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European Journal of Pharmacology 526 (2005) 226–239
www.elsevier.com/locate/ejphar

Do similar neural systems subserve aggressive and sexual behaviour in male rats? Insights from c-Fos and pharmacological studies

Jan G. Veening [a,b,*], Lique M. Coolen [c], Trynke R. de Jong [a,b], Henk W. Joosten [a], Sietze F. de Boer [d], Jaap M. Koolhaas [d], Berend Olivier [b,e]

[a] Department of Anatomy, University Medical Center St Radboud, Nijmegen, The Netherlands
[b] Department of Psychopharmacology, Utrecht Institute for Pharmaceutical Sciences and Rudolf Magnus Institute of Neurosciences, Utrecht University, Utrecht, The Netherlands
[c] Department of Cell Biology, Neurobiology, and Anatomy, University of Cincinnati, Cincinnati, OH 45267-0521, USA
[d] Department of Animal Physiology, University of Groningen, P.O. Box 14, 9750 AA Haren, The Netherlands
[e] Department of Psychiatry, Yale University School of Medicine, Park Street, New Haven, CT, USA

Accepted 23 September 2005
Available online 2 November 2005

Abstract

It is a common belief that male aggressive and sexual behaviour share many of the underlying neurobiological, neurological, pharmacological and neuroendocrine mechanisms. Therefore, we studied brain activation patterns in male rat after performance of aggressive and sexual behaviour and compared serotonergic pharmacology in the same paradigms to delineate possible similarities and differences.

Patterns of Fos-immunoreactivity induced by aggressive and sexual encounters of Wild-type male Brown Norway rats were studied to localise the commonly activated (functionally shared) parts of the circuitry, and the specific (functionally different) parts of the neuronal circuitry. Some brain areas (caudal medial preoptic area and medial amygdala) were commonly activated, but other areas (e.g. posterodorsal parts of the medial amygdala, rostral preoptic and premammillary hypothalamus) showed remarkably specific differences in neural activation. 5-HT_{1A} receptor agonists inhibit aggressive, but stimulate male sexual behaviour, whereas 5-HT_{1B} receptor agonists inhibit both types of behaviour. Selective serotonin reuptake inhibitors share comparable inhibitory effects in aggression and sexual behaviour, although only at relatively high doses.

We propose that separate hard-wired neural systems exist in the brain for aggressive and sexual behaviours, modulated via hierarchically 'higher-level' brain areas that are involved in the integration (gating) of the behavioural outcome of an organism.

Keywords: Aggression; Sexual behaviour; Neural mechanism; c-Fos; Serotonin; Pharmacology; Male (Rat)

1. Introduction

It is a wide spread belief that male aggressive and sexual behaviour share many of the underlying neurobiological, neurological, pharmacological and neuroendocrine mechanisms (Pedersen, 2004). For example, both types of social behaviour depend on the presence of gonadal steroids such as testosterone and oestradiol. Moreover, both behaviours are accompanied by strong emotional responses such as increased heart rate and blood pressure (Bouwknecht et al., 2001; Meerlo et al., 1999; Sgoifo et al., 1999). Newman (1999) argued that the neurobiology of aggression is embedded in a larger integrated network involved in various forms of social behaviour including male sexual behaviour and parental behaviour. This would imply that the neural circuitry involved in each of these behaviours consists, on the one hand, of a number of commonly activated brain areas (sensitive to olfactory, endocrine or other common cues), and on the other hand of brain areas with a specific function or a selective role in each behaviour separately. In the vomeronasal circuitry such 'specificity' seems to exist (Kumar et al., 1999).

If this view is correct, it is surprising that very few studies focussing on aggression directly address the question of

* Corresponding author. Department of Anatomy, University Medical Center Nijmegen, P.O. Box 9101, 6500 HB, The Netherlands. Tel.: +31 24 3614298; fax: +31 24 3613789.
E-mail address: j.veening@anat.umcn.nl (J.G. Veening).

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doi:10.1016/j.ejphar.2005.09.041

behavioural specificity of the mechanisms under study. The interpretation of the behavioural consequences of experimental manipulations would greatly benefit from the use of a wider range of behavioural tests allowing a conclusion on the behavioural specificity of the manipulation. Along this line of reasoning, one may wonder which part of the neuronal network underlying aggressive behaviour should be considered as belonging to a more integrated network controlling social behaviour in general.

The present study was first aimed at a direct comparison between the patterns of brain activation during male aggressive and sexual behaviour. To this end we applied immunoreactivity for the transcription-factor Fos to see which brain areas are specifically involved in aggressive and sexual behaviour; and second aimed at comparing the serotonergic pharmacology of sexual behaviour and aggressive behaviour of male rats. Although this seems a limited approach, the serotonergic system appears a prime substrate involved in both types of behaviour and is one of the best-investigated areas thus far.

1.1. Aggression and sexual behaviour: comparison of Fos-activation in the CNS (central nervous system)

Male rats display aggressive behaviour under a variety of conditions (Olivier and Young, 2002), but the present study only focuses on the situation in which a residential male defends his territory against an intruder-male (the 'resident–intruder' paradigm). A virtually identical situation was used for male sexual behaviour, i.e. instead of a male; a receptive female of the Wistar strain was introduced into the cage of the resident. In this situation extensive 'anogenital investigation' occurs, followed by copulatory activities like mounting and intromissions, but no ejaculations.

This experimental setup allowed a comparison of the pattern of Fos-immunoreactivity induced by aggressive behaviour in the 'resident–intruder paradigm' and the pattern of neural activation induced by 'copulatory-behaviour-without-ejaculation', in order to assess which parts of the brain possibly play a specific role in each of these behaviours and which parts might be recruited by both behaviours.

For this part of the studies, we used Wild-type Brown Norway rats. This strain has been derived from a feral population of rats and is bred by now in the Groningen laboratory for more than 25 generations. High and stable levels of aggressive behaviour, not found in the domesticated male Wistar rat, characterize these rats.

1.2. Aggression and sexual behaviour: comparison of serotonergic pharmacology

There is a considerable pharmacology performed on male rat aggressive behaviour and male rat sexual behaviour. In the present contribution however, we focus on the role of serotonin and its receptors in male rat aggressive and sexual behaviours because the role of serotonin in both behaviours is firmly established (Hull et al., 2004; Olivier, 2004) and an extensive pharmacology is available, particularly on 5-HT_{1A} and 5-HT_{1B} receptors and serotonin transporters. Other receptors will not be mentioned specifically because only very limited information on aggression or sexual behaviour is available due to a lack of studies using specific ligands for these remaining receptors (Olivier, 2004, 2005). For this comparison only data from resident–intruder paradigms (de Boer et al., 2000; Olivier, 1981) will be used for the aggression studies, whereas standard male–female interactions for sexual behaviour (Pattij et al., 2005) will be used.

2. Materials and methods

2.1. Fos-experiments

2.1.1. Animals

For the present experiments, 15 adult male Wild-type Brown Norway rats, bred in the Dept. of Animal Physiology, University of Groningen, were used. Their weight ranged from 400 to 500 g. The animals were kept with a female partner sterilized by ligation of the oviducts, in cages measuring 50 × 80 × 50 cm, with food and water available ad lib, at 22 °C, under a 12/12 h light/dark cycle, the dark period starting at 8.00 a.m. These males are the 'resident males' as described in the present study. The 'intruder' was either an adult male Wistar rat, weighing about 350 g (Aggression-group, $N=4$) or an oestrous Wistar female weighing about 300 g (Sex-group, $N=4$) or the 'resident' remained alone for the duration of the test (Control-group, $N=3$).

2.1.2. Behavioural test

All tests were performed in the first half of the dark period of the light dark cycle. 5 min before the start of the behavioural test, female partners were removed from the home cage.

The male intruder or the oestrous female was introduced into the home cage of the experimental animal and the animals allowed interaction for 30 min. At the end of the test period, the intruder was removed from the cage and the resident male remained in his home cage undisturbed for 60 min. Consecutively, the resident was deeply anaesthetised (Nembutal, 0.2 ml/100 g), followed by perfusion, and processing for immunocytochemical staining of brain sections.

In the male–male encounters, frequency and duration were scored of the introductory 'threatening' postures, of the fighting itself (chasing, biting and fighting) as well as of the 'final situation' with the intruding Wistar male lying on its back, and the resident standing over it (Aggression-group, $N=4$).

Two additional experimental Brown Norway males were confronted with a Wild-type Brown Norway intruder, to see if the aggression-induced neural activation pattern would be different, and this turned out not to be the case. These males were not included, however, in the experimental group.

Forty-eight hours before the male–female encounters, Wistar females received a single injection of oestradiol (0.5 μg, s.c.), followed by 500-μg progesterone (s.c.) 4 h preceding the start of the test. Only females sufficiently in oestrous to allow the male to copulate were used and in this group frequency and duration of anogenital investigation was recorded, and also occurrence of

mounts and intromissions (Sex-group, $N=4$). Only one male reached repeated ejaculation. This male was not included in the experimental group, because it has been shown that the occurrence of ejaculation induces a very specific 'ejaculatory pattern' of neuronal activity (Coolen et al., 1997b). Indeed, the Fos pattern in this specific male was identical to that previously described for Wistar rats (Coolen et al., 1997a,b, 1996).

For the control group, the female companions were removed, followed 90 min later by anaesthesia and perfusion (Control-group, $N=3$).

2.1.3. Immunocytochemistry

Deeply anaesthetised animals were perfused via the heart (75–100 ml saline, followed by 400 ml of paraformaldehyde in phosphate buffered saline (4% paraformaldehyde in 0.1 M PBS, pH 7.3). After overnight postfixation in the same fixative at room temperature, brains were stored in buffer. Vibratome sections (50 μm thickness) were cut in a frontal plane, collecting 6 parallel series in 0.1 M PBS.

Per animal, at least one series was used for immunocytochemical staining for Fos-immunoreactivity (Antibody: polyclonal raised in sheep, OA-11-824, Cambridge Research Biochemicals, Billingham, UK, diluted 1:10,000). Some of the other series were used for cellular staining (Giemsa or Cresyl-Violet) or for additional immunostaining (Galanin, CGRP, β-endorphin). Further details of the immunocytochemical staining procedures have been described before (Coolen et al., 1998; Veening et al., 2004).

2.1.4. Quantification procedures

Sections were studied under a microscope, using a Neurolucida-system (Microbrightfield, Williston, VT, USA) and applying a grid square superimposed on the brain sections. Quantification occurred by counting the number of Fos-immunoreactive neurons per grid-square at 10 or 16× magnification. Depending on the size of the brain area, 1 to 6 squares per section were counted, separately on the left and the right side of the brain. This method of analysis has been described extensively before (Coolen et al., 1998). After quantifying the numbers of Fos-immunoreactive neurons, the statistical analysis of the numbers obtained in the different groups comprised an Univariate ANOVA (Analysis of Variance) test, followed by Scheffé's post hoc analysis, with 5% significance levels.

As a first general indication of their primary role in aggressive vs. sexual behaviour, the aggression/sex ratio (increase in Fos-immunoreactivity induced by aggression/increase in Fos-immunoreactivity induced by mating) was calculated for each brain area and included in Table 1.

Table 1
Neuronal activation (Fos-IR) after aggression or sex

Brain area	Fos-immunoreactive neurons[a]			Significance: **A**: Aggression vs. Control; **B**: Sex vs. Control; **C**: Aggression vs. Sex[b]			Ratio[c] Fos-immunoreactivity aggression/sex
	"Aggression"	"Sex"	"Control"				
Bed nucleus of stria terminalis							
Posterolateral part	76±24.0	25±5.2	3±1.3	**a**		C	3.0
Posteromedial part	36±12.0	56±33.4	1±1.3	b			**0.7**
Intraamygdaloid part	48±11.1	19±6.4	1±1.4	A	b	C	2.5
Amygdala							
Bed nucleus of the accessory olfactory tract	21±4.9	28±5.9	2±0.8	**a**	B		**0.75**
Medial part, posterodorsal medial nucleus	63±13.3	51±14.9	3±2.0	A	**b**		1.2
Caudal part, posterodorsal medial nucleus	79±7.1	29±8.8	2±1.3	**A**	**b**	**C**	2.7
Anterior part, basolateral nucleus	34±2.6	12±2.4	4±2.4	**A**	b	**C**	2.8
Hypothalamus							
Rostral part, medial preoptic nucleus	25±6.4	123±11.3	9±6.6		**B**	**C**	**0.2**
Caudal part, medial preoptic nucleus	111±24.7	90±24.6	5±3.0	**a**	B		1.2
Anterior hypothalamic area	96±11.9	34±12.0	11±13.7	**A**		C	2.9
Intermediate hypothalamic area	61±17.7	14±1.1	5±3.9	A		**c**	**4.3**
Dorsomedial part, ventromedial hypothalamic nucleus	64±10.8	5±4.1	7±5.5	**A**		**C**	**12.8**
Ventrolateral part, ventromedial hypothalamic nucleus	39±10.3	10±5.6	1±0.7	**A**		C	**3.9**
Medial part, dorsal premammillary nucleus	41±4.5	13±6.0	1±0.8	**A**	b	**C**	3.1
Lateral part, dorsal premammillary nucleus	111±20.8	29±8.7	4±3.9	**A**		**C**	**3.9**
Ventral premammillary nucleus	56±14.5	90±27.9	2±1.7	a	**b**		**0.6**
Brainstem							
Dorsal periaqueductal gray	126±17.0	41±8.7	10±2.6	**A**	b	**C**	3.1

[a]Depending on the size of the brain area: number of Fos-immunoreactivity neurons in 1 to 6 grids (150 μ) was counted. [b]*P*-values after Scheffé's post hoc test; a: < 0.05; **a**: < 0.01; A: < 0.001; **A**: < 0.0001., idem for B and C. [c]Ratio Fos-immunoreactivity aggression/sex: areas showing the highest (aggression-induced) and lowest values (copulation-induced) are shown in bold type.

2.2. Pharmacology experiments on male rat aggressive and sexual behaviour

This part of the study is based on published studies, mainly from work performed in the DeBoer/Koolhaas-Groningen lab on Wild-type Brown Norway rats and in the Olivier-Weesp/Utrecht lab on Wistar and Tryon maze Dull-S3 (TMD-S3) rats. For extensive descriptions of methodology see de Boer et al. (2000), Mos et al. (1992), and Olivier (1981).

Basically, all studies use adult male rats (residents) that are housed in a rather large cage (territory) with a female for at least a month. During an experiment, the male is injected with the experimental compound or vehicle (depending on the route of administration this could range from 60–5 min), the female removed from the cage and an unknown male rat (intruder) introduced for some time (5–15 min) into the cage. The ensuing behaviour of the resident is recorded and the effects of the drug described.

All results are given as summaries, for the individual results we refer to the original publications.

3. Results

3.1. Behaviour

In the Aggression-group, after a short introductory period of threatening postures, the intruder was attacked rapidly, sometimes including a short period of chasing-biting-fighting. As a rule, however, the intruder submitted very soon, lying on his back for some time, without receiving any further attacks. If the intruder started moving around again, other successive attacks were elicited, each of them followed rapidly by another period of submission, until the end of the test. Copulatory activities were never observed during these male–male encounters.

In the male–female encounters (Sex-group), intensive anogenital investigation was displayed from the beginning of the test period. This anogenital sniffing was followed by copulatory activities like mount attempts, mounts and occasionally intromissions. Ejaculation did not occur in the males included in this experimental group, while threatening postures or overt attacks were never observed in the male–female encounters.

3.2. Fos-immunocytochemistry

Fos-immunoreactivity was quantified in 32 different brain areas in the amygdala, bed nucleus of the stria terminalis, hypothalamus, and in the caudal thalamus and brainstem. In Table 1 the main findings are summarized.

3.2.1. Bed nucleus of the stria terminalis

Four parts of this nuclear complex were analysed in detail. The ventral bed nucleus of the stria terminalis (not shown) and the posterolateral bed nucleus of the stria terminalis (Table 1) showed a similar activation pattern, with a stronger increase in Fos-immunoreactivity after aggression (Fos-Ratio Aggr/Sex: ~3), while the posteromedial bed nucleus of the stria terminalis (Table 1) showed the strongest activation after sexual encounters (Fos-Ratio Aggr/Sex: ~0.7).

The most ‘ectopic’ part of the bed nucleus of the stria terminalis complex: the intraamygdaloid part, lying ventral to and ‘in front of’ the amygdalopetal stria terminalis fibers (Paxinos and Watson, 2005), showed a strong activation pattern after aggression (Fig. 1E, F), but not after sexual behaviour (Table 1).

3.2.2. Amygdala

Eight subregions of the amygdalar complex were analysed in detail.

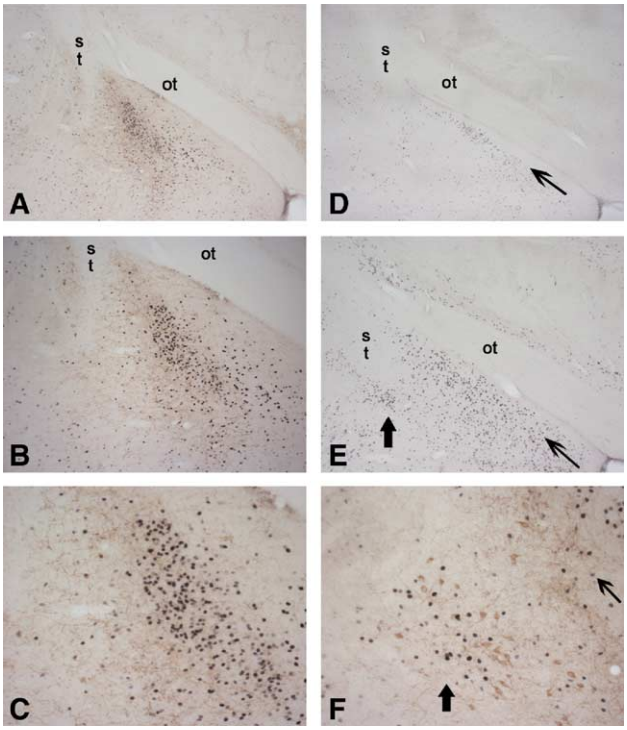

Fig. 1. Panels A, B and C show a section double-immunostained for Fos-immunoreactivity and galanin-immunoreactivity, including the location of the well-known cluster of Fos-immunoreactivity in the lateral zone of the posterodorsal medial amygdala, as appearing after (repeated) ejaculation. Most Fos-immunoreactivity neurons are observed in the galanin-rich zone of the posterodorsal medial amygdala (C). Panel D shows a section stained for Fos-immunoreactivity. Compared to panel A, the distribution of Fos-immunoreactivity is very different after intensive anogenital investigation of the female and limited to the most medial zone of the posterodorsal medial amygdala, bordering the ot (optic tract). Panel E shows the pattern of Fos-immunoreactivity in the posterodorsal medial amygdala after aggression. The general activation of the posterodorsal medial amygdala (thin arrow) is clear, and the ‘ejaculation-related’ zone of panels A and B shows no activation. However, a new cluster of Fos-immunoreactivity appears more laterally (thick arrow) in the intraamygdaloid bed nucleus of the stria terminalis. This area was completely empty under other test conditions (A, B). Panel F shows a section double-immunostained for Fos-immunoreactivity and galanin-immunoreactivity after aggression. The thick arrow indicates the ‘aggression-related’ Fos-immunoreactivity cells in the intraamygdaloid bed nucleus of the stria terminalis, lateral to the galanin-rich ‘ejaculatory-zone’ (thin arrow to the right). Galanin-immunoreactive cell bodies can be observed alongside and in between the activated neurons of the intraamygdaloid bed nucleus of the stria terminalis, but double-labelled neurons were never observed. The number of galanin-immunoreactive cell bodies seemed to be larger than after (repeated) ejaculation (B, C).

The bed nucleus of the accessory olfactory tract (Table 1) was one of the few regions where activation was stronger after Sex (Fos-Ratio Aggr/Sex: ~ 0.75). In all other amygdalar nuclei the activation was stronger after aggression.

In the medial part of the posterodorsal medial amygdala (Table 1) activation occurred under both circumstances (Fig. 1B, E). Interestingly, in one male a remarkably strong Fos-immunoreactive concentration in a thin layer of the medial part of the posterodorsal medial amygdala, alongside the optic tract, was observed (Fig. 1D). This particular subject displayed a few mounts, but no intromissions, and instead displayed vigorous anogenital investigation.

Activation was not observed in the lateral zone of the posterodorsal medial amygdala following aggression or sexual behaviour, except for the animal that displayed ejaculation. This is in agreement with our earlier reports that ejaculation induces Fos-immunoreactivity specifically in this lateral zone of the posterodorsal medial amygdala (Fig. 1A, B, C, included for the appreciation of the differences in the location of Fos-immunoreactivity).

The caudal part of the posterodorsal medial amygdala (Table 1) was considerably strongly activated after aggressive encounters.

The anteroventral medial and the posterior amygdaloid nuclei (not shown; Swanson, 2004) were also activated after sexual but stronger after aggressive encounters.

The anterior part of the basolateral amygdala (Table 1; Swanson, 2004) and the ventromedial part of the lateral amygdala (not shown; Paxinos and Watson, 2005) were strongly activated after aggression (Fos-Ratio's Aggr/Sex: ~3 to ~4).

3.2.3. Hypothalamus

Three preoptic as well as 12 other hypothalamic areas were analysed for the present study.

The medial preoptic nucleus showed very different activation patterns in its rostral and caudal parts. In the rostral medial preoptic nucleus (Table 1), ventral to the anterior commissure, the activation pattern was specifically related to sexual behaviour. Aggressive encounters did hardly result in increased Fos-immunoreactivity and the Fos-Ratio Aggr/Sex was lowest of all brain areas analysed for the present study: ~0.2. In contrast, the caudal medial preoptic nucleus (Table 1, Fig 2D), caudal to the anterior commissure, showed an equally strong activation in response to both aggressive and sexual behaviour (Fos-Ratio Aggr/Sex: ~1.2). A similar result was found in the anterodorsal preoptic nucleus (data not shown).

Of the rostral hypothalamic regions, the dorsal hypothalamic area and the paraventricular hypothalamic nucleus (data not shown) were activated only after aggressive encounters. The same holds true for the anterior hypothalamic area (Table 1, Fig. 2B) and especially for the intermediate hypothalamic area (Geeraedts et al., 1990) (Table 1, Fig. 2A, B, C), also known as 'hypothalamic attack area' (Kruk et al., 1983; Roeling et al., 1993). In the latter area, the Fos-Ratio Aggr/Sex (>4) was among the highest observed during the present study, underlining the strong and specific activation occurring after aggression.

In the ventromedial hypothalamic nucleus a strong and specific activation occurred only after aggressive encounters. Its dorsomedial part (Table 1, Fig. 2E) showed the highest Fos-Ratio Aggr/Sex (13) of the present study, while its ventrolateral part (Table 1, Fig. 2E) ranked among the highest (~4).

Several surrounding areas, the dorsomedial hypothalamic nucleus, the medial tuberal nucleus and the transition zone between the ventromedial hypothalamic nucleus and the arcuate hypothalamic nucleus (not shown) showed increased Fos-immunoreactivity under both conditions, with the higher levels after aggression.

In the premammillary part of the hypothalamus a differentiated pattern of Fos-IR was observed under the different conditions. In the medial part of the dorsal premammillary nucleus, some activation occurred after sexual behaviour, but the increase in Fos-immunoreactivity was considerably stronger after aggression (Table 1, Fig. 2G) (Fos-Ratio Aggr/Sex: ~3). Much stronger activation occurred, only after aggression, in the lateral part of the dorsal premammillary nucleus (Table 1, Fig. 2G, H) (Fos-Ratio Aggr/Sex: ~4). Activation patterns in the ventral premammillary nucleus showed almost opposite results, with the highest activation occurring after sexual behaviour (Table 1, Fig. 2G, I) and among the lowest Fos-Ratio's Aggr/Sex observed in the present study (only 0.6).

3.2.4. Caudal thalamus and brainstem

Several thalamic and brainstem areas were analysed during the present study. In both the magnocellular and the parvicellular subparafascicular nuclei of the thalamus, Fos-immunoreactivity was induced under both conditions but more extensively after aggression (not shown). The specific activation occurring in the medial part of the SPFp after sexual behaviour (Coolen et al., 1996) was observed only after ejaculation (Fig. 2F).

In the brainstem, especially the dorsal part of the periaqueductal gray showed an interesting pattern with a strong increase in Fos-immunoreactivity, especially after aggression (Table 1). A moderate increase in Fos-immunoreactivity after aggression was also observed in the supragenual nucleus (not shown).

Summarizing the data obtained in the present study:

- Aggression induced the strongest neural activation in the following brain areas: the posterolateral and intraamygdaloid parts of the bed nucleus of the stria terminalis; the caudal part of the posterodorsal medial amygdala, and parts of the basolateral and lateral amygdaloid nuclei; the 'hypothalamic attack area', the ventromedial hypothalamic nucleus and the dorsal premammillary nucleus as well as the dorsal part of the periaqueductal gray in the brainstem.
- Four brain areas were more strongly activated after sexual behaviour: the rostral part of the medial preoptic nucleus, the posteromedial part of the bed nucleus of the stria terminalis,

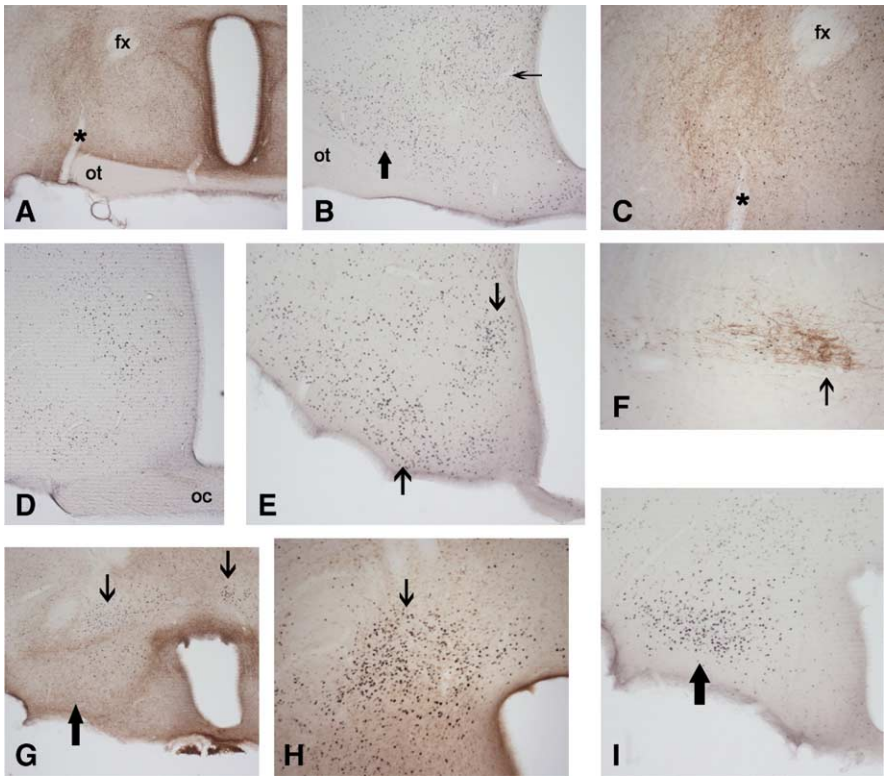

Fig. 2. Panels A, B and C show the intermediate hypothalamic area or 'hypothalamic attack area' after aggression. Panel A is taken from a section double-immunostained for Fos-immunoreactivity and galanin-immunoreactivity and shows galanin-immunoreactive innervation of the dorsal part of the intermediate hypothalamic area. Panel B, stained only for Fos-immunoreactivity, shows the pattern of neural activation after aggression, mainly in the ventral intermediate hypothalamic area (thick arrow). In addition, the anterior hypothalamic area is consistently activated (thin arrow). Panel C (detail of panel A, * = lateral hypothalamic artery) shows that the galanin-rich part and the aggression-activated parts of the intermediate hypothalamic area hardly overlap. Panel D shows the pattern of Fos-immunoreactivity in the caudal medial preoptic nucleus after aggression. Similar activation may occur after sexual encounters, different from the rostral subcommissural part of the medial preoptic nucleus, panel E shows the pattern of Fos-immunoreactivity in the ventromedial hypothalamic nucleus. The ventromedial hypothalamic nucleus appears hardly activated, but distinct clusters of Fos-immunoreactivity become apparent in the dorsomedial and in the ventrolateral parts of the nucleus (arrows). Panel F shows a double-immunostained (Fos-immunoreactivity and galanin-immunoreactivity) section through the parvicellular subparafascicular thalamic nucleus after aggression. Some activation occurred in its lateral part, but its galanin-rich medial part (related to ejaculation) showed no Fos-immunoreactivity. Panels G, H and I show the premammillary region. Panel G shows a section double-immunostained for Fos-immunoreactivity and galanin-immunoreactivity after aggression. The dorsal premammillary nucleus is strongly activated and shows Fos-immunoreactivity in its medial part (right thin arrow, contralateral side of the section) and in its larger lateral part (left thin arrow). The ventral premammillary nucleus (thick arrow) is hardly activated. Panel H, double-immunostained for Fos-immunoreactivity and endorphin-immunoreactivity shows in more detail the extensive activation of the dorsal premammillary nucleus after aggression. Panel I, stained only for Fos-immunoreactivity, shows the strong activation of the ventral premammillary nucleus after female encounters.

the bed nucleus of the accessory olfactory tract and the ventral premammillary nucleus.

- Other brain areas like medial amygdala and the caudal part of the medial preoptic nucleus were equally activated after aggressive and copulatory activities.

4. Discussion

4.1. Fos-experiments

The present study shows that the patterns of neural activation, observed as an increase in Fos-immunoreactivity in the brains of Wild-Type Brown Norway rats after performance of aggressive or sexual activities, induced by introduction of a male or an oestrous female intruder into the residents home cage, are partially similar and partially different. Therefore, it confirms the idea that aggressive and sexual behaviours share parts of an integrated neural network including some brain areas that seem to be more selectively activated after performance of either sexual or aggressive behaviour.

4.1.1. Shared activation following aggressive and sexual behaviour

In several brain areas, activation occurs about equally strong after both types of social behaviour, like in the anterodorsal preoptic nucleus, the caudal part of the medial preoptic nucleus, and in the posterodorsal medial amygdala. This occurrence of common Fos-immunoreactive areas has been observed before in the male Syrian Hamster (Kollack-Walker and Newman, 1995), and may reflect that parts of the neural substrate sensitive to androgens as well as pheromonal stimulation, both play a role in sexual as well as aggressive behaviour (Kollack-Walker and Newman, 1995). The existing functional dichotomy within the vomeronasal system (Kumar et al., 1999) suggests, however, that activation patterns are not necessarily identical after male or female pheromonal stimulation. Other aspects, inherent to the

experimental situation created by introducing an unknown male or female into the home cage, may have induced Fos-immunoreactivity in other parts of the commonly activated neural circuitry, as the result of activation of the pituitary–adrenal axis, of the sympathetic nervous system or of bodily contact stimuli.

4.1.2. Effects related to aggressive behaviour

Several brain areas were selectively activated after aggressive encounters in the resident–intruder paradigm.

The posterolateral part of the bed nucleus of the stria terminalis showed high numbers of Fos-immunoreactive neurons after aggression. This activation has been observed before in the hamster (Kollack-Walker and Newman, 1995). Numerous other studies imply the bed nucleus of the stria terminalis as one of the regions involved in agonistic behaviour (Halasz et al., 2002), but the possible subdivisions of the bed nucleus of the stria terminalis did not receive sufficient attention. Functional anatomical studies, however, suggest important differences between the posteromedial (sexually dimorphic, steroid-receptive, mating-related) and the posterolateral parts, including their relationships (Coolen et al., 2003a, b). The present study shows its involvement in (aspects of) aggression. The intraamygdaloid part of the bed nucleus of the stria terminalis, lying at the 'amygdaloid end' of the stria terminalis (Paxinos and Watson, 2005), alongside the posterodorsal medial amygdala, also showed strong activation, specifically after aggression. The possible involvement of this area has not been indicated before in studies related to offensive behaviour.

In the amygdala, the posterodorsal nucleus in the medial amygdala shows interesting functional subdivisions. While a *lateral zone* shows the characteristic 'ejaculation-related cluster' (Fig. 1A, B, C) (Coolen et al., 1996; Veening and Coolen, 1998), the *medial zone* appears to be activated under many more different circumstances, among them sexual as well as aggressive encounters. Most probably, pheromonal and other olfactory cues are involved in this general medial activation pattern, not related to a specific behaviour. As shown in Fig. 1D, however, special conditions may induce a specific olfactory activation pattern alongside the optic tract. The *caudal part* of the posterodorsal medial amygdala showed a characteristic response to aggression that has not been described before. Two other parts of the amygdaloid complex also showed a remarkably strong activation after aggressive encounters: the anterior part of the basolateral nucleus (Swanson, 2004) and the ventromedial part of the lateral amygdala (Paxinos and Watson, 2005). The basolateral nucleus has been related to agonistic behaviour in earlier studies (McGregor and Herbert, 1992a,b; Shibata et al., 1982). This nucleus is connected to the lateral amygdala (Stefanacci et al., 1992) and the caudate–putamen complex (De Olmos et al., 2004; Veening et al., 1980).

In the hypothalamus, several brain areas were responding to the resident–intruder interaction. Notably, the intermediate hypothalamic area or 'hypothalamic attack area', and the anterior hypothalamic area, the ventromedial hypothalamic nucleus and the dorsal premammillary hypothalamic nucleus were strongly activated after the aggressive encounters. There is ample evidence for extensive mutual relationships between these brain areas and the medial amygdala (Canteras et al., 1995; Canteras and Swanson, 1992; Krettek and Price, 1978; Luiten et al., 1985; Petrovich et al., 2001; Risold et al., 1994; Roeling et al., 1994; Veening, 1978). All of these areas are known to be involved in agonistic behaviour (Kollack-Walker and Newman, 1995; Kruk et al., 1979, 1983; Lammers et al., 1988; Luiten et al., 1985; Roeling et al., 1993, 1994; Siegel et al., 1999; Veening, 1992).

In the brainstem, the dorsal part of the periaqueductal gray was strongly activated after aggressive encounters. This increase in Fos-immunoreactivity is in agreement with its anatomical relationships with the ventromedial and anterior hypothalamic nuclei (Holstege, 1987; Mantyh, 1982; Semenenko and Lumb, 1992; Veening et al., 1991) and many reports relate this brain area to agonistic, especially defensive behaviour (Bereiter and Gann, 1990; Brutus et al., 1985; Carrive et al., 1986).

4.1.3. Effects related to sexual behaviour

The rostral 'subcommissural' part of the medial preoptic nucleus was strongly activated after mating (Table 1), as has been shown before in many studies.

The bed nucleus of the accessory olfactory tract also showed a selective increase in Fos-immunoreactivity. This nucleus is sexually dimorphic, forms part of the vomeronasal system, has extensive reciprocal relationships with the medial preoptic nucleus, and plays, in females, an important role in maternal behaviour (Collado et al., 1998; Guillamon and Segovia, 1997; Komisaruk et al., 2000). This suggests that the bed nucleus of the accessory olfactory tract may be another nodal point in the neural circuitry, influenced by both olfactory and endocrine factors, but subserving different kinds of behaviour.

The ventral premammillary nucleus has been observed before as one of the regions activated after sexual behaviour, but in the male Syrian hamster this brain area is activated after agonistic encounters as well (Kollack-Walker and Newman, 1995). Under the circumstances chosen, the Brown Norway rat shows a more differentiated pattern of activation. Pheromonal stimulation already suffices to activate this brain region (Greco et al., 1998b; Heeb and Yahr, 1996; Yokosuka et al., 1999). The ventral premammillary nucleus is extensively and reciprocally connected to sexually dimorphic nuclei, including the medial preoptic nucleus (Canteras et al., 1992).

The pattern of activated brain regions, appearing after sexual activity, turns out to be very similar to what has been observed in domesticated Wistar rats and other rodents. The relatively strong activation of the bed nucleus of the accessory olfactory tract and ventral premammillary nucleus may reflect the importance of pheromonal cues in guiding the behaviour of the Wild-type Brown Norway rat.

4.1.4. Specificity of neuronal activation

Comparing the present findings after aggressive and sexual encounters suggests that large areas of the brain (hypothalamus, amygdala and bed nucleus of the stria terminalis) show a

general increase in activation. Within these general areas, however, a more detailed picture emerges of smaller (sub) areas, or 'clusters' (Coolen et al., 1996) that play a clearly different role in both behaviours.

The medial preoptic nucleus apparently has a rostral (subcommissural) part, important for mating, while its caudal (postcommissural) part, extending upward in a dorsolateral direction towards the posterior bed nucleus of the stria terminalis-complex becomes about equally activated after aggressive and sexual encounters. Inside the latter complex, two parallel areas, the posteromedial and the posterolateral parts seem to be involved in different activities. The posteromedial zone, where 'ejaculation-related' clusters appear after ejaculation (Coolen et al., 1996) is activated by sexual activities, while the lateral zone seems to be more agonistic-related in its activities. This differentiation in the bed nucleus of the stria terminalis-complex is in accordance with differences in steroid–receptor-distribution (Greco et al., 1998a,b; Wood and Newman, 1993) as well as with differences in amygdaloid and other anatomical relationships (Coolen et al., 2003a,b).

In the amygdalar complex, it has been shown before that a specific 'ejaculation-related' cluster appears in the most lateral zone of the posterodorsal medial amygdala (Coolen et al., 1996). This particular zone is rich in fibers containing galanin (Fig. 1C), is reciprocally connected with the medial preoptic nucleus (Coolen et al., 1998) and may be reflecting 'sexual satiety' (Parfitt and Newman, 1998). Interestingly, the medial part of posterodorsal medial amygdala is generally activated after both sexual and agonistic encounters, but a specific medial activation zone, alongside the optic tract (Fig. 1D) has been observed only in female encounters, suggesting the possibility that part of the sexual dichotomy in the pheromonal circuitry (Kumar et al., 1999) is showing up, here. In addition, a specific cluster of neuronal activation was observed at the 'amygdalar end' of the stria terminalis (Fig. 1E). In the atlas of Paxinos and Watson (2005), this area is indicated as the intraamygdaloid part of the bed nucleus of the stria terminalis. According to the atlas of Swanson (2004), this area seems to form part of the capsular zone of the central amygdaloid nucleus. As visible in Fig 1A, B, C and E, F, this aggression-activated region is lying lateral to the galanin-rich zone involved in sexual behaviour. So, at strikingly short distances within this particular part of the centro-medial amygdala, clusters or subareas of cells are apparently involved in different behavioural activities. In addition, the caudal part of the posterodorsal medial amygdala, ventral to the tip of the lateral ventricle, is again involved in mainly aggressive activities. These findings support the hypothesis that a finely differentiated participation of amygdalar (sub)areas exists, involved in very different behavioural activities.

Finally, in the caudal hypothalamus a clear functional differentiation was observed. The finding that the ventral premammillary nucleus is much more strongly activated by female than by male pheromonal cues, as observed in the present study, suggests that it may play a role in leading the male into sexual behaviour. The dorsal premammillary nucleus, however, is apparently much more involved in agonistic activities. This difference in activation patterns may reflect some of the dichotomy in the vomeronasal system, as described by Kumar et al. (1999).

4.1.5. Localisation of serotoninergic fibers and 5-HT-receptors

Serotonergic fibers are present in all areas listed in Table 1 (Steinbusch, 1981; Steinbusch and Nieuwenhuys, 1981). In addition, the presence of 5-HT_{1A} receptors has been shown in the bed nucleus of the stria terminalis, the medial preoptic area, the medial and basolateral amygdala, the anterior hypothalamic area, the dorsomedial and ventrolateral parts of the ventromedial hypothalamic nucleus, the dorsal and ventral premammillary nuclei and the dorsal periaqueductal gray (Aznar et al., 2003; de Paula Soares and Zangrossi, 2004; Kia et al., 1996; Li et al., 1997; Pompeiano et al., 1992; Wright et al., 1995). A very similar distribution has been reported for 5-HT_{2C} receptors (Abramowski et al., 1995; Clemett et al., 2000). Much less is known about the localisation of 5-HT_{1B} receptors in these areas: only the bed nucleus of the stria terminalis and the ventromedial hypothalamic nucleus have been reported to express 5-HT_{1B} receptors (Makarenko et al., 2002; Neumaier et al., 1996). Unfortunately, the 5-HT receptor distribution in the intermediate hypothalamic area, the different subareas of the bed nucleus of the stria terminalis and separate zones of the posterodorsal medial amygdala has not yet been studied in sufficient detail.

We conclude that direct effects of 5-HT on the neural circuitry involved in mating and agonistic behaviour can be expected, but indirect effects via serotonergic innervation of nodal regions in the circuitry probably play an important role.

4.2. Pharmacology experiments on male rat aggressive and sexual behaviour

4.2.1. Effects of 5-HT_{1A} receptor agonists and antagonists on resident–intruder aggression in male rats

An extensive and still increasing range of 5-HT_{1A} receptor agonists and antagonists is available (Olivier et al., 1999). Prototypic agonists like 8-OH-DPAT ((±)-8-hydroxy-2-*n*-(dipropylamino)tetralin), buspirone and flesinoxan or receptor antagonists like WAY 100,635 have been used in resident–intruder aggression studies. All studies with partial and full receptor agonist find anti-aggressive effects in the RI-paradigm, but the specificity of this effect is questionable, in the sense that anti-aggressive effects occur at doses that also compromise non-aggressive elements of the behavioural repertoire (Miczek et al., 1998a,b; Olivier et al., 1995), buspirone (Olivier et al., 1984a,b), 5-Me-O-DMT (5-methoxy-*N*,*N*-dimethyltryptamine) (Olivier et al., 1990a,b), 8-OH-DPAT (Olivier et al., 1990a,b), ipsapirone and gepirone (Olivier and Mos, 1990), and flesinoxan (Olivier et al., 1990b) all had this anti-aggressive profile. Recent studies (de Boer et al., 1999, 2000) confirm the non-specific anti-aggressive profile of 5-HT_{1A} receptor agonists like buspirone, ipsapirone and 8-OH-DPAT, but certain 5-HT_{1A} receptor ligands like alnespirone and S-15535 (4-(benzodioxan-5-yl)1-(indan-2-yl)piperazine) display a different and rather specific anti-aggressive profile (for an extensive discussion on this topic: Olivier and van Oorschot, in press). The common finding therefore is that activation of 5-HT_{1A} receptors (apparently

independent whether pre- and/or postsynaptic receptors are involved) leads to anti-aggressive activity in the RI-paradigm. Although various 5-HT_{1A} receptor antagonists have been described, the only ligand used in RI-aggression is WAY 100,635 (*N*-[2-(4-[2-methoxyphenyl]-1-piperazinyl)ethyl]-*N*-2-yridinylcyclohexanecarboxamide), a potent receptor antagonist. Several studies have reported that WAY 100,635 was able to antagonize the anti-aggressive effects of 5-HT_{1A} receptor agonists (de Boer et al., 1999; Olivier et al., 1995), but all studies have found absence of intrinsic anti-aggressive effects of WAY 100,635 (de Boer et al., 1999). Similar data have been found in mouse RI studies, cf. Miczek et al. (2002) (Table 2).

4.2.2. Effects of 5-HT_{1A} receptor agonists and antagonists on sexual behaviour in male rats

In male sexual behaviour in the rat, 5-HT_{1A} receptor agonists have a stimulating effect on sexual behaviour. The first report on such a prosexual activity was already published on 8-OH-DPAT in 1981 (Ahlenius et al., 1981) and since then all 5-HT_{1A} receptor agonists, partial or full, showed a comparable effect on male rat sexual behaviour (Ahlenius and Larsson, 1997; Ahlenius et al., 1989, 1991; Andersson and Larsson, 1994; Coolen et al., 1997a; Haensel et al., 1991; Haensel and Slob, 1997; Mathes et al., 1990; Mendelson and Gorzalka, 1986; Morali and Larsson, 1984; Olivier and Mos, 1991; Rasia-Filho and Lucion, 1996; Rehman et al., 1999; Schnur et al., 1989; Sura et al., 2001). In studies using sexually naive, moderately sexually experienced or very sexually experienced male rats all types of males showed a prosexual activity of 8-OH-DPAT (Mos et al., 1990). Under these conditions flesinoxan showed a comparable pattern, whereas ipsapirone and buspirone had no prosexual effect in moderately experienced rats, and only marginal prosexual effects in naive rats, indicating that in particular full 5-HT_{1A} receptor agonists have this stimulating pattern. In an experiment where two males, one treated with drug and the other with vehicle, were tethered and the females could decide the pacing of the sexual interactions, flesinoxan and gepirone stimulated the visiting time of the females towards the drug-treated male and consequently more sexual behaviour was executed (Mos et al., 1990). This strongly suggests that 5-HT_{1A} receptor agonists might induce prosexual effects via modulating motivational aspects, including post ejaculatory ultrasounds, of male rats (Haensel et al., 1991; Mos et al., 1991). No chronic studies with 5-HT_{1A} receptor agonists in male rats have been reported.

5-HT_{1A} receptor antagonists do not have intrinsic effects on male sexual behaviour (Ahlenius and Larsson, 1998, 1999; de Jong et al., 2005a) but are able to antagonize the prosexual effects induced by 5-HT_{1A} receptor agonists (Ahlenius and Larsson, 1999; Hillegaart and Ahlenius, 1998).

4.2.3. Effects of 5-HT_{1B} receptor agonists and antagonists on resident–intruder aggression in male rats

5-HT_{1B} receptor agonists (partial and full) strongly and selectively reduce aggressive behaviour in the RI paradigm in rats (Olivier, 2004; 2005; Olivier et al., 1994a; Olivier and van Oorschot, in press). Although extremely selective anti-aggressive compounds (serenics) are partial 5-$HT_{1A/1B}$ receptor agonists (Olivier et al., 1990a,b), there is abundant evidence (see for a discussion: Olivier and van Oorschot, in press) that the effects on aggression are modulated by activation of (postsynaptic) 5-HT_{1B} receptors. More recently synthesized 5-HT_{1B} receptor agonists, including anpirtoline, CP-94,253 (5-propoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-pyrrolo[3,2-b] pyridine) and zolmitriptan, are far more selective for the 5-HT_{1B} receptor and exert a similar anti-aggressive profile, cf. Miczek et al. (2002). All compounds having 5-HT_{1B} receptor agonistic activity exert anti-aggressive activity not only in rats but also in mice, cf. Olivier et al. (1995) and Olivier and van Oorschot (in press). Studies on the effects of chronic treatment of 5-HT_{1B} receptor agonists on aggression are scarce: only eltoprazine and fluprazine have been tested and these compounds (that are also partial 5-HT_{1A} receptor agonists) exerted anti-aggressive activity after chronic administration (Mos et al., 1996; Olivier and Mos, 1990).

5-HT_{1B} receptor antagonists have no intrinsic effects on aggression, but are able to antagonize the anti-aggressive effects of 5-HT_{1B} receptor agonists (de Boer et al., 1999; Miczek et al., 2002; Olivier and van Oorschot, in press). No chronic studies using 5-HT_{1B} receptor antagonists have been reported.

4.2.4. Effects of 5-HT_{1B} receptor agonists and antagonists on sexual behaviour in male rats

5-HT_{1B} receptor agonists inhibit male sexual behaviour, as demonstrated by various 5-HT_{1B} receptor ligands, including anpirtoline (Hillegaart and Ahlenius, 1998), TFMPP (*N*-[3-(trifluoromethyl)phenyl] piperazine), mCPP (*m*-chlorophenylpiperazine) (although mCPP has considerable 5-HT_{2C} receptor agonistic effects), RU24969 (5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridyl)-1*H*-indole) (Fernandez-Guasti et al., 1989;

Table 2
Summary of the effects of ligands for 5-HT_{1A} and 5-HT_{1B} receptors and the 5-HTT (5-HT transporter) on aggressive behaviour as measured in the resident–intruder paradigm and in male–female sexual behaviour

Receptor	5-HT_{1A}				5-HT_{1B}				5-HTT	
Ligand	Agonist		Antagonist		Agonist		Antagonist		Antagonist	
Treatment	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic
Aggressive behaviour	↓	nd	−	−	↓	↓	−	nd	↓	↓↑
Sexual behaviour	↑	nd	−	−	↓	nd	−	nd	−	↓−

nd=not determined, ↑=enhancement, ↓=decrease, −=no change.

Fernandez-Guasti and Rodriguez-Manzo, 1992; Olivier and Mos, 1988) and eltoprazine (Olivier et al., 1994b).

5-HT_{1B} receptor antagonists (isomoltane) have no intrinsic effects on male sexual behaviour but are able to antagonize the inhibition induced by 5-HT_{1B} receptor agonists (Ahlenius and Larsson, 1998; Hillegaart and Ahlenius, 1998). Neither study on other 5-HT_{1B} receptor antagonists nor chronic studies have been reported.

4.2.5. Effects of SSRIs (selective serotonin reuptake inhibitors) on resident–intruder aggression in male rats

Although there is a lot of discussion on SSRIs and (enhanced) aggression in humans, cf. Bond (1998), Miczek et al. (2002), and Troisi et al. (1995), not many rat studies in RI-aggression have been performed. Fluvoxamine showed acutely anti-aggressive activity but this only occurred at doses that also decreased other behaviours, including social interest and inactivity (Mos and Olivier, 1988; Olivier et al., 1993, 1995). Other SSRIs (fluoxetine, sertraline, paroxetine, citalopram, zimelidine) have similar activity profiles after acute administration in various species, cf. Miczek et al. (2002). Chronic studies on fluvoxamine (Olivier; unpublished) found a similar pattern; no specific anti-aggressive activity but at higher doses some sedative effects. Although most human studies point to anti-aggressive effects of SSRIs upon chronic treatment, in line with the animal data, some chronic SSRI studies in rats have indicated that aggression can be enhanced (Mitchell and Fletcher, 1993; Mitchell et al., 1991; Mitchell and Redfern, 1992, 1997, 2005). Under these conditions, low-aggressive rats display low-intensity aggressive interactions. Whether high-aggressive rats would show a similar outcome is unclear, the more because chronic treatment of isolated, aggressive male mice with clomipramine clearly inhibits aggression (Delini-Stula and Vassout, 1981).

4.2.6. Effects of SSRIs (selective serotonin reuptake inhibitors) on sexual behaviour in male rats

Analogous to the human situation, also in male rats a distinction can be made between the effects of acute and chronic SSRI administration on ejaculation (Olivier et al., 2005). Acute administration of various SSRIs, such as citalopram, clomipramine, paroxetine, sertraline, fluoxetine and fluvoxamine did not have any delaying effects on ejaculations as shown by our group (Mos et al., 1999) and others (Ahlenius and Larsson, 1998; Vega Matuszcyk et al., 1998). On the other hand, chronic administration of fluoxetine (Cantor et al., 1999; Frank et al., 2000; Vega Matuszcyk et al., 1998) and paroxetine (Waldinger et al., 2002) did have delaying effects on ejaculation in male rats. Nonetheless, as in humans not all SSRIs potently delay ejaculation after chronic administration in male rats. For instance, fluvoxamine slightly affected some aspects of sexual behaviour, but did not affect ejaculation even after chronic administration (Waldinger et al., 2002). Furthermore, preliminary results obtained in our laboratory suggest that also chronic citalopram does not delay ejaculation in rats that are sexually active, although it completely abolished sexual behaviour in some rats (de Jong et al., 2005a).

Until now it is still unclear why the various SSRIs differ in their ability to delay ejaculation after chronic administration. The delay in onset of the therapeutic effect of SSRIs in depression and anxiety disorders has been related to adaptive changes of serotonergic autoreceptors, see for instance: Haddjeri et al. (1998) and Le Poul et al. (2000). Therefore it is conceivable that also the ejaculation-delaying effects of various SSRIs are due to adaptive changes of, for instance, 5-HT receptor subtypes.

Ahlenius and Larsson (1999) have studied the mechanism of SSRI-induced delay of ejaculation in more detail and showed that acute treatment with citalopram did not affect ejaculatory behaviour. Nonetheless, when the 5-HT_{1A} receptor antagonist WAY-100635 was co-administered with citalopram, ejaculation latencies were strongly delayed, suggesting the involvement of 5-HT_{1A} receptors in effects of citalopram on ejaculation. de Jong et al. (2005a) also showed that doses of citalopram, acutely or chronically, that did not inhibit sexual behaviour on itself, when combined with one sexually inactive dose of WAY100,635, completely abolished sexual behaviour. Subsequently, Ahlenius and colleagues showed that the ejaculation delaying effects of the combination of citalopram and WAY-100635 could be fully blocked by a selective 5-HT_{1B} receptor antagonist, suggesting a role for this receptor subtype in the delay of ejaculation (Ahlenius and Larsson, 1999). Interestingly, a previous study from the same laboratory also suggested a role of 5-HT_{1B} receptors in the delay of ejaculation. In this study it was shown that the 5-HT_{1B} receptor agonist anpirtoline dose-dependently delayed ejaculation in rats (Hillegaart and Ahlenius, 1998).

Interestingly, the adaptive changes in 5-HT receptors after chronic SSRI administration have been shown to affect neuroendocrine systems as well. One of these systems is the oxytocinergic system, which is generally known to facilitate sexual behaviour (see for review: Argiolas, 1999). Chronic fluoxetine (de Jong et al., 2005b,c) and paroxetine administration (Li et al., 1996) have been shown to reduce G-protein levels in the hypothalamus. As a consequence, neuroendocrine responses, including oxytocin release, to 5-HT_{1A} receptor agonists were blunted in animals chronically treated with SSRIs compared to controls. It may be possible that the blunted oxytocin responses due to adaptive changes of G-proteins are responsible for the sexual side effects of SSRIs. Evidence supporting this comes from a recent study where it was shown that the sexual side effects of fluoxetine in rats could be completely reversed by co-administration of oxytocin (Cantor et al., 1999).

To summarize, until now the sexual side effects of SSRIs are not fully understood yet. Nevertheless, some recent findings suggest that adaptive changes in the 5-HT system and its interactions with neuroendocrine systems may be responsible for their sexual side effects.

4.3. Are male rats aggressive and sexual behaviour mediated by similar brain structures and mechanisms?

Pedersen (2004) approaches the roots of violence and aggression from the evolutionary development of brain systems

involved in emotional bonds. The developments of neurochemical systems within the CNS that control these processes include monoamines (dopamine, serotonin and noradrenaline) but also neuropeptides like oxytocin and vasopressin. This are systems typically involved in the regulation of aggressive and sexual behaviour and it is worthwhile to investigate the hypothesis that neural systems in the brain that modulate aggression and sex could be for a large part overlapping systems. This was investigated in the present study in male adult rats by two approaches: (1) Are the same neural systems activated during the performance of (aspects of) aggressive and sexual behaviour, and (2) does the serotonergic system display a comparable pharmacology in modulating aggressive and sexual behaviour?

The present study shows that the patterns of neural activation, observed as an increase in Fos-immunoreactivity in the brains of Wild-type Brown Norway rats after performance of aggressive or sexual activities, induced by introduction of a male or an oestrous female intruder into the residents home cage, are partially similar and partially different, pointing to partially overlapping and partially different neural systems involved.

The psychopharmacology of aggressive and sexual behaviour in the male rat also reflects a similar dichotomy: modulating 5-HT_{1A} receptors shows a large discrepancy. 5-HT_{1A} receptor agonists stimulate sexual behaviour and inhibit aggressive behaviour. 5-HT_{1B} receptor stimulation on the other hand, inhibits both sexual and aggressive behaviour. This also points to (partially) different neurochemical systems, at least with respect to the serotonergic system.

Our findings should be considered as very preliminary and cautiously be interpreted. We have selected very specific conditions and other situations and test paradigms should be studied before general conclusions can be drawn.

However, there is quite some support for anatomically segregated systems in the brain involved in various different aspects of reproductive and defensive/offensive behaviours (Choi et al., 2005). There is conclusive evidence that these behaviours, often quite stereotypic of nature, are 'hard-wired' in the brain. On the other hand, these systems have to talk to each other, because if an attractive mate is present, aggression should be completely inhibited and vice versa. The neural mechanisms that determine the priority setting of these hard-wired behaviours are poorly understood and the present study is helpful in delineating some of them. In a very elegant study, Choi et al. (2005) outlined reproductive and defensive pathways, which converge in the ventromedial hypothalamus. They propose that a potential neural substrate exists that integrates the influences of conflicting behavioural cues, including aggression and sex. Amygdalar and hypothalamic structures seem to play an important role in this "gate control" mechanism and seem also important in the activation patterns we have observed in the present study. Moreover, serotonin and serotonergic receptors are abundantly present in the relevant structures and might indeed influence this gating mechanism. Many other explanations remain possible but the exciting idea that the brain probably uses separate hard-wired systems to steer specific functions and behaviours (like offensive aggression and sexual behaviour), but on the other hand also uses (hierarchically) higher (probably also hard-wired) systems to modulate the priority setting of these behaviours and thus enhance the chance of survival, is in line with the findings in this paper.

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