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Brain sex differences and the organization of juvenile social play behavior

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Abstract

Juvenile social play behavior is one of the earliest forms of non-mother directed social behavior in rodents. Juvenile social play behavior is sexually dimorphic, with males exhibiting higher levels compared to females, making it a useful model to study both social development and sexual differentiation of the brain. As most sexually dimorphic behavior, juvenile play behavior is organized by neonatal steroid hormone exposure. The developmental organization of juvenile play behavior also appears to be influenced by the early maternal environment. This review will focus briefly on why and how rats play, some brain regions controlling play behavior, and how neurotransmitters and the social environment converge within the developing brain to influence sexual differentiation of juvenile play behavior.

Overview of play

Juvenile social play behavior is regarded as one of the earliest forms of non-mother directed social behavior in rodents (1). An appealing aspect of juvenile social play behavior is that it is sexually dimorphic, with males exhibiting higher levels of social play than females, making it an attractive model behavior to understand both normal juvenile social development and sex differences in social behavior in a non-reproductive context. It is also becoming clear that while this sexually dimorphic behavior is organized by neonatal steroid hormone exposure, the differentiation of social play can be also influenced by the early social environment, such as the amount of maternal care received. Investigations of social play are centered on why and how rats play, brain regions controlling play behavior, sex differences, and how neurotransmitters and the social environment might influence the organization of play behavior. It will be interesting to understand how the social environment impinges on neurotransmitters to influence the steroidreceptor mediated organization of juvenile social play behavior.

Why do rats play?

There are several intriguing concepts as to why rats play. Juvenile play behavior is considered to be rewarding, as the opportunity to play can be used as an incentive for maze learning (2,3) and juvenile rats develop conditioned place preferences for areas associated with play (4). Anticipation of play also elicits 50 KHz ultrasonic vocalizations (5), which are associated with positive affect (6). Indeed, it has been suggested that play is “joyful” (7), and that some vocalizations during juvenile play might be akin to human laughter (8).

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Another possible function of play is to establish dominance in the group. Following multiple play bouts, juveniles develop dominance hierarchies which remain relatively stable over the juvenile period (9,10), although play dominance does not always appear to predict dominance in adulthood (11). Play may also function to better prepare for adult behaviors such as male sexual and aggressive behaviors (12), as play behavior predicts adult aggressiveness in males (13). Preventing males from playing has lasting consequences on social (14–16), aggressive (16), and sexual behavior (16,17). The effect of juvenile isolation on these behaviors appears mainly due to deprivation of play, as isolated animals provided with a brief daily period of play do not develop these deficits (16). Therefore play may serve to prepare for more adaptive social behaviors in adulthood.

How do rats play?

Juvenile social play behavior starts to form around 18 days, peaks during the peripubertal period (days 30–40), and wanes after puberty. Play is observed as bites, boxing/wrestling, pouncing, pinning. Pouncing, the act of jumping on or attacking the nape of a conspecific, is considered an initiation or solicitation of play (10). If the conspecific responds playfully, boxing or wrestling frequently ensues. Boxing occurs when both rats stand on their hindpaws and push at each other with their forepaws. Wrestling occurs when two rats roll and tumble over each other. Pinning, or one rat holding a conspecific in a supine position, is often the result of boxing and wrestling bouts. Pinning is used to determine dominance status among juveniles (10).

Interestingly, the expression of some types of play changes over the course of the juvenile period. For example, play initiation accounts for most of the temporal changes in the frequency of play behavior (18). In contrast, the probability of responding to a playful attack remains relatively constant over time, although the defense tactics used by males do change with age (18). Younger animals appear to withdraw from play sooner than older animals following boxing or wrestling bouts (19). In older animals, boxing and wrestling are more likely to end with pinning (19), and occurs more frequently (10). The target of play also appears to change over time. Prior to postnatal days 31– 35, males prefer to play with other males; however, preference shifts towards females as males approach puberty (10,18). These studies suggest that the combinations of play and the target of play are changing over age, and that the functional role of play may also be changing over time.

Methods to assess play

Paired-exposure testing is one method used to assess play behavior. In this paradigm, animals are isolated before testing to increase motivation to play. A pair of animals is then placed into a neutral arena and allowed to interact for a short time, while play behavior is observed (20). This method allows for observation of many play bouts within a short time, and often requires only a single test session per animal; however, it does investigate levels of social play in response to brief isolation. Alternately, play behavior can be examined in a more naturalistic manner by observing group-housed animals undisturbed in their home cages using a focal observation method (21). Although this method requires longer observation periods, it exposes animals to multiple play partners and does not require isolation or exposure to a novel environment, both of which can act as stressors. As discussed below, the method of testing impacts the reliability of observed sex differences in social play.

Neuroanatomy of play

Several brain regions have been implicated in juvenile play behavior. For example, lesions to the cortex, nucleus accumbens, hypothalamus, and the amygdala have been shown to

decrease social play behavior. In contrast, lesions to the septum increased social play behavior. Interestingly, lesions to the medial preoptic area appear to be without effect of social play behavior. These findings are summarized in a review by Vanderschuren et al on the neurobiology of social play behavior (1). A recent study examining changes in Fos mRNA expression following social play behavior in juvenile rats reports increased Fos mRNA levels within the tectum, inferior colliculus, striatum, somatosensory cortex, and the ventromedial hypothalamus; however, no changes were observed in the amygdala (22). This is intriguing as neonatal lesions of the amygdala severely disrupt social play behavior (23), and local implant of steroids increase the organization of social play (24,25).

While few studies have critically examined the role of the BST on social play behavior, its connections with the amygdala do suggest that it may be pertinent to this behavior. Indeed, numerous investigators consider the BST as an extension of the amygdala. This is referred to as the extended amygdala hypothesis. These regions share numerous connections and chemical similarities. Both contain dopamine (26), vasoactive intestinal peptide (27), and dopamine receptors (28). Indeed, the concept of the central extended amygdala includes the central nucleus, substantia innominata, and lateral bed nucleus (29). As the amygdala is critically involved in social play behavior, it is likely that the BST will play a role. Indeed, a relatively recent report examined the influence of social play deprivation on opioid receptors and found that from around 40 different brain regions examined, the bed nucleus and the amygdala exhibited the same up regulation of opioid receptors (15). In addition, our own data suggest that the BST responds in a similar manner to dopaminergic activation of ERs as does the central amygdala (30).

Social play and activity level

Although few of the studies discussed address whether the reported effects on social play are due to changes in overall playfulness, social motivation, or motor activity, social play appears to be regulated separately from each of these factors. For example, although juvenile males engage in more social play than females, solitary locomotor play is not sexually dimorphic (31). Additionally, juvenile females engage in more general motor activity than juvenile males (32). Neonatal treatment with estradiol or testosterone does not alter juvenile motor activity (33), although these hormones do increase juvenile social play (30,34). Similarly, lesions or pharmacological treatments that reduce social play do so without altering arousal, responses to non-social motivating stimuli (35), or general motor activity (36). Naloxone, which acutely reduces play behavior, does not alter motivation for social interaction (35). Cannabinoid receptor agonists (37) increase social play, but do not influence social investigation or overall motor activity. Although these data do not rule out the possibility that changes in overall playfulness, motivational processes, or motor activity can impact the expression of social play, these data suggest that social play can be regulated separately from these processes.

Sex differences in play

As in many mammalian species, including cats (38), dogs (39), nonhuman primates (40) and humans (41–43) males engage in more rough-and-tumble juvenile social play than females. Similarly, the frequency of social play in rats is sexually dimorphic, with male rats engaging in social play more often than females (10,19,21,24,44,45). This sex difference has been attributed largely to an increased rate of play initiation by males (10,18,34,46). Interestingly, prospective partners are also more likely to respond to play solicitation by males compared to females (18). In addition to play initiation, other components of social play are also sexually dimorphic. For example, males are more likely to counterattack (18), thus extending the play bout, than females. Males also engage more frequently in boxing (10),

and pin their play partners more often than females (9,10). Pellis and Pellis have reported that defensive responses to play initiation are also sexually dimorphic. Females are more likely to allow themselves to be pinned by a play partner and this difference increases with age, as males adopt defensive tactics that lead more frequently to boxing (18).

The reliability of sex differences in the frequency of social play appear to depend upon the method of testing. Consistent sex differences are found when animals are group housed and observed undisturbed (19,21,47). In contrast, sex differences are less reliably found in paired exposure paradigms. Particularly when long-term isolation or short testing times are used, sex differences are often not detected using this method (48–50), although some sex differences have been observed (34,44). Sex differences in paired exposure testing are more reliable following shorter isolation periods (i.e. about 24 hours) and longer observation periods (18,51,52).

Hormones and play development

Sexual differentiation of social play behavior depends upon differential exposure to testosterone during the perinatal period. Male rats castrated early in the postnatal period engage in female-typical levels of juvenile social play (21,53). Additionally, the social play behavior of females can be masculinized by peripheral testosterone (34) treatment or following implants of testosterone into the amygdala (24,25) during the early neonatal period. Androgen receptors (ARs) are known to play a major role in mediating the effects of testosterone on the organization of social play. For example, males exposed perinatally to the AR antagonists flutamide (45,54,55) or vinclozolin (55) display reduced levels of juvenile social play. Additionally, peripheral treatment with 250μg testosterone or 250μg of its androgenic metabolite, dihydrotestosterone, during the neonatal period can masculinize social play behavior. Low doses (5μg) of estradiol benzoate (EB) during the neonatal period appear to have little effect on juvenile play (21). In contrast, higher doses (100 μg) of EB, which resemble male-typical levels of estradiol in the neonatal brain (56), appear to masculinize juvenile social play in females to male-typical levels (30). Although males with the testicular feminization mutation (Tfm), which renders them insensitive to androgens, showed decreased play behavior compared to normal males (45), Tfm males did tend to play more frequently than females. Recent evidence from Tfm males also suggests that while these males engage in some aspects of play at female-typical levels, Tfm males display other components of social play at male-typical levels (57), supporting the idea that ERs also play a role in differentiating social play behavior. Additionally, perinatal exposure to the environmental estrogen, bisphenol A, can masculinize play behavior in female rats and hypermasculinize play in males (58). Perinatal treatment with the synthetic estrogen, diethylstilbestrol, has also been reported to increase the social play of females [Hines et al, 1982 cited in (59)]. Additional data from non-human primates also suggest the possibility that ERs may contribute to the masculinization of play. While androgen systems contribute strongly to the masculinization of juvenile social play behavior in nonhuman primates (60), female rhesus macaques exposed prenatally to the synthetic estrogen, diethylstilbestrol dipropionate, show increased social play behavior during the juvenile period (40). Therefore, the organization of social play behavior may involve both AR and ER; however, as neonatal estrogen exposure increases AR mRNA expression (61), it is possible that ERs influence play development by increasing AR sensitivity.

Neurotransmitters and play development

While the effects of numerous neurotransmitters and drugs on play behavior have been examined, most appear to decrease juvenile play with only a few increasing play behavior [see review (59)]. One neurotransmitter, dopamine, appears to be important in sexually

differentiating the brain. Male sexual behavior can be disrupted by neonatal treatment with dopamine receptor agonists (62) and antagonists (63), as well as dopamine synthesis inhibitors (62). Furthermore, the adult female sexual behavior is defeminized following perinatal treatment with dopamine agonists (64,65). Dopamine also appears to be important for sexual differentiation of social play behavior. Neonatal treatment of females with a dopamine receptor agonist, lisuride, masculinizes the juvenile and peripubertal play behavior (64,65). We have recently confirmed that neonatal treatment of female rats with the dopamine D1-like receptor agonist, SKF 38393, also masculinizes juvenile social play (30). Within the developing brain, dopamine appears to be sexually dimorphic. While females have more catecholaminergic neurons than males within the anteroventral periventricular nucleus of the hypothalamus (66), males have more catecholaminergic neurons in the mediobasal hypothalamus (67). Males also have increased DA content in the hypothalamus (68) and cortex (69), as well as greater hypothalamic DA release (70) during the early postnatal period contrasted to females. Taken together, these data indicate that increased DA activity in some areas might contribute to the masculinization of social play behavior. In addition to dopamine, the opioid system appears to contribute to the organization of social play behavior. Prenatal treatment with morphine, an opioid receptor agonist, increases the juvenile social play of male rats (71–73).

Possible convergence of neurotransmitters and steroid receptors on play development

In 1994, Mani and colleagues reported that progestin receptors in female rat brain can be activated in a ligand-independent manner by dopamine to facilitate female sex behavior (74). Since then, numerous factors have been found to ligand-independently activate progestin receptors in female rats (75–77). ERs are also activated in a ligand-independent manner (78,79), and recent data indicate that this may be occurring in the adult female rat brain to influence reproductive behavior (80). We recently reported that dopamine can alter gene expression within regions of the developing central extended amygdala via an ER-dependent mechanism (30,81). As discussed above, dopamine and ERs appear to both influence the organization of social play behavior, and the central amygdala is an important area controlling play behavior. This led us to hypothesize that the effects of dopamine on the development of social play may be mediated in part by ERs (30). To address this question, we first confirmed a role for ERs and dopamine in the organization of social play. Neonatal treatment with a male-like dose of estradiol increased the social play of females to male-typical levels and this effect was blocked by pretreatment with an ER antagonist. Similarly, female rats treated as newborns with the dopamine D1-like receptor agonist, SKF 38393, displayed increased levels of social play. To determine if ERs mediate the effect of SKF 38393 on play, we treated neonatal females with an ER antagonist prior to SKF 38393 treatment. ER antagonist pretreatment completely blocked the SKF-induced increase in social play, suggesting that dopamine might be altering the development of social play via an ER-dependent mechanism (30). It is not known if dopamine converges directly upon ER containing cells or indirectly through other factors known to activate ER in a ligand-independent manner, such as EGF, IGF, cAMP, or protein kinase A. It is also not known if any of these factors can locally increase the synthesis of neurosteroids. As neurotransmitters are sensitive to the social environment, it will be important to determine how early social interactions influence neurotransmitters in the developing brain. As state above, increased ER activity in developing brain can increase AR expression (61); therefore, it is not clear if ERs regulate play development via AR-independent mechanisms or by increasing AR sensitivity.

Social experience and play development

Work in non-human primates has demonstrated that social environment, particularly maternal interaction, is important for the development of social play (82). Prior to the start of juvenile social play, the primary social contact experienced by rat pups is interaction with the dam. This maternal interaction influences the development of behavior in the offspring. Interestingly, the amount of maternal grooming provided to pups is sexually dimorphic; male pups receive more maternal grooming of the anogenital region than females (83). This sex difference depends upon the pup's gonadal hormone exposure (84) and influences the development of sexually dimorphic behavior, including juvenile social play. The outcome of increased maternal grooming appears to reduce later juvenile social play. For example, male offspring of dams treated throughout lactation with intranasal zinc sulfate or dietary saline, treatments which specifically reduce maternal anogenital grooming, display increased social play behavior between days 33 and 42 (85). Similarly, reducing maternal grooming by applying perfume to the pups' anogenital region leads to more frequent social play in males (86). Naturally occurring variations in maternal care also impact the development of social play. Male pups of dams that provide low levels of grooming play more frequently compared to male offspring of dams that provide high levels of grooming (87). Interestingly, maternal grooming does not appear to impact the social play of females (85–87).

Because increased maternal grooming is associated with gonadal hormone exposure (84), which increases social play, it is counterintuitive that maternal grooming reduced social play. It is important to note that the studies discussed above all examined social play after day 30. It is possible that maternal grooming may alter the expression of play prior to day 30, or may change the developmental timing of social play, such as advancing the onset and/or peak of social play. For this reason, it is important to examine the effects of maternal grooming on social play earlier in the juvenile period. Alternately, it has been proposed that some developmental sex differences act to reduce the expression of sex differences later in life (88); therefore, it is possible that maternal grooming may act as a compensatory mechanism to limit the effects of gonadal hormones or factors that impact sexual differentiation social play

Epigenetic contributions to play development

Emerging data suggest that there is a convergence of both steroid hormones and the social environment on DNA to program lasting differences in juvenile social play behavior. Interestingly, it is not clear if this convergence is synergistic or opposing, as discussed in the previous paragraph. Differences in maternal care received are reflected in differences in the methylation status of ER promoter region (89). As dams maternally groom males more than females during the early neonatal period, it will be intriguing to determine if this sex difference in amount of maternal grooming received creates a sexually dimorphic epigenome. Our recent data indirectly support the possibility that the methylation status of DNA influences the organization of social play. We recently reported that expression of the methyl-binding protein, Mecp2, is sexually dimorphic within the developing rat brain, with males expressing lower levels of Mecp2 within the amygdala during the first week of postnatal life (90). We then used siRNA targeted at Mecp2 within the developing amygdala during the first few days of postnatal life and assessed the enduring impact on juvenile social behavior. We found that neonatal Mecp2 siRNA treatment reduced the frequency of juvenile social play behavior in males to female typical levels. Interestingly, females remained resilient to this disruption and exhibited typical levels of juvenile play behavior. As Mecp2 binds methylated DNA (91), and DNA methylation patterns are sensitive to maternal cues (92), the functional role of this protein in social organization may be dictated by the maternal and hormonal environment. It is also likely that steroid hormones and

environmental factors converge on DNA to create a sexually dimorphic epigenome that underlies lasting sex differences social behavior.

Conclusions

The data discussed above indicate that gonadal steroid hormones, neurotransmitters, social experience, and epigenetic factors contribute to the development of social play and suggest a possible convergence of these factors in sexually differentiating juvenile social play. Future research should examine the mechanisms of convergence, and whether these mechanisms influence similar or different components of play. As the organization of juvenile play is similar across a variety of species, the biological investigation of how this particular behavior is organized may give us a better insight into the development of typical and atypical juvenile social behavior.

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