theoretical basis of arousal theory, using the statistical tool Principle Components Analysis (PCA), behavioral data from several experiments that measured arousal behavior was analyzed to discover the underlying causes of the statistical relationships. Generalized arousal accounted for about one-third of the data (Garey *et al.*, 2003). In convincing support of generalized arousal theory, this result held true across different mouse populations, different investigators, different experimental manipulations, different arousal measurements and data collection methods, and even different configurations of factor analysis solutions.

A second set of experiments used ‘gene knockout’ mice. In such mice the DNA has been carefully mutated to eliminate a specific gene and no other gene. Importantly, mice with such knockouts of genes coding for the estrogen receptors revealed genetic contributions to arousal. In these experiments using female mice, knockouts for estrogen receptor- α or β were tested for motor activity and sensory responsiveness. Compared with wild type littermate controls, estrogen receptor- α mice, lacking the gene for the classic estrogen receptor, had less voluntary motor activity and were significantly less responsive to the sensory stimuli than the estrogen receptor- β and their wild type littermate controls (Garey *et al.*, 2003). Therefore, the two genes encoding for nuclear estrogen receptors contribute to arousal differently.

Arousal theory

Treating behavior as a physical variable, an operational definition of arousal makes it possible to quantify arousal. In order to address the elementary nature of generalized arousal, the components of the definition must not be limited by specific conditions or behaviors and must be able to describe ‘the most elemental responses to any sensory stimulus, preparatory for every behavioral response that follows’ (Pfaff, 2006). Therefore, the operational definition was developed, for example, to consider responses to all sensory modalities and to voluntary and emotional behavior

as well as reflex responses. *The definition states: Generalized arousal is greater in an animal that is (1) more motorically active, (2) more alert to sensory stimuli and (3) more emotionally reactive.* Furthermore, a theoretical equation that addresses generalized arousal mathematically, describing the activation of brain and behavior, incorporates the compound function the primitive brainstem system with the forces related to specific biological needs (see Pfaff, 2006 for details). It states that arousal is a function of generalized arousal and specific forms of arousal (for example, related to fear, hunger and sexual behavior or other social encounters) and that these factors are constrained by constants that reflect the animal’s temperament. Individual differences in temperament are of especial interest.

Arousal assay

Using this definition of generalized arousal, we have begun to quantify generalized arousal using a specially designed apparatus that monitors behavior during a series of measures, collecting data about the animal’s motor behavior, sensory responsivity and emotional reactivity (Figure 3). With the goal that the animals are tested in their home cage environment ‘undisturbed by human hands’, arousal behavior is measured using an automated infra-red beam break behavior monitoring system integrated with a stimulus delivery system, all surrounding a mouse home cage.

Fig. 3 Cartoon of assay apparatus. Cartoon of the arousal assay apparatus. An infra-red beam break behavior monitoring system surrounds the mouse home cage (left) and a custom cage top encloses the cage (right). An optional door in the cage wall provides access to the attached running wheel to record voluntary motor activity. Sensory stimuli are administered through integration with a stimulus delivery system, cued by the mouse’s behavior. Available stimuli include tactile (air puff) and olfactory (through jets on cage top), auditory and visual (in isolation chambers) and floor shock (fear training). Additionally, the unit is mounted on an orbital shaker to administer a vestibular stimulus.

Voluntary motor activity is measured as general voluntary activity in numbers of beam breaks or as number of running wheel revolutions. For sensory responsiveness measurements, the equipment is capable of providing stimuli testing a range of sensory modalities (tactile, vestibular, olfactory, auditory and visual) using hardware that controls each stimulus delivery through integration with the behavior monitoring system. Finally, the emotional reactivity measure, a cued and contextual fear conditioning paradigm, is similarly automated using shock floors that are integrated into standard mouse home cages with behavioral responses being measured by the integrated beam break system.

Phenotypic breeding of arousal extremes

One way to validate the behavioral arousal assay and, therefore, the operational definition of arousal, is to breed divergent lines of high and low arousal mice using a selection process that uses behavioral criteria from each of the arousal domains: motor activity, sensory responsivity and emotional reactivity. Initial maximum heterogeneity is required of the foundation stock for a broad selection of innate arousal levels and the unknown genes that control arousal. Breeding animals and guidance have been provided by professors Gerry McClearn and David Blizard of Penn State University who generously donated an allotment of Het-8 animals (McClearn *et al.*, 1970). Breeding pairs from this generation and subsequent generations were selected based on the arousal scores of a specific measurement from each of the three domains, summed and ranked, followed by mating of high-ranking pairs and of low-ranking pairs. To date, the vast amount of data collected on the Het-8 mice has revealed that arousal levels in individuals, indeed, follow the standard bell curve with a few individuals of each gender exhibiting high arousal or low arousal behavior, and the first generation of selection had substantial effects on the phenotype in the predicted direction. Continued testing of subsequent generations will also contribute to our understanding of factors affecting arousal including possibly gender differences, circadian affects or relative response characteristics across the three arousal domains of arousal behavior.

Arousal and drive interactions

Secondly, using the automated arousal assay, we have investigated arousal mechanisms influenced by estrogens and their interactions with drive states. One such experiment measured the effects of estrogen treatment and food restriction, imposed separately and together to investigate the interaction of the hunger and sex drives effects on generalized arousal—the physiological controls of reproduction and metabolic fuel intake being interconnected (Wade and Jones, 2004). Both foraging and courtship behaviors involve active responses and energy expenditure by the female and, therefore, would require CNS arousal. The combined treatment particularly reduced arousal-related

motor and sensory activity, perhaps increasing cautionary behavior, since fear responsivity was increased as well (Shelley *et al.*, 2005). The treatments also decreased receptivity and increased rejectivity of females during sexual behavior and other social interactions (Shelley and Pfaff, unpublished data).

In summary, regarding these CNS arousal mechanisms and using our assay, we are attempting to study complex genetic determinations of arousal in the service of hormone-dependent social behaviors that require CNS arousal, including affiliation and aggression.

HORMONAL AND GENETIC INFLUENCES ON SOCIAL RECOGNITION FUNDAMENTAL TO AFFILIATIVE BEHAVIORS AND AGGRESSION

Essential for group living in mammalian species is social recognition (Gheusi *et al.*, 1994), the capability of recognizing and remembering other individuals within the group (Choleris *et al.*, 2004). This allows for the establishment of hierarchical organizations as well as various social bonds, such as pair bonds and mother–infant bonds (Carter and Keverne, 2002; Choleris *et al.*, 2004). Learning about the neurobiological bases of social recognition and the use of social information is, thus, important to gain an understanding not only of the proximal mechanisms of sociality, but also of its functional and evolutionary implications (Tang-Martinez, 2003).

Mechanisms of social bonding

A series of comparative investigations have elucidated some aspects of the neurobiological mechanisms underlying social bonding. The neurohypophyseal hormones, oxytocin and vasopressin, were both implicated in parental care and the establishment of pair bonds in the monogamous prairie vole, *Microtus ochrogaster* (Carter, 1998), but not in the polygamous montane vole, *M. montanus* (reviewed in Insel, 2003). Similar results have been obtained with a monogamous and a polygamous rodent species of the genus *Peromyscus* (*californicus* and *maniculatus*, respectively, Insel *et al.*, 1991). As well, pair bonds could be induced in the polygamous montane vole (Lim *et al.*, 2004) and the laboratory mouse through administration in the brain of the gene that codes for the vasopressin receptor 1a (Young *et al.*, 1999). These studies (reviewed in Lim and Young, 2004) all point to an important role of these two neuropeptides in the evolution of social behavior and the underlying social recognition processes.

Investigations with gene ‘knockout’ mice have confirmed the key role of oxytocin in social recognition in mice. Both male (Ferguson *et al.*, 2000) and female (Choleris *et al.*, 2003) mice whose gene for oxytocin had been made non-functional showed a highly specific deficit in social recognition that could be reversed through administration of oxytocin in the medial amygdala (Ferguson *et al.*, 2001). More recently, the deficit of the oxytocin knockout mice has been confirmed using a more sensitive

(Engelmann *et al.*, 1995) behavioral paradigm where individual recognition was assessed through a direct choice between a familiar and an unfamiliar mouse (Choleris *et al.*, 2006). Accordingly, oxytocin receptor knockout mice also showed a specific and marked impairment in social recognition (Takayanagi *et al.*, 2005).

The interplay of estrogens and oxytocin in social recognition

Other investigations with knockout mice have then expanded our understanding of the neurobiology of social recognition highlighting a key role for estrogens. Estrogen-dependent social recognition in females is likely adaptive in relation to reproduction in that it allows for better discrimination of potential mates of different quality (e.g. parasitized vs non-parasitized males, see Kavaliers *et al.*, 2005a, b). Both male (Imwalle *et al.*, 2002) and female (Choleris *et al.*, 2003) estrogen receptor- α and β knockout mice were as impaired in social recognition as the oxytocin knockout mice (reviewed in Choleris *et al.*, 2004). This prompted the development of the 4-gene 'micronet' model to explain the interplay, in two areas of the female mouse brain, of estrogens and oxytocin in the regulation of social recognition (Choleris *et al.*, 2003). This model involves the four genes coding for the two estrogen receptors- α and β , oxytocin and the oxytocin receptor and two brain areas; the hypothalamus and the amygdala. Through the estrogen receptor- β estrogens control oxytocin production in the paraventricular nucleus of the hypothalamus, and through the estrogen receptor- α they regulate the expression of the OTR gene in the medial amygdala (Choleris *et al.*, 2003). In rodents the medial amygdala is the site of convergence of socially relevant (Beauchamp and Yamazaki, 2003; Dulac and Torello, 2003; Johnston, 2003) olfactory sensory input from the main and accessory olfactory systems and it is here that they are processed for the recognition of individuals.

The 4-gene micronet model (Figure 4) represents a synthesis of behavioral, genetic and molecular information. At the biochemical level, evidence derives from studies showing that the estrogen receptor- β is highly expressed in the mouse hypothalamic paraventricular nucleus (PVN) (Mitra *et al.*, 2003), where it regulates the production of oxytocin. Accordingly, in estrogen receptor- β knockout male (Nomura *et al.*, 2002) and female (Patisaul *et al.*, 2003) mice, but not in their wild type littermates, treatment with estrogens fails to induce oxytocin expression in the PVN. Also in agreement with the 4-gene micronet model are studies showing the high expression of the estrogen receptor- α in the amygdala (Mitra *et al.*, 2003) where it is necessary for the induction of the oxytocin receptor (Young *et al.*, 1998). As well, investigations with female estrogen receptor- β knockout mice have confirmed that oxytocin production is regulated by the estrogen receptor- β in the PVN, while binding to the oxytocin receptor in the

Fig. 4 Choleris' micronet affecting social recognition. Cartoon of 4-gene micronet regulating social recognition. Ovarian estrogens regulate oxytocin (OT) secretion in the PVN of the hypothalamus through their binding to the estrogen receptor- β (ER- β). OT, through axonal projections of the PVN neurons, reaches the amygdala, where estrogens regulate the expression of OT receptors (OTR) through their binding to ER- α . Estrogen mediated OT-OTR activation in the amygdala ultimately facilitates social recognition. (Adapted from Choleris *et al.*, PNAS, 2003).

medial amygdala seems to be independent of the estrogen receptor- β (Patisaul *et al.*, 2003).

The involvement of the neuropeptide oxytocin in social recognition in male and female rodents has been shown repeatedly in both normal (Popik and van Ree, 1998) and gene knockout rodents (reviewed in Young, 2002 and Choleris *et al.*, 2004). In rats, estrogens were shown to be directly involved in oxytocin production (de Kloet *et al.*, 1986; Dellovade *et al.*, 1999) and in the expression of the gene for the oxytocin receptor in various areas of the brain (Quinones-Jenab *et al.*, 1997). Social recognition in female mice (Sanchez-Andrade *et al.*, 2005) and rats (Juraska *et al.*, 2001) varied with the phase of the estrous cycle, with improved social recognition shown during proestrus, when levels of circulating estrogens are high. Consistently with these findings, treatment with estrogens improved social recognition in ovariectomized female rats (Hliäák, 1993) and mice (Tang *et al.*, 2005). Furthermore, both estrogen receptor- α and β gene knockout mice showed impaired social recognition (Imwalle *et al.*, 2002; Choleris *et al.*, 2003). Interestingly, it later emerged that when tested in a more sensitive paradigm (Engelmann *et al.*, 1995), the impairment in the estrogen receptor- β knockout mice was partial, rather than complete (Choleris *et al.*, 2006). This allowed further refining of the gene micronet model; the estrogen

receptor- β gene may play a modulatory role in social recognition, possibly by up-regulating baseline production of oxytocin in the PVN (Mitra *et al.*, 2003). Accordingly, baseline oxytocin levels and mRNA of the oxytocin gene in the PVN of estrogen receptor- β knockout mice are normal, even though they fail to respond to stimulation by estrogens (Nomura *et al.*, 2002). At the behavioral level, baseline levels of oxytocin likely allow for a certain degree of social discrimination that could be improved by further estrogen receptor- β -induced production of oxytocin.

The 4-gene 'micronet' and disorders of social behavior

The understanding of the neurobiological mechanisms underlying social recognition can help the understanding of human disorders of sociality such as autism, schizophrenia, social phobias and violence (Nesse, 1999; Troisi, 1999; de Waal, 2000; Young, 2001; Young *et al.*, 2002). Oxytocin and gonadal hormones have been implicated in both pro and anti-social human behavior (Ogawa *et al.*, 2004; Pedersen, 2004). An altered oxytocinergic system has been observed in people affected with autism (Modhal *et al.*, 1998), schizophrenia (Mai *et al.*, 1993; Bernstein *et al.*, 1998; Feifel and Reza, 1999) and depression (Bernstein *et al.*, 1998; Uvnäs-Moberg *et al.*, 1999). Autistic children were shown to have lower plasma concentrations of oxytocin (Modhal *et al.*, 1998) and an altered oxytocin production from its prohormone precursor (Green *et al.*, 2001). As well, initial clinical trials showed that intravenous administration of oxytocin improved stereotypical repetitive behavior in an adult autistic patient population (Hollander *et al.*, 2003). The higher incidence of autism in males than females (Insel *et al.*, 1999) and the proposed masculinization of the brain of female autistic patients (Baron-Cohen, 2002) are consistent with animal data showing estrogen control on the oxytocin system in its mediation of individual recognition (reviewed in Choleris *et al.*, 2004). In this regard, it is intriguing that autistic patients show impaired face and individual recognition (Heffer *et al.*, 2005).

Oxytocin, estrogens and aggression

Oxytocin appears to regulate both affiliative and non-affiliative, aggressive behaviors in females with oxytocin antagonists (Lubin *et al.*, 2003) and antisense DNA increasing maternal aggression in rats (Giovenardi *et al.*, 1998). As well, oxytocin knockout female mice showed heightened aggression toward both familiar females and unfamiliar male and female intruders when placed in semi-natural conditions (Ragnauth *et al.*, 2005). Conversely, oxytocin administration, reduced infanticide and agonistic aggression in female mice (McCarthy, 1990) and facilitated affiliative behaviors in female hamsters (Harmon *et al.*, 2002) and gerbils (Razzoli *et al.*, 2003). In agreement with the 4-gene micronet model of social recognition (Choleris *et al.*, 2003), oxytocin control of aggression was shown to be

sexually dimorphic (Bales and Carter, 2003) and modulated by estrogens (Razzoli *et al.*, 2003).

In conclusion, the 4-gene micronet model involving estrogenic regulation of oxytocin in the mediation of social recognition can provide important insights into the understanding of both social and anti social behavior in mammalian species. This model forms the core around which increasingly complex genetic, hormonal and neural interactions associated with social behaviors and recognition can be organized. The proper operation of this net allows for the expression of the appropriate social behavior, either affiliative or aggressive and the utilization of social information.

IMPLICATIONS: SOCIAL ENVIRONMENT AND NEURONAL MECHANISMS

Social information can be acquired either as direct social signals or indirectly as inadvertent social information (Danchin *et al.*, 2004). Animals can directly communicate to each other information about factors such as their own status (i.e. cues associated with sex, status or condition) or threats in the environment (e.g. alarm signals indicating the presence of predators) through the use of specifically evolved communication signals. In rodents and other mammals, olfactory information is of particular importance, with chemical signals providing direct information about sex, sexual and social status, individuality and condition (e.g. Brown, 1979; Halpin, 1986; Johnston, 2003).

Social information can also be obtained indirectly from cues inadvertently produced by others with similar interests and requirements ('inadvertent social information' (ISI)) (Danchin *et al.* 2004). These inadvertent cues provide publicly available information ('public information') that others can use to guide their own behavior (Valone and Templeton 2002). The use of inadvertent social information occurs when an animal observes another animal engaged in a behavioral event that is not specifically aimed at communication. This has been examined in birds and fishes where the mate choice decisions of several species have been shown to be influenced by public information (e.g. Dugatkin and Godin, 1992; Gibson and Hoglund, 1992; Galef and White, 1998). In this case, a female typically observes another female mating with a male and later displays a preference for that male. In other words, one female's mate choice decision influences another female's choice resulting in what has been termed 'mate copying' (Dugatkin and Godin, 1992). Although social influences on human mate choice are suggested (Danchin *et al.*, 2004), until recently little was known about the possible use of ISI in determining social preferences of mammals. As well, the genomic correlates of ISI use were unexplored until recently when the gene for oxytocin (OT) was shown to be involved in the use of both direct and indirect, inadvertent olfactory mediated social information (Kavaliers *et al.*, 2006).

Oxytocin and direct social information

A major cost of social behavior is the increased risk of exposure to parasites (Moller *et al.*, 1993). Social behaviors facilitate interactions between conspecifics, increasing the probability of exposure to and transmission of parasites from infected to uninfected individuals. Parasites have been shown to affect mate choice and mating patterns with females preferentially selecting parasite-free or -resistant males through a variety of cues (reviews in Kavaliers *et al.*, 2005a, b). Female mice can directly discriminate between uninfected and specific subclinically infected (i.e. no evident sickness) males on the basis of odor, displaying aversive and avoidance responses to infected males and their odors (e.g. Kavaliers and Colwell, 1995; Penn and Potts, 1998; Kavaliers *et al.*, 2003, 2004, 2005a). Likewise humans stigmatize and avoid sick people and 'healthy' individuals that we perceive may pose a risk of disease and parasite transmission (Crandall and Moriarty, 1995; Park *et al.*, 2003; Faulkner *et al.*, 2004). As such, direct social information (i.e. individual odors in the case of rodents) is used for the: (i) distinction between infected and uninfected conspecifics; (ii) recognition and avoidance of specific infected individuals and (iii) expression of appropriate avoidance and aversive responses to infected individuals.

Recently, it was shown that the gene encoding for OT was associated with olfactory-mediated recognition of and discrimination against parasitized individuals (Kavaliers *et al.*, 2003, 2005a, b, 2006). Oxytocin knockout female mice were impaired specifically in their discrimination of, and display of aversive responses to, the urine cues of parasitized males. In contrast to oxytocin knockout females, OT-wild type and OT-heterozygous females readily distinguished the odors of uninfected males from infected males. In addition, oxytocin knockout females displayed attenuated aversive responses to infected males and did not discriminate between familiar and infected males. In contrast, OT wild type females recognized and displayed attenuated aversive, though not avoidance, responses to familiar infected males. These responses indicated that at least one normal copy of the gene encoding for OT is part of the central mechanism (or mechanisms associated with estrogen receptors- α and β , as per the 'micronet' of Choleris *et al.*, 2003) by which female mice distinguish parasitized individuals and recognize specific parasitized individuals on basis of direct odor cues. In view of the suggestive evidence for the involvement of OT in modulating human social behavior (e.g. Kirsch *et al.*, 2005), it is tempting to speculate that equivalent mechanisms may underlie the recognition of, and responses to infected and sick individuals displayed by humans.

Oxytocin and inadvertent social information

As indicated, odors guide the social behavior and mate responses of rodents with females using odors to determine the quality, condition and health (including infection status)

of a male as a potential mate. Female mice are, however, also known to deposit scent marks and to investigate the odors of other females (Kavaliers *et al.*, 2006). As such, female odors that are associated with that of male encompass a potential source of inadvertent social information that may be used to guide the social interests and mate choice of other females. It was recently shown that sexually naïve estrous female mice expressed a specific interest in, and investigated the odors of, either a less preferred uninfected male (i.e. male with a lower testosterone level) or a parasitized male if the odors of a another estrous female were associated with that of the male (Kavaliers *et al.*, 2006). In addition, the aversive (elevated corticosterone, analgesia) and avoidance responses of females to the odors of parasitized males were attenuated by this ISI.

The presence of these added cues suggests that another estrous female had expressed some interest in that male and that he may potentially be suitable as a mate. As such, these findings raise the possibility that female mice may use or 'copy' the olfactory based mate interest of other females in a manner evocative of mate copying reported in other species (e.g. Dugatkin and Godin, 1992; Gibson and Hoglund, 1992). Uninfected here does not necessarily imply a parasite resistant and/or better quality male. High-quality males can have both better health and more parasites than low-quality males (Getty, 2002). As such, the alterations in odor responses induced by the presence of the odor cues of another female can be considered as reflective of shifts in female choice.

It was further shown that OT gene-deficient (oxytocin knockout) females were impaired in their use of this ISI to modulate their responses to either uninfected males of differing sexual conditions or infected males (Kavaliers *et al.*, 2006). In an odor choice, oxytocin knockout females failed to display a significant interest in, and initial choice of the odor of a female that was associated with the odor of an estrous female. Likewise, when ISI, in the form of the odor of an estrous female, was associated with that of a less attractive male, oxytocin knockout females did not reverse their choice. In this regard, oxytocin knockout females can be considered to fail to 'trust' the mate interests and preferences of other females. OT involvement here can be speculated as paralleling the suggestion for OT having a pro-social role in enhancing trust in humans (Kostfeld *et al.*, 2005). Together, these findings suggest that the gene for OT is associated with the use of both direct and inadvertent social information and the processing and integrations of social information in a broader context.

The odor information regarding the condition and identity of the scent owner (male and female odors) is assessed by the main and accessory olfactory systems and conveyed to the amygdala (Dulac and Torello, 2003). OT at the level of the amygdala provides a target at which direct and inadvertent social information can be integrated and assessed.

INTERGRATION AND OUTLOOK

We have supplied (Section 'Mechanisms of Sexual Behavior') references to the body of literature on mechanisms for a specific sexual behavior whose elucidation proves for the first time that defined chemical reactions in particular nerve cell groups in the mammalian brain govern a biologically crucial behavior. The sexual arousal that underlies that behavior comprises one manifestation of generalized CNS arousal forces. A new operational definition of generalized arousal (Section 'Generalised CNS Arousal: Theory and Quantitative Assay') coupled with a quantitative 'high-throughput' assay should help us to unravel some of the complexities involved in the structure of CNS arousal mechanisms, be they neuronal or genomic. We note that arousal influences response to social information and conversely that social information influences the state of arousal. Expanding from a specific sex behavior to a broader range of affiliative (or aggressive) behaviors (Section 'Hormonal and Genetic Influences on Social Recognition Fundamental to Affiliative Behaviors and Aggression') we see that some of the same hormones and genes are involved in the regulation of social recognition, at least in mice. This allows us to use the well-developed endocrine chemistry of ER- α and ER- β further to explore genetic mechanisms, but also (Section 'Implications: Social Environment and Neosonal Mechanisms') to envision the roles of these mechanisms in normal environments in which females must make mate choices among males.

Conflict of Interest

None declared.

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