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Research report

Brain structures involved in the sexual behaviour of Ile de France rams with different sexual preferences and levels of sexual activity

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ABSTRACT

Using Fos, as a marker, we analysed the brain structures of rams, with different libidos or sexual preferences that had been activated by contact with males or females. Ile de France rams aged from 1.5 to 7 years were used. Fos immunoreactivity (Fos IR) was analysed in rams with high (HL) or low libido (LL) after 90 min of direct contact with females (HL DirF $n = 7$ or LL DirF $n = 7$) or in rams of high libido having indirect contact through a fence, with females (HL IndF $n = 6$) or males (HL IndM $n = 5$) and finally, in males who preferred other males as partners by indirect contact through a fence with males (MO IndM $n = 4$). Direct or indirect contact with a preferred sexual partner (LL DirF, HL Dir F, HL IndF, MO IndM) induced the appearance of Fos-IR cells in several diencephalic and cortical structures. Conversely, indirect contact with males did not induce Fos-IR in males interested in females (HL IndM). In the medial preoptic area (MPOA), the paraventricular nucleus and the medial bed nucleus of the stria terminalis the cell density of Fos IR cells was higher in HL Dir F than in LL DirF suggesting involvement in sexual motivation whereas only the MPOA seemed involved the consummatory component of sexual behaviour (Fos IR density HL DirF > HL IndF). The enthorinal cortex was the only structure specifically activated by males attracted to other males (Fos IR density MO IndM > HL IndM) whereas Fos IR density did not differ between the HL IndF and HL IndM groups.

1. Introduction

The survival of a species depends ultimately on reproduction and one of the key elements in reproduction is sexual behaviour. This behaviour between a male and a female must be displayed at a physiologically appropriate time so that fertilization can occur. The coordination of these behavioural and physiological changes is achieved primarily by gonadal steroids acting on particular brain structures [1]. In many species, some males, with functional testes and normal blood concentrations of testosterone, do not show sexual behaviour [2–5], or some prefer other males as sexual partners [6–8]. These animals cannot reproduce and in farm animals, these patterns of behaviour can decrease reproduction rate and farm productivity and lead to economic losses. The cause of this lack of sexual behaviour or this preference for a partner of the same sex is still unclear.

In most species, sexual behaviour is a sequence of specific events starting with a phase of attraction between sexual partners followed by phase courtship phase often referred to as the appetitive or motivational phase and ending in mating or the consummatory or copulatory phase [1,9–13].

The identification of brain areas that mediate male sexual behaviour has been the subject of investigation for at least fifty years [14–16]. In 1990, Everitt [14] suggested that in rats, the appetitive and copulatory phases of male sexual behaviour were controlled by different brain structures. A similar conclusion has been drawn recently by Taziaux et al. [17] in the quail but, this dissociation is not always clear and can differ among species.

In all species, the medial preoptic area (MPOA) is the key structure involved in male sexual behaviour and lesions in this area severely disrupt male sexual behaviour in all mammalian species that have been studied (for review see Ref. [18]). However, rats with lesions in the MPOA continue to show non-contact erections [19], to bar-press when this action has been conditioned to indicate access to an oestrus rat [20] and to prefer oestrus to anoestrus rats [21]. So for Everitt [14] the MPOA is "crucially" involved in the control of the consummatory phase of sexual behaviour but not in the appetitive responses and reward-related aspects of male sexual behaviour. However, other studies found an effect of lesions to the MPOA on partner preferences and in the frequency and duration of pursuit of the female [22,23] suggesting an involvement in the motivational components of male sexual behaviour. Some studies suggested a regional specialisation of the MPOA. Implants of anti-androgens in the MPOA suppressed sexual behaviour in male rats

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but preference for an oestrus versus an anoestrus female was only inhibited if anti-androgens were implanted in the antero-ventral and not the posterodorsal MPOA [24].

Other hypothalamic nuclei such as the paraventricular nucleus (PVN), the suprachiasmatic nucleus (SCN) and the lateral septum (LS) have been also associated with consummatory responses [25]. Fos expression was observed in these structures after intromission [26], ejaculation and sexual satiation [27]. Lesions of the PVN impaired sexual behaviour [28,29] but if lesions were restricted to the parvocellular portion of the PVN they only decreased non-contact erections and they did not prevent copulation [19,20]. The ventromedial nucleus of the hypothalamus (VMN) is a key structure for female sexual behaviour (for review see [30]) and it is also a site with a high density of androgen receptor [31] and local administration of the androgen receptor antagonist flutamide, reduced the proportion of male rats showing mounts, intromissions and ejaculations [32]. Local administration of testosterone propionate did not restore copulation but restored preference for an oestrus versus an anoestrus female [33] suggesting in rats, a role in the motivational component of male sexual behaviour.

The corticomedial amygdala which is a point of integration for chemosensory, somatosensory and hormonal information and the bed nucleus of the stria terminalis (BNST) with which it forms the extended amygdala are also key structures in the control of male sexual behaviour. Lesions in these regions impair copulation in rats, hamsters and gerbils but the deficits vary with the species and the precise location of the lesion [34–36]. Mating stimulated Fos expression in the extended amygdala in many species (for review see [18]) and the level of Fos increased with the number of copulations [37,38]. In rats, a subset of neurons in the medial amygdala (MeA) appeared to be specifically associated with ejaculation and sexual satiety [39,40]. In rats, hamsters and gerbils Fos expression was also stimulated in the extended amygdala by the perception of female chemosensory cues suggesting a role in appetitive behaviour.

The accumbens nucleus which is connected to the amygdala was involved in arousal and reward in sexual behaviour as it is in other motivational behaviours [41,42]. The concentration of dopamine was increased in these structures following exposure to sexually relevant stimuli or mating [43–45]. The expression of Fos was higher in sexually experienced males [46]. But the effects of lesions in this nucleus vary among published studies [47,48] suggesting that compensatory mechanisms exist.

Most studies of the structures involved in sexual behaviour used sexually active animals and the question of the absence of sexual motivation in males with normal levels of testosterone has been raised in few studies. In rats, De Gasperín-Estrada et al. [49] showed that such males were able to discriminate between the odours of oestrus and anoestrus females but they were not attracted by these odours [50]. Furthermore, these males did not express Fos in the MPOA, the BNST and the MeA when exposed to bedding from oestrus females [51]. Portillo and Paredes [51] proposed that the reduced sexual motivation of these males was due to altered activity in the vomeronasal pathway. In sheep, males with low sexual performance had greater expression of Fos in the MPOA and the BNST when exposed to ewes compared to males with high sexual performance [52] and these authors suggested that inhibitory neurons had been activated. The action of oestradiol has also been suggested as an explanation; the content of nuclear oestradiol receptor and the level of aromatase activity were both lower in the MPOA of non-copulatory than in copulatory rats [53–55]. Lower proportions of occupied oestradiol receptors were also found in the MPOA of rams with low sexual activity when compared to sexually active rams [56]. In humans, no change was detected in the MPOA by positron emission tomography (PET) but hypoactive sexual desire has been linked to an absence of activation or deactivation of the somatosensory cortex and the inferior parietal lobules and to a continuous activation of the medial orbitofrontal cortex [57].

The question of the brain structures involved in establishing the sex of a preferred partner has been topical since the 1990s. Several authors have attempted to link patterns of sexual differentiation of brain structures by peri-natal steroids, with the preferred sex of a sexual partner (for review see [58,59]). Interest was first directed towards the SCN which in humans is larger in homosexual men [60]. In rats, peri-natal treatment with the aromatase inhibitor ATD, which prevented sexual differentiation of the brain resulted in increased numbers of neurones that expressed vasopressin in the SCN compared to untreated controls and in an interest in both male and female sexual partners [61]. But lesions of the SCN did not affect partner preference [62] so the role of this sexually dimorphic structure remains unclear. The focus shifted to the MPOA after the discovery that in humans, the INAH3, a sexually dimorphic nucleus of the MPOA was smaller in homosexual men [63]. However this finding was not confirmed in another study [64] and in female macaques, the preference for a sexual partner of the same sex was not associated with a male type of sexually dimorphic nucleus in the MPOA [65]. In sheep, Roselli et al. [66] identified a sexually dimorphic nucleus in the MPOA (oSDN) that was larger and contained more cells in “female-oriented” males than in “male oriented” males. Female-oriented rams also had a higher level of aromatase activity in the MPOA [66,67] and pre-natal treatment with testosterone increased the volume of the oSDN and aromatase expression, characteristics associated with masculinised brain structures and male sexual behaviour [68]. In rats, the size of the of the SDN-POA following peri-natal treatment with ATD, was positively correlated with a preference for a female rat [69] but in other studies this treatment did not disrupt partner preference [70,71] and pre-natal ATD had no effect on partner preferences in sheep [72]. In male rats and ferrets, lesions of the MPOA including the sexually dimorphic nuclei (SDN POA) caused them to approach males or male odours in preference to oestrus females [73–75] and to show female-like patterns of Fos activation [76]. An inversion of partner preference was also observed in rats following the temporary inactivation of the MPOA by lidocaine [77]. In humans, current imaging techniques do not have the resolution required to analyse responses in sexually dimorphic nuclei. But in a PET study, self-identified homosexual men had female-typical profiles of hypothalamic activity following application to the upper lip, of 4, 16-androstadien-3-one, an odorant present in male sweat [78].

Other studies using functional magnetic resonance imaging (fMRI) in homosexual men have shown either less activation of the hypothalamus or no change in hypothalamic activation [79] after watching a preferred erotic video, when compared to heterosexual men [80]. Some interest has also been directed to the amygdala and in one study using fMRI; this structure was the only one with more brain activity in homosexual men in response to sexual images of their preferred sex [79]. A difference in the amygdala was also found in sheep where female-oriented rams had a higher number of oestradiol receptors in the amygdala than male-oriented rams [81] but, the level of Fos expression after exposure to females or males was not different between male and female-oriented rams exposed to females or males [52]. So the role of these structures in male sexual behaviour is still open.

In this field of research, the sheep is a valuable experimental model because 5–35% of the males are either sexually inactive or show sexual interest only in other rams [4,8,82]. Several studies have attempted to define the endocrine and neural correlates of a low sexual interest or of a preference for a sexual partner of the same sex (for review see [83,84]). But surprisingly, only one study has analysed Fos expression in rams [52] although this technique has proven useful in understanding male-female sexual