

The Neurobiology of Social Play Behavior in Rats

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VANDERSCHUREN, L. J. M. J., NIESINK, R. J. M. AND VAN REE, J. M. *The neurobiology of social play behavior in rats.* NEUROSCI BIOBEHAV REV 21(3) 309–326, 1997.—Social play behavior is one of the earliest forms of non-mother-directed social behavior appearing in ontogeny in mammalian species. During the last century, there has been a lot of debate on the significance of social play behavior, but behavioral studies have indicated that social play behavior is a separate and relevant category of behavior. The present review provides a comprehensive survey of studies on the neurobiology of social play behavior. Evidence is presented that opioid and dopamine systems play a role in the reward aspect of social play behavior. The role of cholinergic, noradrenergic and opioid systems in attentional processes underlying the generation of social play behavior and the involvement of androgens in the sexual differentiation of social play behavior in rats is summarized. It is concluded that there is not only behavioral, but also neurobiological evidence to suggest that social play behavior represents a separate category of behavior, instead of a precursor for adult social, sexual or aggressive behavior. © 1997 Elsevier Science Ltd.

Social behavior Play behavior Reward Attention Sexual differentiation Opioid Dopamine Acetylcholine
Noradrenaline Androgens

1. SOCIAL PLAY BEHAVIOR: STRUCTURE AND FUNCTION

1.1. Social play behavior

ALTHOUGH it was not our primary reason for writing it, this review might celebrate that it is now nearly a century ago that two (and to our knowledge, the first two) significant articles on animal play behavior were published (93,226). Animal play has been defined as: “all locomotor activity performed postnatally that appears to an observer to have no obvious immediate benefits for the player, in which motor patterns resembling those used in serious functional contexts may be used in modified forms. The motor acts constituting play have some or all of the following structural features: exaggeration of movements, repetition of motor acts, and fragmentation or disordering of sequences of motor acts. Social play refers to play directed at conspecifics; object play refers to play directed at inanimate objects; locomotor play refers to apparently spontaneous movements which carry the individual about its environment, and predatory play refers to play directed toward living or dead prey” (30,137).

Social play, one of the earliest forms of non-mother-directed social behavior observed in mammals, has been observed to contain behavioral patterns related to social, sexual and aggressive behavior, displayed in an exaggerated

and/or out-of-context fashion (29,193,204). One of the characteristics of social play behavior is its reward value; social play can be used as an incentive for maze-learning (112,171) and place-preference conditioning (47,59). It is the interaction between two rats, rather than just the initiative of the soliciting animal, that gives social play behavior its reward value; in juvenile rats, it has been shown that interaction with a play partner that displays various forms of social interaction, but does not respond to play soliciting, is much less rewarding (47,112,190). Social play does not have the highest priority and is not displayed unconditionally (28); animals will learn a task to obtain the opportunity to play (59,112,171), but social play will be performed only when the primary needs of an animal have been satisfied. Food deprivation, for instance, suppresses social play in rats (223). It has been shown also that rats preferably play in sheltered places (106), and social play has been found to be suppressed when animals are tested under intense light conditions (185,258).

1.2. Structure of social play behavior in rats

In descriptive studies of social play in rats, it has been reported that, in young rats, behavioral acts related to adult social, aggressive or sexual postures occur, some of them in

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a modified ("exaggerated") form (204,205). In other studies (1,146,191,235), it has been reported that, independently of social experience, acts of aggressive and sexual behavior already are displayed at onset in their adult form, but in inexperienced animals often out of context. Social play has been suggested to represent a separate category of behavior (11,29,107,185) and considerable differences between social play and aggressive behavior have been found (106,188,191). Thus, although the postures displayed in social play share similarities with other behaviors, they are likely to represent more than just precursors of adult sexual or aggressive behaviors.

The composition of social play behavior in rats has been described in several studies. Behavioral acts occurring during social play include pouncing, chasing, social grooming, crawling over/under, charging, boxing, wrestling, pinning, social sniffing and lateral display (11,40,146,177,204). Mostly, a bout of social play starts off with one animal approaching and soliciting another (pouncing), during which the soliciting rat attempts to nose or rub the nape of the neck of the play partner. From this situation, e.g. chasing, boxing, wrestling, social grooming or pinning may follow. Pinning, regarded as the most characteristic posture in social play in rats, is defined as one of the animals lying with its dorsal surface on the floor with the other animal standing over it. Comprehensive analysis revealed that pinning occurs as follows: when a rat tries to nose the nape of a conspecific, the animal that is pounced upon can respond in various ways, which have been shown to vary with age (192). If the animal fully rotates to a supine position, pinning is the result (188,191). Thus, both pinning and being pinned are active phenomena. From the supine position, the defending rat can easily launch a counterattack. Thus, in social play, the supine position functions as a social releaser of a prolonged play bout, rather than as the endpoint of an interaction (196,204). From a pounce, chasing might follow if one of the participants moves away quickly. Interestingly, if it is the soliciting rat that moves away (approach-pounce-retreat), the play-soliciting pattern resembles the sexual solicitation ("darting") of the female rat (149). Social grooming also might follow from pouncing or pinning. If the animal that is pounced upon does not evade or rotate to supine, or when after pinning, the animal on bottom re-rotates, the initiator (who stands with its forepaws on the back of the partner) might proceed by grooming its partner. Thus, when a bout of social play in rats is viewed in relation to adult functional contexts, the play initiation (nosing the nape → social grooming) is related to social behavior and what follows to sexual behavior (approach-pounce-retreat → darting), or aggressive behavior (rotation to supine → submission).

In a variety of studies it has been shown that, in juvenile rats, social activities in general are different from social play (47,107,112,171,185). These findings suggest that, within the social repertoire of juvenile rats, there is a possible distinction between social play (social behaviors related to play) and social behaviors unrelated to play. Other observations support the existence of such a differentiation. It has been reported that, in juvenile rats, several behaviors occur in their adult form, while others do not (204,205). The behaviors occurring in their adult form might represent social behaviors occurring as in adult animals, while

behaviors that do not merely represent social (behaviors related to) play behaviors. In the period before sexual maturation, pinning, chasing and "rough-and-tumble play" correlate significantly with each other, but not with social investigation (177). Furthermore, regarding appearance during ontogeny, social behaviors related to play mainly occur before sexual maturation (11,40,105,175, 177,205), while other forms of social behavior occur during the entire lifespan of rats. A variety of studies also have reported that social play and social investigation are influenced differentially by drug treatment (16,23,108,189, 228, 242,259). These findings support the notion that social play behavior is a separate category of behavior.

1.3. Functions of social play behavior

Naturally rewarded behaviors, such as feeding, drinking, and sexual behavior, are important for the survival of an individual, group, or species. From the findings that social play in rats (47,59,112,171), as well as in other species (29), has a high reward value, it may be inferred that social play behavior is important as well. This notion is supported by the findings that rats are very susceptible to the effects of social isolation during the period between weaning and sexual maturation, when social play is most abundant (hereafter termed "play deprivation") (71,72,102,103,206). The effects of play deprivation can be attenuated by allowing the animals short daily periods of social play (72,206), while social interactions with an adult partner (that is less likely to engage in play), or a partner that had been rendered unresponsive to play initiation could not substitute for social play in these experiments (72).

Social play in juvenile rats has been observed to consist of behavioral patterns related to social, sexual and aggressive behavior. Interestingly, play deprivation causes abnormal patterns of social (102,103,144,187), sexual (85,97) and aggressive behaviors (102,103,134,235). Play deprivation does not influence the capacity to perform aggressive, or sexual motor acts; most forms of behavior are at onset already displayed in their definite form, independent of social experience (1,146,191,235). However, in play-deprived rats, the contextual settings in which aggressive or sexual behavior is displayed are affected (85,97, 102,103,134), while decreases in social interest in play-deprived rats also have been reported (102,144). In this respect, interesting effects recently have been found of social isolation during postnatal weeks 4 and 5 (102,103), when levels of social play behavior markedly increase and subsequently peak (11,105,146,175,205,244). After weeks 4 and 5, the isolated animals were rehoused in groups. When, during adulthood, the previously isolated animals were confronted with a social stressor (defeat in a resident-intruder paradigm), their behavioral and neuro-endocrine responses were disturbed severely. For instance, isolates took significantly longer to assume a submissive posture when attacked by a highly aggressive resident. Shortly after the agonistic encounter, the resident was confined in a small cage inside its territory, so that the intruder rat could no longer be attacked. The experimental rats were then placed back into the territory of the resident, and their behavior was observed. During this period, the non-isolated rats spent almost the entire observation period in immobility. In isolates, however, immobility was

decreased dramatically while a significant part of the observation period was spent with exploration and self-grooming. In addition, in isolates, the increases in plasma adrenaline and corticosterone levels caused by social defeat were significantly potentiated. In contrast, behavioral and cardiovascular responses to a non-social stressor in the shock-prod burying paradigm were not affected by early social isolation (102,103).

Social play is suggested to be an affiliative form of behavior functioning to facilitate social development. Experiments using play deprivation have indicated various possible functions for social play behavior, each representing a different aspect of social development. (1) Social play might function to establish social organization in a group, or between partners. Within one litter, rats have preference for specific play partners (205), and for various mammals it has been shown that animals who play less have weaker ties with the group in later life (29,149). (2) The merits of social play also might lie on a cognitive level, as social play serves to develop the ability of animals to express and understand intraspecific communicative signals (28,134,146,149,235), which may serve to inhibit aggression and increase group stability. (3) The experiments described above (102,103) indicate that social play might facilitate the ability to cope with social conflicts. (4) The disturbances observed in the sexual behavior of play-deprived rats indicate that social play serves to canalize innate forms of behavior into situation-dependent, specific sequences. It has been noted that, during social play, different behavioral acts are displayed in a variety of combinations, as if to find out which forms of behavior fit together. Not that the execution of aggressive or sexual acts is supposed to be facilitated by social play, but the ability to perform these behaviors in adequate sequences and the appropriate contexts (28,146,235). This hypothesis is supported by observations that the coherence of behavioral (including play) patterns increases when rats mature (146,187,205). Summarizing, social play behavior facilitates different aspects of social development, all of which contribute to the acquisition of adequate social functioning.

2. THE NEUROBIOLOGY OF SOCIAL PLAY BEHAVIOR IN RATS

2.1. Pharmacological studies

For a summary of drug effects on social play behavior, see Table 1.

2.2. Acetylcholine

Scopolamine, the muscarinic cholinergic antagonist, blocked social play (16,190,228,242,266). In fact, scopolamine treatment reduced both initiation of social play as well as reactivity to play initiation (190). Treatment with scopolamine increased (228,242) or did not affect (16,190) social investigation and motor activity, indicating that the suppressive effect of scopolamine was specific for social play. The effect of scopolamine was exerted in the central nervous system (CNS), since methylscopolamine, which hardly crosses the blood-brain barrier, did not influence social play (16,242,266). With repeated administration, tolerance was observed to the social play-blocking effects

of scopolamine (242) and, upon withdrawal, social play actually increased (243). However, from an ensuing study (266), it appeared that the muscarinic cholinergic agonists pilocarpine and arecoline also depressed play. In addition, it was shown that administration of combinations of the agonists and antagonists produced additive rather than counteractive effects.

Drugs acting on nicotinic acetylcholine receptors also affect social play. Nicotine dose-dependently depressed social play, whereas a nicotine receptor antagonist, mecamylamine, slightly increased social play behavior. Mecamylamine, but not scopolamine, pretreatment was capable of abolishing the nicotine's depressing effect on social play (185).

2.3. Adenosine

Caffeine, an adenosine antagonist, depressed social play (108–110) as well as play soliciting (241). The suppressing effect of caffeine on social behaviors seemed to be specific for social play, since caffeine increased social investigation as well as motor activity (108). Upon repeated caffeine administration, social play increased (109). However, it is doubtful that adenosine systems are involved primarily in the regulation of social play behavior, since the adenosine agonist, 2-chloroadenosine, also depressed play, whereas combined administration showed a competitive action of the two drugs (110).

2.4. Catecholamines

In this section, studies using drugs affecting both dopamine and noradrenaline systems are discussed. Drug studies aimed at influencing only one of these systems are discussed in the following two sections.

In a variety of studies, it was shown that amphetamine, which stimulates the release and inhibits the reuptake of catecholamines, profoundly depresses social play behavior (18,22,23,72,112,234) and play soliciting (75,234,241). Similar to the effects of scopolamine and caffeine, amphetamine treatment increased social investigation (23,112,234) and motor activity (234). Methylphenidate, a drug with pharmacologically similar properties to amphetamine, also depressed play soliciting (241), social play, and increased social investigation (23).

The mechanism through which amphetamine depresses social play is unclear. Its social play-depressing effect is exerted in the central nervous system, since a form of amphetamine that poorly penetrates the blood-brain barrier could not mimic amphetamine's effects. In addition, adrenal medullectomy or 6-hydroxydopamine (6-OHDA)-induced peripheral sympathectomy did not influence social play and did not disrupt the potency of amphetamine to depress it (18). The decrease of social play caused by amphetamine could not be prevented by pretreatment with the dopamine antagonists haloperidol or chlorpromazine, the noradrenaline antagonists phenoxybenzamine or propranolol, the α_2 -noradrenergic agonist clonidine or with the catecholamine synthesis inhibitor α -methyltyrosine (22). Therefore, it can be doubted whether amphetamine suppresses social play through interactions with catecholamine systems. In addition, reduction of brain serotonin function by pretreatment with para-chloro-phenylalanine (PCPA)

TABLE 1
DRUG EFFECTS ON SOCIAL PLAY BEHAVIOR IN JUVENILE RATS

Drug	Action	Effect	Dose (mg/kg)	Reference
Pilocarpine	Muscarinic ACh agonist	↓	5.0–15	(266)
Arecoline	Muscarinic ACh agonist	↓	5.0–10	(266)
Scopolamine	Muscarinic ACh antagonist	↓	0.125–4.0	(16,190,228,242,266)
Nicotine	Nicotinic ACh agonist	↓	0.125–0.5	(185)
Mecamylamine	Nicotinic ACh antagonist	↑	0.125–0.5	(185)
2-Chloroadenosine	Adenosine agonist	↓	1.0–10	(110)
Caffeine	Adenosine antagonist	↓	10–40	(108–110)
Apomorphine	DA agonist	↓	0.06–0.1	(165)
Apomorphine	DA agonist	↑	0.125–0.25	(22)
Quinelorane	D2–DA agonist	↑	0.003	(221)
Quinelorane	D2–DA agonist	↓	0.03–0.1	(221)
7-OH-DPAT	D3–DA agonist	–	0.003–0.1	(221)
Chlorpromazine	DA antagonist	↓	0.5–5.0	(22,72,112)
Haloperidol	D2–DA antagonist	↓	0.025–10	(22,110,165)
Amphetamine	DA/NA releaser	↓	0.125–1.0	(18,22,23,72,112,234)
Methylphenidate	DA/NA releaser	↓	0.5–4.0	(23)
DE γ E	Putative DA reuptake inhibitor	↑	0.05	(165)
α -Methyltyrosine	DA synthesis inhibitor	↓	50	(22)
Ephedrine	α -, β -NA agonist	↑	10–80	(22)
Phenoxybenzamine	α -NA antagonist	↓	10–20	(22)
Propranolol	β -NA antagonist	↓	20	(22)
St 587	α_1 -NA agonist	–	0.5–1.0	(219)
Prazosin	α_1 -NA antagonist	↓	0.1–1.0	(219)
Clonidine	α_2 -NA agonist	↓	0.0005–0.2	(22,170)
Yohimbine	α_2 -NA antagonist	–	0.3–5.0	(170)
Idazoxan	α_2 -NA antagonist	↑	1.0–8.0	(218,219)
RX821002	α_2 -NA antagonist	↑	0.05–0.4	(219)
Fluprazine	5-HT _{1B/2C} agonist	↑	4.0	(176)
Quipazine	5-HT ₂ agonist	↓	1.0–10	(169)
Methysergide	5-HT _{1B/1D} antagonist	↓	5.0–10	(169)
Fenfluramine	5-HT releaser	↓	1.0	(183)
PCPA	5-HT synthesis inhibitor	–	100	(183)
Morphine	μ -Opioid agonist	↑	1.0	(165,171,180,181,222,259,260)
Methadone	μ -Opioid agonist	↑	0.3	Present study
Fentanyl	μ -Opioid agonist	↑	0.01–0.03	(257)
β -Endorphin	μ -Opioid agonist	↑	0.001–0.01	(165)
Naloxone	μ -Opioid antagonist	↓	0.5–10	(19,171,180,181,216,217,222)
Naltrexone	μ -Opioid antagonist	↓	0.1–1.0	(115,165)
β -Funaltrexamine	μ -Opioid antagonist	↓	3.0	(257)
BUBUC	δ -Opioid agonist	–	0.1–1.0	(257)
Naltrindole	δ -Opioid antagonist	–	0.3–3.0	(257)
U50,488H	κ -Opioid agonist	↓	1.0–3.0	(257)
Nor-binaltorphimine	κ -Opioid antagonist	–	0.1–3.0	(257)
Chlordiazepoxide	Benzodiazepine agonist	(↑)*	5.0	(183)
Picrotoxin	Cl [–] -channel blocker	↓	0.5	(183)
γ -OHBA	GABA agonist	↓	200–400	(183)
Pentobarbital	Barbiturate	↓	5.0	(183)
Pentobarbital	Barbiturate	↓	20.0	(183)
Ethanol	Various	↑	1.0	(183)
Ethanol	Various	↓	2.0–4.0	(183)
MK-801	NMDA antagonist	↑	0.025	(220)
MK-801	NMDA antagonist	↓	0.1–0.2	(220)

See text for a detailed description of effects. Note that only acute effects, and no interactions between drugs or effects of repeated treatment, are listed. Symbols: ↑, increase; ↓, decrease; –, no effect. Abbreviations: ACh, acetylcholine; DA, dopamine; NA, noradrenaline; 5-HT, 5-hydroxytryptamine (serotonin); GABA, γ -aminobutyric acid; NMDA, *N*-methyl-D-aspartate.

*Chlordiazepoxide only increased social play behavior when it was suppressed in a conditioned emotional response paradigm.

also failed to affect the effect of amphetamine on social play (183).

Prenatal treatment with cocaine decreased social play behavior (270). The neurobiological bases for these effects require further investigation. Prenatal cocaine treatment, in similar dose regimens as employed in the aforementioned study, affects the functioning of dopaminergic (3,46,68,153,212,230), serotonergic (4) and opioid systems (55,90), although these findings are not universal (62,99).

Interestingly, prenatal cocaine treatment also has been shown to disrupt the reinforcing efficacy of cocaine (100,101), suggesting that prenatal cocaine treatment might cause dysfunctioning of reward pathways.

Neonatal intraventricular injection of 6-OHDA disrupted the organization of social play as lesioned rats did not respond to play initiation in an appropriate way (189). This treatment resulted in an almost complete depletion of dopamine in the caudate putamen and nucleus accumbens.

Noradrenaline levels also were reduced in these brain areas, whereas serotonin levels were increased. Since neonatal 6-OHDA treatment affected all monoamine systems in caudate putamen and accumbens, this study yields more information about a possible involvement of these brain structures in the regulation of social play than about the neurotransmitter system involved.

2.5. Dopamine

Reduction of dopaminergic neurotransmission decreased social play behavior. Treatment with the catecholamine synthesis inhibitor α -methyltyrosine slightly decreased social play (22). Decreases of social play also have been found upon treatment with blockers of dopaminergic transmission, such as chlorpromazine (22,72,112) or haloperidol (22,110,165), as well as low doses of apomorphine (165), that decrease dopaminergic activity through interaction with presynaptic dopamine receptors. The effect of a low dose of apomorphine could be counteracted by pretreatment with haloperidol in a dose that in itself did not affect pinning but increased social grooming (165). The non-opioid neuropeptide des enkephalin- γ -endorphin (DE γ E), that blocks the effects of low doses of apomorphine in other behavioral tests (254) did not antagonize apomorphine's depressant effect on social play. The DE γ E itself, which is thought to act as a functional antagonist on presynaptic dopamine receptors (254), or to block the reuptake of dopamine (208,264), increased social play (165). Stimulation of dopaminergic function by treatment with higher doses of apomorphine, acting at postsynaptic dopamine receptors, increased social play (22). In a recent study, the involvement of dopamine D2 and D3 receptor types was investigated. It appeared that treatment with the D3 receptor agonist 7-OH-DPAT did not affect social play. The D2 receptor agonist quinolorane had biphasic effects on social play: low doses increased, while higher doses decreased, social play behavior, suggesting that dopamine might act at D2 receptors to regulate social play behavior (221). In addition, turnover rates of forebrain dopamine have been found to be increased upon social play (176). It seems, therefore, that social play behavior is accompanied by increases in forebrain dopaminergic neurotransmission.

2.6. Noradrenaline

The aspecific (α and β) adrenergic agonist ephedrine, the α -antagonist phenoxybenzamine, the α_2 -agonist clonidine, and the β -antagonist propranolol all decreased social play (22), although these effects were found using relatively high doses of the various drugs. In another study, low doses of clonidine depressed play, an effect that was reversible by pretreatment with the α_2 -antagonist yohimbine. Yohimbine itself hardly affected social play; at the highest dose tested, yohimbine slightly decreased social play (170). Idazoxan, a more specific α_2 -antagonist, increased pinning, play solicitation and motor activity (218). In a follow-up study (219), the α_2 -antagonists idazoxan and RX821002 increased social play behavior and either did not affect (idazoxan), or increased (RX821002), play solicitation. Prazosin was found to reduce social play behavior and play solicitation. This effect probably was mediated through blockade of α_1 -adrenoceptors, because the α_1 -agonist St 587, which itself

did not affect social play, attenuated the effects of prazosin. Since α_2 -adrenoceptors mainly are localized presynaptically and α_1 -adrenoceptors postsynaptically, it was concluded that an increase of noradrenergic neurotransmission by blockade of presynaptic α_2 -adrenoceptors enhanced, whereas decrease of noradrenergic neurotransmission by blockade of postsynaptic α_1 -adrenoceptors decreased social play (219). However, since depletion of brain noradrenaline, depending on the procedure employed, only slightly decreased or did not influence social play (183), a primary role for noradrenergic systems in the regulation of social play is questionable.

2.7. Serotonin

Quipazine, a serotonin (5-hydroxytryptamine; 5-HT)₂ agonist, reduced pinning, an effect that could be attenuated by pretreatment with the 5-HT_{1B/1D} antagonist methysergide. At higher doses, however, methysergide itself also reduced social play (169). The 5-HT_{1B/2C} agonist fluprazine increased social play behavior (176). Treatment with parachloro-phenylalanine (PCPA), or a low tryptophan diet, used to decrease brain serotonin neurotransmission, did not affect play. Interestingly, fenfluramine, a serotonin releasing agent, was very powerful in inhibiting play, an effect that was even observed in PCPA-pretreated animals (183). These data seem to exclude a specific role for serotonin systems in play, but studies with receptor-specific serotonin drugs are needed to resolve this issue.

2.8. Opioids

Treatment with the μ -opioid receptor preferring agonists morphine (165,171,180,181,222,259,260), methadone (Fig. 1), fentanyl (257) or β -endorphin (165) enhanced social play behavior. Accordingly, treatment with the aspecific opioid antagonists naloxone or naltrexone (at very low doses, suggesting that these effects were mediated through μ -opioid receptors, (165) reduced social play (19,115,165,171,180,181,216,217,222), as did treatment with the μ -opioid receptor antagonist β -funaltrexamine and the κ -opioid receptor agonist U50,488H (257). The δ -opioid receptor agonist BUBUC and the δ -opioid receptor antagonist naltrindole had no effects on social play behavior, while treatment with the κ -opioid receptor antagonist nor-binaltorphimine only abolished the initial suppression of social play behavior induced by testing in an unfamiliar environment (see below) (257).

In contrast to the other classes of drugs, the nature of the effects of opioids on social play has been more thoroughly investigated. A derivative of naltrexone that does not cross the blood-brain barrier, quaternary naltrexone, did not mimic naltrexone's decreasing effect on play. When quaternary naltrexone was administered into the lateral ventricle, it did reduce play, indicating that opioid effects on social play are mediated in the CNS (115). The preliminary finding that intracerebroventricular treatment with β -endorphin antiserum also reduced social play (Van Ree, unpublished results) adds further evidence to the notion that opioid effects on social play behavior are centrally mediated, and suggests that β -endorphin is among the endogenous opioid peptides involved. The locus in the CNS where opioids exert

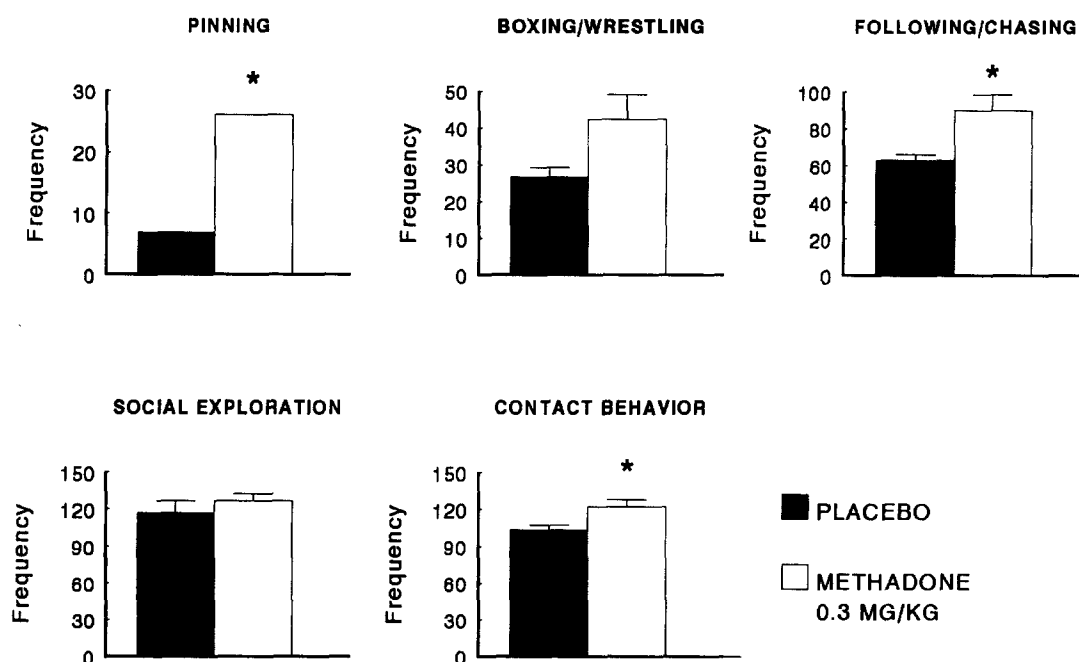


FIG. 1. Effects of treatment with 0.3 mg/kg methadone on the frequencies per 15 min of social behaviors in pairs of juvenile rats. Twenty-one-day-old male Wistar rats were isolated socially for 3.5 h prior to testing and treated s.c. with methadone or placebo 1 h before testing. Both animals of a pair received the same treatment. Testing was performed under dim light/unfamiliar conditions. Behavior was recorded on videotape and scored afterwards by an observer who was unaware of the treatment condition. Social exploration: sniffing any part of the body of the test partner, including the anogenital area. Contact behavior includes crawling over/under the test partner and social grooming. For more details on the experimental procedure (258,259). Data are presented as medians (pinning) or means \pm SEM (other behaviors). *Different from placebo [$p \leq 0.05$, Mann-Whitney (pinning), Student's *t*-test (following/chasing, contact behavior)].

their effects on social play behavior has been investigated using *in vivo* autoradiography (178,262). Upon social play, [^3H]diprenorphine binding was decreased in certain brain areas, suggesting that, during social play, opioid peptides had been released in these areas. The most marked decreases in binding upon social play were found in rostral nucleus accumbens and the paratenial and dorsolateral thalamic nuclei. Opioid binding was increased upon social play in the paraventricular hypothalamic nucleus, which probably represents an effect of the singly testing in control animals, while small, more complex effects were found in claustrum, globus pallidus and arcuate hypothalamic nucleus (262). In an early *in vivo* autoradiographic study, social play behavior was shown to cause decreases in [^3H]diprenorphine binding in central amygdala, periaqueductal gray, dorsomedial and paratenial thalamic nuclei, medial hypothalamus and pre-optic area (178). Other methodologies are most likely underlying the somewhat different results between the two studies. The finding that in both studies the paratenial thalamic nucleus showed decreases in binding upon social play suggests a central role for this nucleus in the central opioidergic regulation of social play behavior. In addition, these studies suggest involvement of various brain areas in the regulation of social play behavior by endogenous opioid systems.

The ability of morphine to increase social play behavior was found to be independent of duration of previous short-term isolation (used to increase levels of social play behavior), suggesting that morphine did not act through increasing social need (259). In addition, morphine treatment increased measures of social behavior related to play (pinning, boxing/wrestling, following/chasing), but not

those unrelated to play (social exploration, crawling over/under, social grooming) (259,260). When the sequential structure of social play behavior was investigated, marked associations between measures of social play behavior (pinning, boxing/wrestling and following/chasing) on one hand, and between social behaviors unrelated to play (social exploration, crawling over/under, social grooming) and non-social behavior on the other were found, corroborating the suggested distinction between measures of social behavior related to play and those unrelated to play (260). Morphine treatment, while markedly increasing the amount of social play behavior, had no major effects on the sequential structure of social play behavior. However, treatment with morphine enhanced the associations between measures of social play behavior, suggesting that treatment with morphine might increase the coherence of social play (260).

Alongside its increasing effect on social play behavior, morphine also attenuated the effects of an unfamiliar environment on social play behavior (259). When juvenile rats were tested for social play behavior in an unfamiliar environment, levels of pinning were reduced in the first 5 min of a 15 min test period, but net levels of social play as analyzed over 15 min were not affected by unfamiliarity to the test cage (258). Treatment with morphine, in a dose $10\times$ lower than the dose that maximally increased social play behavior, attenuated the effects of unfamiliarity to the test cage. Net levels of social play behavior were not influenced by this low dose of morphine; thus, the animals treated with the low dose of morphine behaved in an unfamiliar environment as if they were tested in a familiar environment. In a familiar environment, treatment of rats with the low dose of

morphine had no effect at all. The observation that morphine exerted the two effects on social play behavior at doses differing by one order of magnitude, suggested that those effects were distinct, although the doses employed indicated that both effects were mediated through μ -opioid receptors (259). Remarkably, nor-binaltorphimine, the κ -antagonist, also counteracted the effects of unfamiliarity to the test cage on social play, suggesting a κ -opioid receptor involvement in this effect as well (257).

It has been postulated that opioids might be involved in the mediation of feelings of social comfort, since opioids reduce distress vocalizations (DVs) (179). Enhanced social comfort, caused by opioid treatment, could increase social assertiveness. Apart from increasing social play, morphine slightly increased dominance in subordinate animals and naloxone, apart from decreasing social play, markedly increased submissiveness in dominant animals (181). However, the criterion used for defining dominance in this study (which rat pinned which the most), should be regarded with caution (194,195,197). The notion that opioid antagonists might increase feelings of social need was supported by the finding that naloxone treatment slightly increased play solicitation behavior (185), although another study failed to show similar phenomena (19).

Chronic neonatal treatment with naloxone or morphine respectively enhanced or delayed sensorimotor and behavioral development in young rats (159). It was found that chronic neonatal morphine delayed the developmental increase in social play behavior (159), which probably reflects opiate-induced retarded development (274,275). Interestingly, chronic prenatal morphine administration, in doses that did not affect sensorimotor development, enhances social play behavior (166,167).

2.9. Miscellaneous

Treatment with the benzodiazepine chlordiazepoxide only influenced social play when it was suppressed using a conditioned emotional response paradigm. Treatment with chlordiazepoxide during acquisition partially reversed the suppression of play, and enhanced recovery of social play

during extinction. Treatment with chlordiazepoxide during extinction had no effect (183). These effects probably are due to anxiolytic properties of chlordiazepoxide. A similar effect of chlordiazepoxide on social interaction in adult rats has been shown (77). The GABA antagonist picrotoxin slightly reduced play, whereas the GABA agonist γ -OHBA markedly reduced play. Central nervous system depressants, such as pentobarbital and ethanol, as well as the non-competitive NMDA channel blocker MK-801, stimulated social play at low doses, and depressed social play at higher doses (183,220). MK-801 dose-dependently increased and decreased, horizontal and vertical activity, respectively, suggesting that general motor effects of MK-801 cannot account for its effects on social play behavior. A possible explanation for these results is a general disinhibitory state induced by low doses of MK-801, ethanol and pentobarbital, whereas higher doses of these substances induce a behavioral state that is incompatible with the behavioral coordination required for the appropriate performance of social play behavior.

2.10. Anatomical studies

For a summary of the effects of brain lesions on social play behavior, see Table 2.

2.11. Cortex

Since social play behavior is most apparent in mammals, and mammalian species have a more elaborated cerebral cortex than non-mammalian species, it was suggested that cortical areas might subserve a crucial role in the regulation of play. Neonatal decortication in rats did not affect the initiation of social play, but decorticated animals appeared hyperactive. Pinning levels were reduced in decorticates because their reaction to play initiation differed from control rats. Juvenile rats mostly react to play initiation by assuming a supine position. This interaction results in pinning. Decorticate rats, however, react to play initiation in a more adult way, i.e. by adopting postures less likely to result

TABLE 2
LESION EFFECTS ON SOCIAL PLAY BEHAVIOR IN JUVENILE RATS

Lesioned area	Method	Effect	Reference
Cortex (parietal)*	Surgical	↓	(184,199)
Nucleus accumbens/caudate putamen*	Chemical	↓	(189)
Amygdala (basolateral, cortical and central)	Electrolytic	↓ (♂) — (♀)	(142)
Septum	Electrolytic	↑	(24,185)
Medial preoptic area	Electrolytic	—	(20,130)
Anterior hypothalamus	Electrolytic	↓ †	(20)
Ventromedial hypothalamus	Electrolytic	↓ †	(20,185)
Dorsomedial thalamus	Electrolytic	↓	(222)
Parafascicular area	Electrolytic	↓	(222,224)
Posterior thalamus	Electrolytic	↓	(224)
Ventrobasal thalamus	Electrolytic	—	(224)
Ventrolateral brain stem	Electrolytic	↓	(224)
Olfactory bulb	Surgical	—	(21)

See text for a detailed description of effects.

Symbols: ↑, increase; ↓, decrease; —, no effect.

*In contrast to the other studies, cortex and nucleus accumbens/caudate putamen lesions were made in neonatal, as opposed to juvenile, rats.

†Anterior and ventromedial hypothalamic lesions decreased play initiation, but not social play.

in being pinned, and shortening the play bout. Thus, in rats, the neocortex is suggested to be involved in the facilitation, but not the initiation of play. The reduced levels of social play in rats with lesions of (mainly the parietal) cortex could be the result of motor as well as somatosensory disturbances, rendering the animals unable to respond appropriately to play initiation (184,199).

2.12. Limbic forebrain

As was already mentioned above, catecholamine depletion of the nucleus accumbens and caudate putamen severely disrupted the organization of social play (189). Patterns of social play behavior were displayed in a normal way, but lesioned rats did not respond to play initiation in an appropriate manner and were very easily distracted. These findings are in accordance with the notion that nucleus accumbens and caudate putamen are involved in the generation of responses to motivationally relevant stimuli (129,154,200,213).

Input to these structures comes, among others, from amygdaloid nuclei (154,213,272,276), lesions of which have been shown to cause severe disruptions of social (119), sexual, and aggressive behavior in rats (140). In these experiments, amygdala-lesioned animals supposedly were unresponsive to social stimuli, consistent with the view that the amygdala is involved in the selection of appropriate responses (87). However, lesions of the amygdala (basolateral, cortical and central nuclei) in juvenile rats only abolished the sexual differentiation of play: as males play more than females, amygdaloid lesions caused social play in males to decrease to the level of females. Lesioning the amygdala did not affect social play in females (142). Accordingly, the sexual differentiation of social play in rats and monkeys seems to be generated by exposure of the amygdala to androgens during the perinatal period (141,143). Apparently, amygdaloid input into striatal areas is not required for the generation of responses to motivational stimuli associated with social play behavior.

Lesioning the septal area increased social play (24,185), which is consistent with increased sociability in adult rats after septal lesions (119). This might reflect the increased probability of emotional responses to environmental or social stimuli after septal lesions, as the septum is supposed to be involved in the inhibition of emotional responses (5,43,82).

2.13. Hypothalamus

As social play for a significant part consists of behaviors related to the aggressive or sexual behavioral repertoire of an animal, it seemed likely that lesions of hypothalamic brain structures, where aggressive (127,128) and sexual (95,130,209) command centers are suggested to be localized, could affect play. Lesioning the medial preoptic area, which causes marked disruptions of sexual (95,130,209) and aggressive behaviors (6), did not affect social play in rats (20,130). Lesions of the anterior and ventromedial hypothalamus, areas where electric stimulation can produce aggression (127,128) decreased play initiation (20). Most likely, lesioning the ventromedial hypothalamus renders animals irritable and unable to respond to play initiation in an appropriate way, since in these animals, social play

escalated disproportionately often into aggression (185). It has been concluded that the ventromedial hypothalamus might be involved in the maintenance of social play by inhibiting aggression (185). Lesion studies have not yet identified a putative hypothalamic social play command center, as has been done for sexual or aggressive behavior (where severe disruption of these behaviors was found after lesioning certain hypothalamic areas (95,127,128,130,209)).

2.14. Thalamus

The involvement of thalamic areas in the regulation of social play has also been investigated. Lesioning the parafascicular (PFA) and dorsomedial (DMT) thalamic areas decreased social play behavior. Furthermore, it rendered animals unresponsive to the effects of morphine (in PFA-lesioned animals) and naltrexone (in both PFA- and DMT-lesioned animals), suggesting that in (projections of) these areas the effects of opioids on social play may be exerted (222). Indeed, the dorsomedial thalamic area seems to be involved in reward-related phenomena (139), and effects of opioids thereon (50). Lesioning of the PFA and related areas was investigated in a subsequent study (224). It appeared that lesioning parts of the extralemniscal system, such as the PFA, the posterior thalamic nucleus and the ventrolateral brainstem (through which fibers of the spinothalamic tract pass on their way to the aforementioned thalamic areas), markedly reduced pinning, but not play initiation. Lesioning the ventrobasal thalamus, an area not associated with the extralemniscal system, had no effect on play. These findings, together with control studies indicating that processing of somatosensory information was in some way disturbed, suggested that lesions of these thalamic areas reduce social play by disrupting the transmission of somatic stimuli related to play.

2.15. Olfactory bulb and sensory systems

Lesioning of sensory systems has been performed to see which form of sensory information was most important in play. It was shown that in contrast to sexual (52,233), aggressive (32,80), or social investigatory behavior (238), olfactory stimuli have a minor role in the generation of social play behavior, or the transmission of signals related to social play behavior. Rendering rats anosmic by rinsing the olfactory epithelium with a zinc sulfate solution reduced social play only when both animals of a dyad were anosmic (239). Neither the potency of social isolation to induce enhanced levels of social play nor the sexual differentiation of social play was affected by anosmia. Lesioning the olfactory bulb did not affect social play behavior or play initiation in male rats, and even increased social play behavior in female rats (21). It has been shown also that tactile stimulation, especially of the nape area, is of major importance for the expression of social play behavior (225). Anesthetizing the nape area with xylocaine rendered animals unresponsive to play initiation. These animals were not disturbed in their play initiation, but were pinned less often than control animals, while they pinned control animals at normal levels. These findings are in line with studies suggesting that pinning is the consequence of a specific initiation-reaction interaction, in which the initiating

animal attempts to nose the partner's nape, while its partner blocks access to its nape by assuming a supine position (188,191). Preliminary lesion studies also indicated a role for auditory but not visual stimuli in play, since experimentally induced deafness, but not blindness, decreased social play (33,225).

2.16. Endocrinological studies: the sexual differentiation of social play behavior in rats

In a variety of studies, using different measurements, it has been shown that male rats play more than female rats (25,34,105,144,146,173,192,205,236,245). It is not quite clear if the difference between males and females is qualitative or merely quantitative.

Male rats have been shown to display and to receive more play-soliciting behavior than females, while there is no sex difference in social investigation (105,240,245). Females are more likely to withdraw from a play initiation and, once involved in play, also are more likely to withdraw than males (146). Males seem to be more attractive play partners than females: male-male pairs display higher levels of social play than female-female or mixed-sex pairs (236) and, in group studies, both males and females played preferably with males (146,205). Prior to the onset of sexual behavior, however, females are a more attractive play target for males (146). It has been suggested also that there is a qualitative difference between male and female social play in rats, as males display more vigorous social behaviors related to play, and females engage more in social grooming (144). In another study, however, no major differences in the sequential organization were found between males and females (205). The differences between male and female social play have been suggested to be quite complex. Males display higher levels of social play initiation than females, whereas the probability for defense is not different between males and females. Males are more likely to counterattack in response to a play initiation than females, and females are more often counterattacked than males (192). In addition, females seem to react earlier (i.e. when the approaching rat is relatively further away) to play initiation than males. This permits females to react in a different way than males (less often rotation to supine, resulting in pinning) (198).

A number of hormonal interventions have been performed to unravel the underlying endocrine mechanisms of social play (for reviews, see (17,141,149). In general, exposure to androgens during the neonatal period (until day 6 of life) is necessary to achieve "male-like" levels of play. If female rats were treated with testosterone during the neonatal period, levels of play soliciting (245), and social play (145,173) increased to the level of male rats. In addition, the greater response distance to play initiation of females could be decreased to male levels by neonatal androgen treatment (198). Accordingly, neonatal castration (25,145,237), or treatment of males with the anti-androgen flutamide (150), reduced social play to the level of females. Male rats with an inherited insensitivity to androgens (Tfm-strain) played less than normal males, and not more than females (150). Castration after day 6 of life did not affect social play in males (25,145). In one study (237), castration on day 10 of life reduced social play, albeit not to the same extent as in males castrated on day 1. In the animals

castrated on day 10, treatment with testosterone after weaning increased social play to the level of untreated animals, while testosterone treatment in neonatally castrated males had no effect on play. Accordingly, treatment after weaning with flutamide, slightly reduced play. Thus, androgens are thought to have an organizational effect on play, although the latter study (237) suggests some activation effects as well. The effects of androgens on social play are "true" androgen effects, and not the result of androgen derived estrogen effects (149). The locus of action of androgens might be the amygdala, as testosterone implants into the amygdala of neonatal female rats increased social play to the level of males (143,246), whereas amygdala lesions in males decreased social play to the level of females, while these lesions had no effect in females (142).

Treatment with corticosterone or dexamethasone during the first 4 days of life decreased social play in males but not in females (148), whereas later treatment (days 9–10 or 26–40 of life) did not affect social play (147,148). These effects of corticosteroids have been attributed to their anti-androgenic effects.

The influence of female sex hormones is less clear. Neither neonatal ovariectomy, nor treatment with estradiol (systemically or into the amygdala) of female rats, nor blockade of the metabolism of testosterone to estradiol or dihydrotestosterone in males affected social play (145,246). It has been reported repeatedly that neonatal progesterone treatment decreased social play (especially play initiation) in both male and female rats (34–36). However, treatment with anti-progesterone antiserum increased social play in males as expected, but decreased social play in females. This effect was attributed to a rebound increase in progesterone release that, in females, caused decreased levels of play. In male rats, the rebound release of progesterone was supposedly overruled by the play-increasing effects of androgens (35).

3. DISCUSSION

Research into the neurobiological backgrounds of social play behavior has been reviewed above. Here, an attempt will be made to integrate the data gathered so far into a hypothesis on the neurobiology of social play behavior in rats. To that aim, the neurobiology of social play behavior will be compared to the neurobiological aspects of other forms of social behavior in rats (social behavior, sexual behavior, aggressive behavior) as well as other rewarded behaviors (such as feeding and non-natural rewards).

The expression of a complex phenomenon like social play behavior involves a wide variety of neuronal systems, so that different aspects of social play are likely to be regulated and/or modulated through different systems. Unfortunately, there has been little thorough research into which aspect of social play is regulated through which system(s). Studies on the involvement of neurotransmitter systems in social play often use too few drugs to yield a clear picture and, in most cases, the drugs studied were administered peripherally, so that one can only speculate on the cerebral locus where these drugs exert their effects on social play behavior. In addition, most studies have measured only one or two parameters of social play (mostly pinning and/or play initiation). The question of which aspect of social play is modulated has actually only been addressed for the reward aspect of

social play, where a role for opioids has been suggested (171,259).

3.1. The reward aspect of social play behavior: role of opioid and dopamine systems

One of the main characteristics of social play behavior is its high reward value. Social play can be used as an incentive for maze-learning (112,171) and conditioned place preference (47,59). It is the interaction between two rats, rather than the initiative of the soliciting animal, that makes social play behavior rewarding; in juvenile rats, interaction with a play partner that does not respond to play soliciting but does display other forms of social interaction, is hardly rewarding (47,112,190).

As opioids have been implicated in reward processes (41,66,126,252,267), opioid systems were suggested to be involved in the regulation of the reward aspect of social play. Indeed, there is both direct and indirect evidence that administration of opioid drugs influences the reward value of social play behavior. In a social play-rewarded T-maze task, treatment with morphine or naloxone did not influence the rate of learning, suggesting that opioid systems are not primarily involved in regulating the motivation for social play. Morphine, however, increased and naloxone decreased social play in the goal box of the T-maze, indicating that opioid systems do influence performance of social play. Furthermore, morphine treatment during acquisition of the task delayed, whereas naloxone enhanced, extinction. Thus, morphine treatment enhanced, whereas naloxone treatment decreased, social play-induced place preference (171), indicating that the reward, most likely consummatory, aspect of social play is modulated by opioids. Except for this direct evidence, there is a wide body of circumstantial evidence to suggest that opioid systems may be involved in the regulation of the reward aspect of social play. Upon social play, differences in *in vivo* opioid receptor binding have been found in the nucleus accumbens and the paratenial thalamic nucleus (262), structures involved in opioid-dependent reward processes (41,66,126,207,215, 231,250,267). Thus, during social play, opioid peptides are released in brain structures implicated in reward processes. In addition, the involvement of different opioid receptor types in the regulation of social play behavior parallels their involvement in reward processes. Similar to reward processes, where μ - and κ -receptors are suggested to work in a functionally antagonistic way (84,157), treatment with μ -opioid receptor-preferring agonists, such as morphine, fentanyl, methadone or β -endorphin, increases (165,171,180,181,222,257,259,260), while treatment with μ -opioid receptor preferring antagonists, such as naloxone, naltrexone, or β -funaltrexamine, as well as with the κ -agonist U50,488H suppresses social play (19,115,165, 171,180,181,216,217,222,257). Under intense light circumstances, when social play is suppressed completely, treatment with morphine does not restore social play behavior (259). If morphine increases social play by enhancing its reward properties, morphine treatment could be without effect if social play is not performed (and social play reward is not available). Also, morphine increased social play without markedly altering the sequential structure of social play (260). This indicates that morphine acts by increasing social play as a whole, rather than by

influencing behavioral elements that could secondarily increase social play, which are likely to lead to marked alterations in the sequential structure of social behavior. This suggests that morphine acts directly upon a physiological mechanism underlying the performance of social play behavior (e.g. its motivational and/or reward aspect). Finally, social play, but not social behaviors unrelated to play, has a high reward value in juvenile rats (47,112); accordingly, treatment with opioid drugs increases social behaviors related, but not those unrelated, to play (257,259,260).

The cerebral circuitry through which opioids affect the reward component of social play behavior is not clearly established. There are various structures in the brain via which opioids are suggested to influence reward processes (for review, see (126)). The finding that in the nucleus accumbens opioidergic activity is increased upon social play (262) suggests that this area (suggested to be involved in opioid-dependent reward processes, (41,66,126,207, 215,267) is implicated. Reward processes mediated via the nucleus accumbens have been suggested to involve both dopaminergic and non-dopaminergic systems (66). The dopaminergic system involved is the mesocorticolimbic dopamine system, the cell bodies of which are located in the ventral tegmental area (VTA), with projections to limbic forebrain structures, such as the nucleus accumbens, septum, central amygdala and medial prefrontal cortex (60,92,129,156,213). This system generally is accepted to be implicated in motivational and/or reward processes (66,126,129,202,213,215,267,268). Opioids act indirectly upon this system, primarily through μ - and, to a lesser extent, δ -opioid receptors, inhibiting inhibitory GABAergic interneurons in the VTA, thus indirectly stimulating the activity of VTA dopaminergic neurons (64,94,118,120, 138,229). The exact anatomical properties of the non-dopaminergic, possibly opioidergic, pathway are not known. Regarding the role of opioids in reward processes, research on the involvement of the VTA–accumbens pathway generally has focused on the VTA. For instance, rats self-administer opioids into the VTA (42,253,263), and opioid infusion into the VTA can be used to establish conditioned place preference (14,215). However, there is also evidence that opioid systems in the accumbens mediate reward processes. Rats self-administer opioids into the accumbens (88,172), and injection of morphine (251) or naloxone (214) into the accumbens elicited a conditioned place preference and aversion, respectively. Also, although there is some controversy about this issue (248,268), there is a fair amount of data to suggest that reward aspect of opioids themselves might not primarily involve mesolimbic dopamine mechanisms (26,69,73,86,98,201,256). The non-dopaminergic accumbal reward circuit might involve efferent projections of the accumbens, such as ventral pallidum and substantia nigra (91,92,227,271). Recently, a role for opioids in two phases of rewarded behavior has been postulated (66). During the preparatory phase, which seems to involve primarily dopaminergic mechanisms (66,202), opioids exert their effects indirectly, namely by influencing dopaminergic activity. Consummatory aspects of rewarded behaviors (both natural and non-natural rewards) seem to involve directly endogenous opioid systems (10,12,66) (e.g. in the accumbens, (12,70,201,249) or ventral pallidum, (111,117,126).

Experimental data suggest that both dopaminergic and non-dopaminergic circuits may be involved in the regulation of the reward aspect of social play. The findings that forebrain dopaminergic turnover was enhanced upon social play (176) and, similar to social play behavior, activity of dopaminergic neurons projecting to the nucleus accumbens was increased by μ - and decreased by κ -opioid-receptor stimulation (65,94,132,229), argue in favor of mesolimbic dopaminergic involvement in the regulation of the reward aspect of social play behavior. In addition, septal lesions increased both social play (24,185) and accumbens dopamine activity (89). The observations from pharmacological studies that stimulation of dopaminergic neurotransmission increased social play (22,165) might reflect dopaminergic involvement in the motivational and/or reward aspect of play. However, several drugs that have been found to increase (mesolimbic) dopamine release, such as amphetamine (see above, but also see (22), the κ -opioid antagonist nor-binaltorphimine (229) (see above) or nicotine (57,65,168,273) (see above) did not increase, or even decreased social play. Thus, while social play behavior is accompanied by increases in forebrain dopamine turnover, stimulation of dopaminergic neurotransmission might not always be sufficient to increase social play. It might also be that while administration of nicotine or amphetamine does stimulate mesolimbic dopamine release, other effects of these drugs in the brain (for instance, nicotine's effects on cholinergic neurotransmission) induce a behavioral state in which social play is inhibited. In this respect, it is worth noting that while the κ -opioid antagonist nor-binaltorphimine increases accumbal dopamine release, it has no reward-enhancing effects (27,51,84,161). Opioid systems influence forebrain dopaminergic activity through disinhibition of dopaminergic neurons in the cell body areas (64,94,118,120,138,229). If opioids exerted their effects on social play behavior mainly through activation of the mesolimbic dopaminergic pathway, one would expect that, upon social play, opioid activity would be increased in the cell body areas of the dopamine projections to the limbic forebrain (VTA), instead of in the terminal areas (accumbens), which is what was actually found (262). This suggests that opioids exert their effects on social play reward not primarily through dopaminergic mechanisms. The increased forebrain dopamine turnover found upon social play might then reflect the increases in mesocorticolimbic dopaminergic activity that take place during motivational or preparatory phases of social play behavior, as also has been found for feeding, sexual behavior and cocaine self-administration (124,202). However, the social play-induced increases in forebrain dopamine turnover are probably not opioid-mediated. There are behavioral data available to suggest that opioids exert their effects by increasing the consummatory, but not the motivational aspect of social play reward (171). According to the aforementioned, recent hypothesis (66) this would imply that the effects of opioid treatment on social play behavior are not mediated primarily through dopamine systems, but rather directly through opioid systems.

There is some additional information available on the cerebral circuitry underlying opioid-dependent social play reward. Upon social play, opioidergic activity was enhanced in the paratenial thalamic nucleus, which is involved in opioid-dependent reward processes (231,250). The nucleus

paratenialis sends projections to the accumbens (31,49,122), and receives projections from the ventral pallidum (54), which has reciprocal connections with the accumbens (91,92,227,271). Lesioning the dorsomedial (DMT) and parafascicular (PFA) thalamic areas not only decreased social play, but also rendered animals unresponsive to the effects of opioids on social play (222). Both PFA (151,186) and (indirectly, via the prefrontal cortex) DMT (92,154,213) send projections to the accumbens. These observations suggest that opioid influences on social play are mediated through circuits involving the accumbens and thalamic areas. Responses to motivationally relevant stimuli have been suggested to be generated through circuits involving neocortical, striatal and thalamic areas (92,126,154,155,213). The clarification of the involvement of such circuits in the regulation of social play behavior deserves further research.

3.2. Integration of environmental and sensory stimuli associated with social play behavior; role of opioid, cholinergic and noradrenergic systems

Noradrenergic and cholinergic systems have been implicated widely in cognitive processes such as attention, arousal and integration of environmental and sensory stimuli. The function that cholinergic mechanisms have in cognitive processing (2,56,63,74,96,211) may be the locus of their involvement in the regulation of social play. Blockade of cholinergic neurotransmission might disrupt the ability to respond to a play partner in an appropriate way. Indeed, treatment with the muscarinic antagonist scopolamine blocked social play behavior (16,190,228,242,266). Noradrenergic systems, through their involvement in behavioral arousal and attention (8,9,61,133,210) might be involved in the regulation of social play (219). The effects of caffeine on social play may be explained by its psychostimulant effects (162), and the behavioral effects of caffeine treatment have been suggested to involve noradrenergic systems (13).

There are also some data available on a possible opioid influence on the integration of environmental stimuli associated with social play. Treatment with a low dose of morphine, as well as with the κ -opioid receptor antagonist nor-binaltorphimine attenuated the unfamiliarity induced initial suppression of social play (257,259). When rats are tested for social play in an unfamiliar test cage, they will explore the test cage before engaging in social play, which leads to an initial suppression of pinning and boxing/wrestling, while total levels of social play are not affected (258). In other words, the opioid-treated animals displayed a time course of social play under unfamiliar conditions as if they were tested in a familiar test cage. The fact that morphine exerted its effects on social play behavior at doses differing by one order of magnitude, as well as the involvement of κ -opioid receptor systems, suggested that this effect was not just an epiphenomenon of opioid effects on the reward aspect of social play. An opioid-induced shift in selective attention due to altered integration of sensory stimuli (8) could underlie this effect; under normal circumstances, rats explore an unfamiliar environment before engaging in social play. Recently, the interaction between cholinergic and opioid systems in the regulation of cognitive processes has been investigated using a spontaneous alternation task. While blockade of muscarinic acetylcholine

receptors and stimulation of μ -opioid receptors impaired, stimulation of κ -opioid receptors improved performance (113,114). These findings parallel the involvement of μ - and κ -opioid receptors in the cognitive processes associated with social play (257).

Both cortical and amygdaloid areas are candidates for a possible neuroanatomical substrate for opioid, cholinergic and noradrenergic regulation of social play, because of their proposed role in the integration of sensory information and in attentional processes (58,121,211,247). Naloxone has been shown to enhance, and morphine to decrease selective attention, probably by altering the activity of brain noradrenergic activity (8). In this respect, it is worth noting that μ -opioid receptor stimulation reduced the release of noradrenaline and acetylcholine in the amygdala, and noradrenaline release in the cortex (81,158). One might, therefore, speculate that the effects of a low dose of morphine involve cortical and/or amygdaloid noradrenergic or cholinergic systems; note that lesions of the neocortex have indeed been found to suppress social play, suggested to be because decorticate rats were unable to respond appropriately to play initiation (184,199). The effect of morphine on the integration of environmental stimuli is most likely not mediated in the ventral tegmental area, since μ -opioid receptors in the ventral tegmental area have been shown not to be involved in behavioral adaptation to a novel environment (48). It is unclear whether morphine and nor-binaltorphimine act at similar or different sites in the brain to counteract the effects of unfamiliarity. In the rat, the major output system of the amygdala, the central nucleus (247), predominantly contains κ -receptors (135,136). Thus, nor-binaltorphimine might exert its effects in the central amygdala. In adult rats, amygdaloid opioid systems have been implicated in the normalization of environmentally induced changes in behavior (78,104,269).

3.3. Comparison to social, sexual, and aggressive behavior: neurobiological differences

In juvenile rats, social activities in general have been shown to be different from social play (47,107, 112,171,185). In addition, although social play consists of behaviors resembling social, aggressive, or sexual behavior, social play differs from these behaviors regarding structure (38,39,146,188,191,196,204,236) and contextual settings (1,106). In the previous sections, evidence has been presented that social play behavior also represents a separate category of behavior on the neurobiological level.

In juvenile rats, social play is decreased by scopolamine (16,242), amphetamine, methylphenidate (23) and caffeine (108) or neonatal 6-OHDA striatal lesions (189) while these treatments did not affect or even increased social investigation. Morphine treatment increases social play but not social behaviors unrelated to play (259). When the sequential structure of social play was analyzed, the dissociation between social behaviors related and unrelated to play was confirmed (260). Thus, social behavior in juvenile rats is suggested to be heterogenous, and can be divided into social behaviors related and those unrelated to play.

These categories of behavior differ regarding appearance during ontogeny, where social behaviors related to play

mainly occur before sexual maturation (11,40, 105,175,177,205), while other forms of social behavior occur during the entire lifespan of rats. Furthermore, these categories of social behavior are suggested to be regulated through different neuronal systems (16,23,108,119, 142,189,242,259).

When data on the effects of opioids on social play in juvenile rats and social behavior in adult rats are compared, it is striking that the effects on social play are more pronounced (see above). Opioid agonists increase and opioid antagonists decrease social play, while studies on the effects of opioids on social interactions in adult rats do not yield consistent results (76,78,152,160,163,164,182,203,255). In addition, treatment of juvenile rats with morphine resulted in an increase of social behaviors characteristic for play (pinning, boxing/wrestling, following/chasing), but not social exploration and contact behavior (259). While opioids have been suggested to regulate the reward value of social play (171), social play, but not a social interaction per se, has a high reward value in juvenile rats (47,112,171). Furthermore, social interaction in adult rats and social play behavior in juvenile rats evoke different patterns of changes in *in vivo* opioid receptor binding (261,262). Amphetamine, which suppressed social play behavior, also has been shown to suppress social behavior in adult animals whilst increasing motor activity (7,232), but only at high doses, since lower doses that do also increase motor activity had no effects on social behavior (163). Interestingly, the effects of high doses of amphetamine on social behavior in adult rats could not be counteracted by treatment with clozapine or haloperidol (which itself also suppressed social behavior) (232). Amphetamine, as well as scopolamine, did not affect aggressive behavior (127), while fluprazine, that stimulates social play, inhibits aggression without influencing other social behaviors (79,127). Lesioning brain areas important for the expression of social and sexual behavior (amygdala, (119,125) and medial preoptic area, (95,130,209), respectively) hardly affected social play behavior (20,130,142). Regarding aggressive behavior, lesioning the ventromedial hypothalamus (an area in which a command center for aggression is suggested to be localized, (127,128) did affect social play (20,185), albeit that these results did not reveal neuronal similarities between social play and aggression. Stimulation of the ventromedial hypothalamus can produce aggression. Lesioning that area renders animals irritable, as play initiation disproportionably often escalated into aggression, suggesting that lesioning the ventromedial hypothalamus in juvenile rats induces some form of aggression as well. Perhaps the most striking difference between social play and other social behaviors is that olfactory bulbectomy, which severely disrupts sexual behavior (209) and increases aggressive behavior (15,67), has no marked effects on social play (21). The main conclusion drawn from these studies is that social play behavior differs from social, sexual and aggressive behavior regarding neuronal organization, which supports the hypothesis that social play represents a separate category of behavior.

4. CONCLUSIONS

In the present paper, research on the neurobiological aspects of social play behavior is reviewed and information

on the structure and function of social play behavior and the importance of social play behavior for behavioral development is provided. In addition, hypotheses on the neuronal bases of the sexual differentiation and reward aspects of rat social play, as well as cognitive processing involved in social play have been put forward.

As social play is suggested to be of paramount importance for the social development of animals, further research is warranted to understand how social play evokes changes in the architecture of the brain and thus how animals become equipped adequately for adult social functioning. Matters to be addressed include for instance: which exactly are the changes evoked by social play, and what is the role of neuronal systems responsible for the occurrence and maintenance of social play in social development? Neurobiological aspects of social play behavior might also be of interest for those investigating human disorders involving

disturbances in social (play) behavior, such as juvenile autism, attention deficit hyperactivity disorder, depression and schizophrenia (37,44,45,83,116,123). For example, the involvement of opioid systems in social play behavior has led several researchers to investigate the possible therapeutic effects of opioid antagonists in autistic patients (53,131,174,265). Although social play behavior is important for behavioral development, until now relatively little research has been devoted to the neurobiological bases and consequences of social play. It is our opinion that this form of behavior deserves a more prominent place in brain research.

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