Neuroendocrine mechanisms underlying appetitive and consummatory elements of masculine sexual behaviour

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Introduction

Investigation of the neurochemical and neuroendocrine mechanisms underlying masculine sexual behaviour has been greatly influenced, perhaps especially so in the past decade, by Beach's concept of the "dual nature of sexual arousal and performance" [1,2]. He suggested that sexual behaviour depends on two, relatively independent processes: (i) a *sexual arousal mechanism,* that determines a male's sexual responses *prior* to the copulatory acts of mounting and intromission, i.e. **appetitive elements of sexual behaviour**. Its main function, therefore, is to bring a male into contact with a female and raise his sexual excitement to the threshold necessary for mounting and intromission, i.e. **consummatory elements of sexual behaviour** to occur. From this point on, a separate *intromission and ejaculatory mechanism,* controls these elements of masculine sexual behaviour, integrating the sequence of mounts and intromissions, further modifying the male's internal state so as to culminate in ejaculation. Sachs and colleagues [3-5] utilised a factor analysis of ten measures of copulatory behaviour in male rats to explore this concept further and revealed four factors, representing relatively independent processes that underlie sexual behaviour: (i) an *initiation factor,* mainly reflecting the latency to mount and intromit; (ii) a *copulatory rate factor*, principally reflecting inter-intromission interval, ejaculation latency and post-ejaculatory refractory period; (iii) a *hit rate factor* which concerns copulatory efficiency and (iv) an *intromission count factor,* which is presumably analogous to the ejaculatory mechanism of Beach's earlier theory. The initiation factor is closely related to Beach's sexual arousal mechanism and is relatively independent of the other three, presumably interrelated, factors.

Pfaus and colleagues [6] extended this factor analysis to include more direct measures of initiation. Using a novel two-level chamber they were able to measure appetitive responses of male rats (active pursuit of a female and 'level-changing' in the chamber whilst pursuing her) independently of mount and intromission latencies. This analysis indicated an 'initiation factor', accounted for by these appetitive, level-changing responses, that was clearly distinct from the earlier 'initiation factor' that principally reflected mount and intromission latencies. Clearly, there are several discrete process underlying appetitive elements of masculine sexual behaviour that may be studied separately.

This more detailed analysis retains Beach's original distinction between initiation and performance and should allow investigation of the neuroendocrine mechanisms underlying sexual behaviour to be conducted within a clearer

conceptual framework. However, the majority of studies have focused almost exclusively on the neuroendocrine basis of *consummatory* sexual behaviour (i.e. the largely reflexive motor acts seen during copulation).

Additional behavioural methods must be employed in order to probe the neural mechanisms that underlie appetitive or preparatory responses [7]. Hitherto, most researchers have relied on mount and intromission latencies and sometimes the relative phase of the post-ejaculatory interval, as indices of "arousal" or "motivation". But, such measures may not be independent of the level of consummatory competence: for example, peripheral effects of drugs that induce erection may result in reductions in mount and intromission latencies, but it would be misleading to interpret such effects as primarily motivational.

Appetitive sexual responses include the locomotor excitement and investigative behaviour, as well as instrumental acts, that serve to bring a male into direct, physical contact with a female such that consummatory responses can occur. One part of my experimental strategy has been to devise new, complementary methods to study these incentive motivational aspects of sexual behaviour. In addition to direct observations of copulatory and pre-copulatory behaviour, several experimental situations have been used that have facilitated the investigation of appetitive elements of sexual behaviour more or less independently of the ability to copulate. They include:

(i) *instrumental behaviour of male rats maintained by sexual reinforcement (the opportunity to copulate with a female in heat) presented under a second-order schedule of reinforcement.* This method is described in detail elsewhere [8] and was developed in order to obtain a measure of a male's appetitive sexual behaviour that is independent of his 'consummatory competence'. In this procedure, males are first allowed to copulate with an oestrous female in the presence of a discrete and arbitrary light stimulus (the conditioned stimulus, CS). Subsequently, when tested in the modified operant chamber in which they had previously copulated, they learn to press a lever at high rates to earn the presentation of the arbitrary CS which itself signals the ultimate presentation of an oestrous female at the end of the session. Thus, the male's instrumental behaviour is maintained by a conditioned reinforcer, which has gained its motivational significance (sexual, in this case) through its prior association with an oestrous female.

(ii) *conditioned level changing in a bi-level chamber* is a procedure that measures the locomotor activation and motivational excitement of male rats when placed in this novel, two level apparatus with a female in heat [9]. Both pursuit and level changing, as well as copulatory behaviour itself can be measured in this apparatus and, as referred to above, it provides a relatively independent measure of sexual arousal in a factor analysis of masculine sexual behaviour.

(iii) *place preference* is conditioned by the repeated exposure of males to a receptive, or an unreceptive, female in the distinctive environments of a three chambered apparatus [see ref 7]. This procedure allows the conditioned approach to the environmental cues associated with prior sexual reinforcement to be measured, again independently of the ability to copulate. The conditioned approach to the distinctive place, in this case a sexual approach, is generally regarded as a measure of the reinforcing properties of the prior sexual experience. A sexually conditioned place preference is relatively rapid and easy

to establish as well as being stable over many weeks. It therefore provides a useful method for investigating the effects of a wide range of neural, neurochemical and endocrine manipulations.

(iv) *sexual partner preference* is the preference of a male for an oestrous (i.e. sexually active) versus an anoestrous female each in one of the two sides of a place preference apparatus [see ref 7]. This method provides information about a male's choice of sexual partner that again is independent of the ability to copulate.

Data derived from these procedures may be especially interesting when, following specific neuroendocrine or neurochemical manipulations, clear dissociations of effects, especially between appetitive and copulatory responses, are observed since they point to dissociable neural mechanisms underlying different aspects of a male's sexual behaviour.

Another reason why it may be helpful to understand the basis of appetitive responses is that this may enable comparisons with the control mechanisms in other species, such as primates, especially man. Comparable attempts to produce models of human sexuality have been fundamentally different. In particular, they have focused not on patterns of behaviour, such as mounting or intromission, but on patterns of physiological response, in particular genital responses and other manifestations of arousal [10]. This in part reflects the assumption that, for a human subject, lying between a physiological state of arousal and a behavioural response is a largely imponderable complex of cognitive processes, with a wide variety of psychosocial influences. Whereas there are very specific behavioural or 'motor' patterns involved in male rodent sexuality, such as mounting and intromission, some of which are clearly reflexive and hormonally determined, there are no comparably predictable 'motor' patterns in the human repertoire. The semi-voluntary tendency to pelvic thrusting which is a feature of human sexual arousal may be related to the reflexive mounting/intromitting pattern in rats, but this has not been systematically studied in men.

A contemporary and attractive model for analysing human male sexual responses has emerged from studies of the hormonal basis of male sexuality [11]. These empirical studies have used what is available, in scientific terms, to analyse the relevant components of the sexual process. Thus, self-ratings of the frequency of sexual thoughts and associated excitement provide 'cognitive' measures of male sexuality. Assessment of the frequency and quality of various sexual acts such as sexual intercourse or masturbation provide 'behavioural' measures. The measurement of spontaneous erections during sleep, or 'nocturnal penile tumescence' (NPT), and the measurement of erectile response to various types of erotic stimuli provide 'psychophysiological' measures. I will make some comparisons between studies of the neuroendocrine basis of sexual responses in rats and men, but these are discussed more fully in Everitt and Bancroft [10].

The impact of testosterone on appetitive and consummatory elements of masculine sexual behaviour

Masculine sexual behaviour, in virtually all species that have been studied, is hormone-dependent; this is a fundamental aspect of its biological basis [5, 12-17]. Castration is followed by a decline in sexual behaviour which is restored by testosterone replacement. Although there is some consistency across species, there are still many aspects of this hormone dependence that await explanation. One particular issue concerns the speed of decline of sexual behaviour after withdrawal of androgens. Testosterone disappears rapidly from the circulation , within hours after castration, yet in rodents and primates the copulatory responses and the expression of sexual interest may continue for much longer [5,12] - weeks in male rats and many months in monkeys. Indeed, in some male rhesus monkeys mounting and even intromission may persist for years following castration. Part of the explanation is that the functional integrity of the genital periphery depends upon testosterone and it is primarily a gradual failure at this level which underlies the cessation of ejaculation, followed by intromission and finally mounting.

The observations of Hansen and Drake af Hagelsrum [16] indicated that, even in rats, some appetitive elements of sexual behaviour are evident after castration. This prompted us to assess the effects of castration under a wider range of behavioural conditions. Initially, we investigated the effects of castration and testosterone replacement on instrumental behaviour under a second-order schedule of sexual reinforcement. The procedure proved not to be optimal for studying the slow consequences of hormone withdrawal [17]. After training males to work to gain access to females, they were castrated and left for many weeks. This time period was based on a parallel study in which similarly trained and castrated rats were allowed to continue to gain access to females until they failed to make mounting attempts. After this time interval, the trained males were placed in the operant chambers having had no interaction with females since they were castrated. A control group of non-castrated males was denied access to females for the same time period. The castrated animals responded in this first session no differently from the intact controls, although both groups responded at slightly lower than their previous rates. When these males earned access to receptive females, the majority made several mounts - that is, interacted sexually with females at a time when other castrated males given weekly tests had long since given up their mounting. However, although these males mounted, they did not intromit. But by the second session, the castrated males responded for access to females at significantly lower rates than intact controls and continued to be much less willing to work for the next eight weeks. Thus, castration impaired these instrumental responses, but it was impossible to attribute this to a primary loss of the motivational effects of the hormone given the surprising results on the first test. The experience of impaired sexual ability (i.e. inability to intromit) on contact with females at this first test may have contributed to the subsequent decline in appetitive sexual behaviour (i.e. instrumental responding).

However, an unambiguous effect of testosterone was observed following the initiation of replacement therapy. Instrumental responding returned to control and pre-castration levels within seven days of testosterone administration. This occurred prior to any sexual interaction with females and

so could not have been due to the feedback of improved copulatory ability. Indeed, only a small proportion of these males intromitted efficiently following access to females after the first, post-testosterone test [17]. Thus, these experiments using a second-order schedule of sexual reinforcement have provided an unequivocal demonstration of an effect of testosterone on a sexual arousal process that is relatively independent of effects on performance variables.

The sexually conditioned place preference procedure has also revealed the marked sensitivity of incentive motivational responses to the removal of testosterone by castration. A previously established sexually conditioned place preference was promptly abolished within a week of castration, prior to any interaction with females - before, therefore, males had experienced any failure of copulatory ability and, in any case, at a time when the majority of them were still able to mount, intromit and even ejaculate [7,18]. By contrast, preference for a sexually receptive female declined after castration in parallel with declining copulatory competence, a failure to intromit during an interaction usually indicating the loss of preference during the next preference test [7,18].

These observations strongly suggest that the sexual reward-related processes that underlie place preference, as well as instrumental sexual acts, are testosterone-dependent but, since medial preoptic/anterior hypothalamic area (mPOA) lesions do not affect either (see below), that a site outside this area most likely mediates these effects of the steroid. However, it is as yet unclear where these steroid-dependent neural systems are located. Obvious candidates might be other, steroid-accumulating limbic structures, such as the amygdala, lateral septum or bed nucleus of the stria terminalis but, surprisingly, there is very little information on the behavioural impact of sex steroids acting in such structures. Part of the explanation may involve the androgen dependence of the genitalia and associated spinal reflexes, since their requirements in terms of 5-α dihydrotestosterone are well known, and local implantation of androgens in the brain would not be effective in restoring the function of these peripheral mechanisms [see ref 5]. But this does not seem to be the whole story, especially when taken in conjunction with the rather specific behavioural consequences of removing the primary sex steroid target, the mPOA.

There is now consistent evidence that androgens, and in particular testosterone, are necessary (though not sufficient) for sexual desire in men. This has been demonstrated most clearly in studies of hypogonadal or castrated adult men where withdrawal and replacement of testosterone leads to a decline and restoration of sexual interest and associated sexual activity [19-21]. Assessment of these changes has involved the simple recording of behavioural events (e.g. sexual activity with partner or solitary masturbation) and the measurement of sexual interest as self-ratings of frequency of sexual thoughts and associated feelings of excitement.

The role of androgens in erectile function has proved to be more difficult to determine. Spontaneous erections that occur during sleep (i.e. nocturnal penile tumescence or NPT) have been shown to be androgen dependent [22-25]. They are impaired in states of androgen deficiency and restored with androgen replacement. The clear association between androgens and sexual desire, and the common occurrence of impaired NPT in men with loss of sexual desire for non-hormonal reasons, has led to the assumption that NPT provides a

neurophysiological window into the androgen-dependent substrate of both sexual desire and sexual arousability in the brain [11].

In contrast, erections in response to visual erotic stimuli are independent of androgens. They persist in hypogonadal men and are not altered by androgen replacement [22,25,26]. Erections in response to erotic fantasy may be androgen dependent [26], though as yet the evidence is inconclusive. If this is so, it suggests that the cognitive processes involved in the generation of erotic fantasy, or at least the interface between such cognitions and sexual arousal, may be androgen dependent. These findings indicate that there are at least two systems in the brain; one androgen dependent, subserving sexual arousability and sexual desire, one manifestation of which can be measured by spontaneous erections during sleep; the other androgen-independent, involving responses to moving visual stimuli. Detailed investigation of such dualism in non-human species has not been undertaken to any great extent and is likely to be difficult.

Effects of hypothalamic lesions and opioid peptides on appetitive and consummatory elements of masculine sexual behaviour.

Heimer and Larsson [27] first reported that large, electrolytic lesions of the entire mPOA abolished copulatory behaviour in male rats. More recently interest has focused on the behavioural specificity of mPOA lesions, in particular the selective sparing of elements of a male rat's sexual responses. Heimer and Larsson themselves reported that when mPOA-lesioned males were presented with a female, they approached, pursued and nuzzled her, engaged in genital investigation and displayed a curious form of mounting, approaching her from the side rather than the rear, and proceeding to climb over her.

Bilateral lesions of the mPOA, induced by the axon-sparing neuronal excitotoxin, ibotenic acid, also abolished copulatory acts in male rats, demonstrating that it is damage to intrinsic mPOA neurons, rather than pathways passing through the area, which is necessary for the behavioural impairment [28,29]. Also, a wide range of so-called displacement behaviours emerged during such sexual interactions, suggesting the thwarting of sexually motivated response tendencies in lesioned males [16]. However, investigative and other appetitive sexual responses, including abortive mounting attempts, were spared following mPOA lesions. These and our own confirmatory observations [7,17] indicate that the deficit in sexual behaviour following mPOA lesions is one of the performance of the reflexive acts of mounting with clasping, pelvic thrusting, intromission and ejaculation. Lesioned males remain interested in oestrous females, are activated in their presence and this excitement may be channelled into apparently purposeless motor acts. Thus, in an appropriate sexual context, males with mPOA lesions show every indication of being sexually aroused.

Comparable effects of mPOA lesions have been seen in other species [30-33]. For example, in male goats in which copulation and ejaculation had been abolished by mPOA lesions, courtship responses and even mounting persisted at preoperative levels, although the mounts were often inappropriately directed [32]. Flehmen, self-enurination and penis licking, which males readily display during sexual encounters, were similarly unaffected by mPOA lesions and were sometimes increased [32]. As in non-primate male mammals, mPOA lesions in

male rhesus monkeys severely impaired copulation when males were with females [34]. However, in their home cages, males were seen to engage in bouts of masturbation and, from the evidence of seminal plugs in the drop pans under the cages, ejaculated as frequently as controls. This again suggests that mPOA-lesioned males may be sexually aroused and display sexual acts resulting in ejaculation, but are unable to copulate during encounters with females. It also suggests that the failure of ejaculation after mPOA lesions is the indirect result of a failure of mounting, pelvic thrusting and intromission.

The nature of the 'spared' sexual responses following mPOA lesions has become clearer through the use of the behavioural methods outlined above that measure appetitive responses. Thus, lesions of the mPOA of male rats [17] did not effect instrumental behaviour to gain access to a receptive female presented under a second-order schedule, even though the males were unable to copulate with females once they gained access to them. Comparable lesions of the mPOA in male rhesus monkeys were also without effect on lever pressing for access to a female, although not under a second-order schedule [34]. Thus conditioned measures of appetitive behaviour, as well as species-specific, unconditioned precopulatory responses to sexual incentives, are spared following hypothalamic damage. This may indicate that the role of the hypothalamus is more to integrate spinal mechanisms governing reflexive responses, such as mounting and thrusting, than to orchestrate more flexible response patterns, such as instrumental behaviour.

Similarly, with conditioned place preference (CPP), lesions of the mPOA had no direct effect on the conditioned approach response, although it declined after several tests in which males were unable to copulate - presumably because attempts to do so were no longer reinforcing [7,18,35]. In fact, preventing intromission in intact, control males resulted in a decrease in CPP over a similar time course. However, it is perhaps surprising that mPOA lesions did not affect a male's preference for a receptive, rather than an unreceptive, female even though he was unable to copulate with her [7].

Thus there appears to be a remarkable specificity in the effects on masculine sexual behaviour of lesions to the preoptic area. Although unable to copulate, such males work for access to a receptive female, approach and spend more time in an environment where they have come to expect a receptive female to be, prefer to be in the presence of a receptive rather than an unreceptive female and spend a great deal of time engaged in olfactory investigation and abortive mounting. In short, the neural mechanisms governing consummatory elements of masculine sexual behaviour, have been dissociated from those governing precopulatory, appetitive responses. The relevance of this to the human is not yet clear.

Chemical manipulations of the mPOA also result in dissociations of this kind, but only in one instance has the comparison of the effects of chemical manipulations of the mPOA been made across a variety of behavioural procedures. Thus, ß-endorphin infused bilaterally into the mPOA dose-dependently inhibited sexual behaviour. Mounts and intromissions eventually ceased to occur and the latencies to mount, intromit and ejaculate were prolonged - eventually to the duration of the 15 minute test session or even longer [36,37]. Subsequent experiments explored the nature of this effect, especially assessing whether males lose interest in females as a result of the treatment. Careful observation of pre-copulatory, investigative responses

revealed that ß-endorphin-infused males actively investigated and pursued females and, to some extent, made abortive mounting attempts [6] - changes in behaviour which were seen in a more emphatic way following lesions of the mPOA [7,18]. Analysis of the behavioural sequence revealed that when a treated male and female first made contact, the pattern of interaction was not significantly different from that seen with control males, but that the sequence broke down at the point when investigative responses usually switched to the copulatory responses of mounting and intromitting; thus, ß-endorphin infused into the preoptic area appears not to affect sexual interest or arousal, but instead the transition between investigative and copulatory responses of mounting and intromitting [36,38].

Infusion of ß-endorphin into the mPOA had no effect on instrumental responding for a receptive female presented under a second-order schedule of sexual reinforcement, nor on the expression of a place preference conditioned by sexual interaction with such a female. However, the same treatment rapidly abolished a male's preference for a receptive, over an unreceptive, female tethered in either side of the place preference apparatus [7,37].

A further dimension to the analysis of the effects of ß-endorphin followed its infusion into the mPOA after an intromission, rather than before interaction with a female had begun. The peptide no longer had an inhibitory effect on mounting, intromission or ejaculation. Furthermore, the inhibitory effects of ß-endorphin were lost or reduced even if a delay of two hours or so was interposed between a single intromission and the infusion, provided the male was re-tested with the same female with which he had intromitted previously. If a different female was placed with the male following intromission, then the inhibitory effect on copulatory behaviour of ß-endorphin reappeared [38]. These results clearly suggest that ß-endorphin does not simply act to prevent copulation, since if the male is allowed to begin interacting sexually with an individual female, the otherwise inhibited behaviour and ejaculation will occur.

Taken together, the results of these experiments reveal the remarkable behavioural specificity of the effects of ß-endorphin infused into the mPOA. The peptide does not, apparently, influence appetitive aspects of sexual behaviour nor reward-related processes, so far as these are assessed in the place preference procedure. Instead, intra-hypothalamic ß-endorphin appears to prevent the display of the copulatory reflexes which together form the consummatory elements of the sexual response sequence. However, even here the effects of the peptide are not absolute, since if the male is allowed to engage sexually with a female, then the inhibitory effects of the peptide are themselves inhibited. The impaired preference for a receptive female which follows ß-endorphin infusion appears to be related to the failure to initiate the copulatory sequence - presumably only if the peptide is infused prior to an intromission, although this has not been tested explicitly by studying its effects on preference when infused after an intromission.

Therefore, a neural mechanism may exist in the mPOA which allows the appropriate behavioural responses of mounting and intromitting to be matched to a relevant sexual incentive stimulus and it is this which is impaired in the ß-endorphin-treated male rat. This may suggest a particular relationship between the intrinsic sensory properties of a receptive female and the species-specific motor output of copulatory reflexes, since acquired motor responses (e.g. lever-pressing or conditioned approach) for conditioned incentives, such as a light CS

or the properties of the preferred place, are completely unaffected by the same ß-endorphin manipulation of the mPOA. The behaviour of a rat in the operant and place preference procedures may, therefore, be controlled by the same mechanisms that underlie unconditioned appetitive or preparatory responses and these appear not to reside within the mPOA, since lesions of this structure are also without effect on these parameters [7].

The effects of the opiate receptor antagonist naloxone on sexual behaviour have also been studied using a number of these behavioural procedures. Systemic naloxone may, in some circumstances, facilitate sexual behaviour in male rats (see above), but if given to intact, sexually active males these effects are small [39]. However, the same treatment *reduced* instrumental responses for a female presented under a second-order schedule of reinforcement, promptly abolished a previously acquired conditioned place preference but had no effect on partner preference [7,18]. Infusing naloxone bilaterally into the mPOA resulted in a powerful *facilitation* of copulatory behaviour; males required fewer intromissions to ejaculate with a much reduced latency, yet had no effect on instrumental behaviour or a conditioned place preference. Partner preference was seen to be reduced following this treatment, but analysis of the data revealed this to be an epiphenomenon of the increased sexual activity, since males spent more of the test period in a state of refractoriness and therefore away from both females in the neutral compartment of the choice apparatus [7,18].

It is clear from these results that opioid mechanisms within the mPOA seem not primarily to be involved with incentive motivational responses to sexual stimuli, but are more involved with consummatory sexual responses. However, more interesting, perhaps, is the indication that such incentive - or reward-related - responses are sensitive to systemic naloxone. In addition, it has been shown that this sensitivity is much greater in animals recently having been castrated [40,41]. Since castration also profoundly affected a sexually conditioned place preference [7,18] and instrumental sexual responses [7,17], while mPOA lesions, as well as intra-mPOA opioid manipulations, were without effect on these measures, opioid involvement in sexual reward-related processes may both be sex hormone-dependent and involve extrahypothalamic substrates [7]. The ventral tegmental area dopaminergic system innervating ventral striatal and limbic structures is an obvious focus for experiments investigating this issue.

Indeed, in a particularly interesting series of experiments, Mitchell and Stewart [42,43] have demonstrated that infusions into the ventral tegmental area of morphine and dynorphin$_{1-13}$ increased the number of males that mounted and showed female-directed behaviour [42]. Morphine, but not dynorphin$_{1-13}$, increased dopamine metabolism in the nucleus accumbens, indicating that the effects of these opioid peptides infused into the A10 region may have dopamine-dependent and dopamine-independent actions on sexual behaviour. In addition, it was demonstrated that masculine sexual behaviour was facilitated when males were placed in an environment that previously had been associated with systemic injections of morphine [43]. This important observation demonstrates that the conditioned reinforcers established through the pairing of a previously arbitrary constellation of cues with the positive incentive effects of morphine can significantly affect, in this case facilitate,

sexual behaviour that is under the control of the conditioned and unconditioned incentive properties of an oestrous female.

Functional activation of limbic structures by copulation and sexual incentive stimuli

Immunocytochemical visualization of the protein FOS, which is the product of the expression of the immediate-early gene c-*fos*, has been used to identify and establish the functional relationships between the neural structures engaged during copulation [44] and also those activated during exposure to conditioned, sexual incentive cues (Everitt, Baum & Morrison, to be published). Sexual interaction culminating in intromissions or ejaculation results in a dramatic increase in the expression of FOS in several structures: the mPOA, medial amygdala, bed nucleus of the stria terminalis and midbrain central tegmental field [44]. We were subsequently able to demonstrate: (i) that the activation of neurons in the central tegmental field was the result of genital somatosensory stimulation during copulation; (ii) that the activation of neurons in the medial amygdala and bed nucleus of the stria terminalis was the result primarily, but not exclusively, of olfactory stimuli encountered during sexual interaction and (iii) by placing lesions in either or both the medial amygdala and homolateral central tegmental field, that the activation of mPOA neurons depended upon the relay of somatic sensory and olfactory information from these specific midbrain and forebrain sites.

Although the dependence of mPOA activation upon the functional integrity of afferents from the medial amygdala and midbrain tegmentum was a novel finding, it was perhaps not surprising to see that this constellation of structures was activated in male rats during copulation, given the results of lesion-based studies conducted over many years [see ref 5 for review]. However, they were not the only structures to show an increase in FOS expression. In particular, neurons in the nucleus accumbens core and shell, as well as in the overlying medial caudate-putamen also showed a marked increase in nuclear FOS-immunoreactivity following sexual interaction. Perhaps more interestingly, these neurons in the ventral and dorsal striatum, along with another population in the basolateral amygdala, also had significantly increased numbers of FOS-immunoreactive nuclei when they were exposed to a context explicitly paired with copulation, but in the absence of a female in heat. Thus, exposure to conditioned sexual incentive stimuli was also associated with activation of these structures. But under these conditions the mPOA, medial amygdala, bed nucleus of the stria terminalis and midbrain central tegmental field were completely quiescent. Thus, sexual interaction itself, specifically anogenital olfactory investigation, mounting and intromitting, were necessary for activation of the latter structures, whereas exposure to stimuli previously associated with copulation, but not copulation itself, was sufficient to activate certain limbic and striatal structures. Experimental investigation of the role of these structures in appetitive elements of masculine sexual behaviour will be discussed in the following sections.

Ventral striatal dopamine and appetitive elements of masculine sexual behaviour

The ventral striatum, including the nucleus accumbens, receives a rich dopaminergic innervation arising in the midbrain ventral tegmental area. Drugs that increase and decrease dopamine transmission have marked effects on aspects of masculine sexual behaviour, and some of these effects can be localized to the region of the nucleus accumbens. Thus, systemic treatment with a range of dopaminergic drugs has long been known profoundly to affect the display of sexual behaviour in rodents. Recently, it has become apparent that these effects of dopamine receptor blockade are not simple; with more careful attention to differential effects on D1 and D2 receptors as well as dosage, discrete effects on precopulatory behaviours have been demonstrated. For example, in male rats all neuroleptic drugs decreased rates of conditioned level changing in a bi-level chamber, and atypical neuroleptics dose-dependently delayed the initiation of copulation, but had little effect on copulatory behaviour once it was initiated [45]. Metoclopramide, on the other hand, dose-dependently reduced the number of intromissions to ejaculation, but had no effect on initiation latencies, whereas the typical neuroleptics haloperidol and pimozide both prolonged mount and intromission latencies and also altered the number of intromissions preceding ejaculation [45].

The differential behavioural effects of these drugs may be interpreted in the light of recent *in vivo* neurochemical data which indicate the differential release of dopamine in the preoptic area, dorsal and ventral striatum that is correlated with relatively discrete epochs of sexual interaction (see below). Thus, those dopaminergic antagonists which more or less selectively block dorsal striatal (i.e. caudate-putamen) dopamine receptors affect only copulatory responses - in fact, they may actually decrease the ejaculation threshold in terms of the number of intromissions required to reach it [45,46]. By contrast, those drugs which predominantly affect ventral striatal dopamine receptors, such as the atypical neuroleptics (e.g. clozapine), delay the initiation of copulation with no other behavioural effects [45,46]. In other words, appetitive rather than copulatory elements of sexual behaviour are primarily affected.

The special sensitivity of such precopulatory responses to dopaminergic blockade was further demonstrated in experiments utilizing a second-order schedule of sexual reinforcement. Thus, the mixed D1/D2 dopaminergic receptor antagonist, α-flupenthixol, dose-dependently decreased responding to gain access to a receptive female [7]. The drug also prolonged mount and intromission latencies, although at doses slightly greater than those that decreased instrumental respones. More importantly, these effects on appetitive, or pre-copulatory, behaviour were achieved at doses of the drug that had no significant effect on mounts or intromissions. Only at the highest doses tested were all measures of sexual behaviour affected, when the majority of males did not intromit or ejaculate [7].

It is important to consider the neural site of action of these behavioural effects of dopaminergic drugs. Infusion of dopamine receptor agonists into the mPOA selectively enhanced measures of copulatory behaviour, such as intromission rates and efficiency, but did not affect latencies to mount and intromit [47]. Dopaminergic receptor antagonists, or presynaptic doses of the agonists, tended to have opposite effects [47]. These effects may depend upon

alterations in the autonomic control of penile reflexes, e.g. lengthening the latency to erection, indicating that such genital changes may mediate the apparent "motivational" effects of drugs - especially when measured as alterations in initiation latencies.

It is evident that the marked changes in appetitive aspects of masculine sexual behaviour that follow systemic [7,45,47] or intracerebroventricular [47] infusion of dopaminergic drugs, do not obviously follow direct intra-hypothalamic treatment, although infusions of haloperidol into the mPOA reduced rates of conditioned level changing [45], an appetitive response that does not appear to depend upon alterations in penile responsiveness. Clearly, sites of action outside the hypothalamus must mediate many of these effects of dopaminergic drugs on appetitive measures of sexual activity, the striatum being an obvious candidate.

Manipulating dopamine in the ventral striatum affects appetitive sexual responses, but not copulation itself. Thus, infusing the dopamine releaser D-amphetamine into the nucleus accumbens, dose-dependently increased instrumental responding for access to an oestrous female, reduced latencies to mount and intromit, but did not alter copulatory responses, such as mounts, intromissions and ejaculation, "hit rate" or ejaculation latency [7,48]. Conversely, lesioning the dopaminergic innervation of the ventral striatum by infusing the neurotoxin 6-hydroxydopamine, significantly lengthened mount and intromission latencies, also without altering copulatory performance [7]. Similarly, infusing the predominantly D2-receptor antagonist, haloperidol, into the ventral striatum reduced rates of conditioned level changing, but did not affect measures of copulation [45,46].

The impact of these manipulations on incentive motivational processes in a sexual context was further demonstrated by a procedure that effectively "devalued" as sexual incentives the receptive females with which neuroleptic-treated males were interacting. This was achieved by injecting hormone-primed females systemically with the neuroleptic, α-flupenthixol. This treatment selectively abolishes the female's proceptive, soliciting responses but actually enhances her display of immobile lordosis postures [49]. In this condition, mounts and intromissions will only occur if the male initiates them and, even in normal males, this results in prolonged mount and intromission latencies [7]. Males infused into the ventral striatum with the D2-dopamine receptor antagonist, raclopride, were markedly affected by this coincident treatment of females with alpha-flupenthixol, such that latencies to mount and intromit were more than doubled. Some males were so affected by this relative immobilization of females, that mounting and intromitting were actually prevented, even though males treated in this way showed only modest increases in their latencies to mount and intromit when with untreated females who were actively soliciting [7]. These data demonstrate the importance of the dopaminergic innervation of the ventral striatum in the display of appetitive responses to sexual incentive stimuli.

Microdialysis has been used to examine extracellular concentrations of DA, its acid metabolites DOPAC and HVA, and the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) during appetitive and consummatory phases of sexual activity in male rats. Dialysates from the nucleus accumbens of sexually active male rats revealed a small increase in DA and its metabolites during the appetitive phase, but a dramatic and sustained increase during

active copulation [50]. In contrast, dialysates from the dorsal striatum revealed a small and progressive increase in DA and its metabolites throughout the test session that was not correlated with any particular aspect of copulation. Subsequent work established that the increases were not due to general locomotor activity, nor were they due to the novelty of the testing chamber [51], and that the increased DA transmission in the nucleus accumbens during these phases of sexual activity did not require sexual experience [52-54].

The interpretation of these results is complex. Fibiger [55] and Pfaus [see ref 46] have suggested that, since DA receptor antagonists bind competitively with DA for occupancy at DA receptors, the greater sensitivity of appetitive responses to the disruptive effects of these drugs may reflect the lower concentration of extracellular DA that is available to compete with the drug. In contrast, consummatory responses may be less susceptible to disruption by DA antagonists because DA release is high during such behaviour. However, consummatory elements of masculine sexual behaviour have not been seen to be disrupted following dopamine receptor antagonist infusions into, or 6-hydroxydopamine-induced lesions of, the ventral striatum. Moreover, it may also be argued that the conditioned and unconditioned sexual incentive stimuli associated with a female in heat that induce small, but significant, increases in extracellular DA in the nucleus accumbens when the male is at a distance, induce a much greater increases in DA during sexual interaction itself, because they are even more efficacious (salient, powerful) when the male is in direct contact with the female. It will be very difficult, but important, to separate the accumbens DA response to copulation *per se*, from the response to the sexual incentive stimulus properties of a female in heat.

The use of *in vivo* voltammetry has further enhanced our understanding of the role of DA in male sexual behaviour [53,56]. This technique has shown a small phasic rise in DA oxidation current in the nucleus accumbens that is of short duration during the appetitive phase, but a larger and sustained increase during copulation [56]. However, the DA oxidation current declines precipitously after ejaculation, during the absolute refractory period, but rises again before the male reinitiates another copulatory series. The dynamic nature of DA transmission in the nucleus accumbens contrasts with that of the dorsal striatum, which, as observed with microdialysis, showed a small but progressive increase throughout the test that was not correlated with any specific phase of sexual behaviour. The DA oxidation current in the nucleus accumbens of male rats also appears to be sensitive to olfactory or pheremonal cues provided by oestrous females [57], although the increases observed during the presentation of oestrous vaginal secretions on a glass slide are less than those obtained during the presentation of an oestrous female [56]. In contrast, DA oxidation currents did not increase in the dorsal striatum during the presentation of sexually-relevant stimuli.

Taken together, these data clearly demonstrate the marked impact of changes in ventral striatal DA transmission on appetitive, rather than consummatory, elements of masculine sexual behaviour. Dopaminergic drugs have also been reported to affect sexual behaviour in men, for example apomorphine, a mixed D1 and D2 dopamine receptor agonist, increases the likelihood of spontaneous erections in normal human volunteers and men with psychogenic erectile dysfunction [58,59], but the D2 side-effects of such agonists, such as nausea or vestibular disturbance, make such positive drug effects

difficult to elicit. Thus, whereas agonists, such as bromocriptine, are effective in reducing prolactin levels and increasing sexual desire in men with hyperproplactinaemia, they are highly likely to produce overpowering side-effects in men with normal prolactin levels [10].

The limbic forebrain and sexual behaviour

In their original paper, Heimer and Larsson [27] discussed the likely neural structures with which the mPOA interacts, such that lesions of the area result in a specific pattern of disrupted masculine sexual behaviour. They emphasized the role of the mPOA in terms of its "strategic position in the limbic system" and especially mentioned its interactions with olfactory structures via the corticomedial amygdala and stria terminalis - structures that we have shown to be activated and serially interrelated by visualising FOS in the central nervous system following mating [44]. The impact of these components of the limbic system on sexual behaviour is particularly obvious in the context of olfactory processes.

However, Heimer and his colleagues [60,61], Kelley and Nauta [62] and, more recently, Groenewegen and his colleagues [63] have subsequently demonstrated that allocortical and sub-cortical components of the limbic system, including the basolateral amygdala, project richly onto the ventral striatum, including the nucleus accumbens. Thus, we see a route through which the affective information processing in limbic structures - such as stimulus-reward associations in the case of the amygdala - might come to affect action through interactions with the striatum, where modulation by the dopaminergic system can occur. Does such a system have any significance for the display of sexual behaviour?

The many reports of enhanced and aberrant sexual behaviour following temporal lobe lesions, originally thought to be due to amygdaloid damage, have been shown more recently to be related to coincident damage to temporal neocortical structures [see 5,7,48 for review]. Lesions restricted to the basolateral regions of the amygdala are without effect on copulation in male rats [48], although lesions which damage corticomedial regions impair sexual behaviour, much as do lesions of other olfactory structures [see 5]. However, there are marked consequences for sexual behaviour of damaging the amygdala, but to demonstrate them an appropriate paradigm must be employed. Thus, under the second-order schedule of sexual reinforcement, bilateral, excitotoxic, axon-sparing lesions of the basolateral parts of the amygdala in male rats permanently depressed instrumental responding maintained by the (sex-associated) conditioned reinforcer. However, when an oestrous female ultimately entered the operant chamber, copulation was unimpaired [48]. Thus, the effects of mPOA and basolateral amygdala lesions are doubly dissociated using this behavioural procedure: mPOA lesions impair copulatory competence but not instrumental sexual responses while amygdala lesions have the opposite pattern of effects [see 7,64].

In these same experiments, evidence of an important functional interaction between the basolateral amygdala and dopamine-dependent events in the ventral striatum was obtained. Thus, in lesioned animals, infusion of the dopamine releasing drug D-amphetamine into the ventral striatum enhanced responding under the second-order schedule of sexual reinforcement (provided

the conditioned reinforcer was presented contingent on responding), that is, it ameliorated to some extent the effects of the lesion [48,64]. The same treatment also reduced subsequent mount and intromission latencies, but did not affect copulatory parameters. The broader implications of these observations are discussed in detail elsewhere [7,48,64,65,66]. In brief it may be suggested that the processes by which stimuli associated with sexual interaction gain motivational significance such that they can elicit and control appetitive sexual responses depend, at least in part, upon the basolateral amygdala. The way that these affective processes change behavioural output depends upon the integrity of interactions between the basolateral amygdala and the ventral striatum - interactions that are profoundly affected by activity of the mesolimbic dopamine system.

Summary

In summary, the discussion in this paper has been focused on the distinctions between appetitive and consummatory elements of sexual behaviour and the notion that discrete neural structures, or systems, are especially associated with these different forms of sexual response. Of fundamental importance is that testicular testosterone is necessary for the full range of these sexual responses to be displayed. Whilst we know about the important sites of action of testosterone (or its metabolites) in the context of the acts of genital investigation, mounting and intromitting, we know relatively little about the sites at which testosterone affects appetitive responses and reinforcement processes. Nor is it entirely clear whether limbic-striatal and hypothalamic circuitries operate in parallel or in series to orchestrate the integrated pattern of sexual behaviour that is normally observed - namely appetitive responses that enable a male to gain close proximity with a female in heat such that the reflexive and stereotyped pattern of copulatory responses can then occur. These are issues for future research.

References

1   Beach FA, Psychosom. Med 1942; 4: 173-198.
2   Beach FA, In: Jones MR, ed. Nebraska Symposium on Motivation. Lincoln: University of Nebraska Press. 1956; 4: 1-31.
3   Sachs BD, In: McGill TE, Dewsbury DA, Sachs BD, eds. Sex and Behaviour. New York: Plenum Press; 1978; 267-295.
4   Sachs BD, Barfield RJ, In: Rosenblatt JS, Hinde RA, Shaw E, Beer C, eds. Advances in the Study of Behaviour. vol 7. Orlando FL, Academic Press; 1976; 91-154.
5   Meisel RL, Sachs BD, In: Knobil E. and Neill J.D, eds. The Physiology of Reproduction Vol 2. Second Edition. Raven Press. 1994; 3-107.
6   Pfaus JG, Mendelson SD, & Phillips AG. Psychoneuroend 1990; 15: 329-340.
7   Everitt BJ. Neurosci Biobehav Rev 1990; 14: 217-232.

8   Everitt BJ, Fray PJ, Kostarczyk E, Taylor S, Stacey P. J. comp. Psychol. 1987; 101: 395-406.
9   Mendelson SD, & Pfaus JG. Physiol Behav, 1989; 45: 337-341.
10   Everitt BJ, Bancroft J. In: Bancroft J, Davis CM, & Ruppel HJ, Jr eds Annual Review of Sex Research. Vol. II. . Society for the Scientific Study of Sex 1991; 77-118.
11   Bancroft J. Human Sexuality and its Problems, 2nd ed. Churchill Livingstone, Edinburgh, 1989.
12   Bermant G, Davidson JM. Biological Bases of Sexual Behaviour. New York: Harper & Row; 1974.
13   Beach FA. Physiol. Rev. 1967; 47: 289-316.
14   Davidson JM. Endocrinology 1966; 79: 783-794.
15   Davidson, J.M. Anim. Behav. 1966; 14: 266-272.
16   Hansen S, Drake af Hagelsrum LJK. Behav. Neurosci. 1984; 98: 868-883.
17   Everitt BJ, Stacey P. J. comp. Psychol 1987; 101: 407-419.
18   Hughes AM, Herbert J, and Everitt BJ. Psychopharmacology 1990; 102: 243-256.
19   Davidson JM, Camargo, CA, Smith ER. J. clin. Endocr. Metab 1979; 48: 955-958
20   Skakkebaek, NE, Bancroft J, Davidson DW, Warner P. Clin Endocrinol 1981; 14: 49-67.
21   O'Carroll RE, Shapiro C, Bancroft J Clin Endocrinol 1985; 23: 527-538.
22   Kwan M, Greenleaf WJ, Mann J, Crapo L, Davidson JM. J clin Endocr Metab 1983; 57: 557-562
23   Everitt BJ, Keverne EB. In: Lightman SL, Everitt BJ, eds. Neuroendocrinology. Blackwells Scientific Publications, Oxford. 1986; 472-536
24   Cunningham GR, Karagan I, Ware JC, Lantz CD, Thornby JI. J Androl 1982; 3: 241-247.
25   Carani C, Bancroft J, Granata A, Del Rio G, Marrama P. 1991 see ref 10.
26   Bancroft J, Wu FCW. Arch Sex Behav 1983; 12: 59-66.
27   Heimer L, Larsson K. Brain Res. 1966/67; 3: 248-263.
28   Hansen, S. In: Sodersten P, ed. Behavioural Neuroscience in Scandinavia. Scand J Psychol (Suppl. 1) 1982; 121-126.
29   Hansen S, Köhler C, Goldstein M, Steinbusch HWM. Brain Res 1982; 239: 213-232.
30   Hart BL. J. comp. physiol. Psychol. 1974; 86: 328-349.
31   Hart BL. Physiol. Behav. 1986; 36: 301-305.
32   Hart BL, Haugen CM, Peterson DM. Brain Res.1973; 54: 177-191.
33   Hart BL, Voith VL. Brain Res. 1978; 145: 406-409.
34   Slimp JC, Hart BL, Goy RW. Brain Res. 1978; 142: 105-122.
35   Everitt BJ. In: Archer T, Hansen, S. eds. Biological Psychology: Neuroendocrine axis New Jersey: Lawrence Erlbaum , 1991; 111-122.
36   Hughes AM, Everitt BJ, Herbert J. Neuroscience 1987; 23: 1063-1073.
37   Hughes AM, Everitt BJ, Herbert J. Neuroscience 1988; 2: 689- 698.
38   Stavy M, Herbert J. Neuroscience 198; 30: 433-442.
39   Pfaus JG, Gorzalka BB. Neurosci Biobehav Rev 1987; 11: 1-34.
40   Mehrara BJ, Baum MJ. Psychopharmacology 1990; 101: 118-125.
41   Miller RL, Baum MJ. Pharmacol. Biochem. Behav. 1987; 26: 781-789.
42   Mitchell JB, Gratton A. Brain Res 1991; 551: 20-27.

43   Mitchell JB, Stewart J. Pharmacol. Biochem. Behav. 1990; 35: 643-650.
44   Baum MJ, Everitt BJ. Neuroscience 1992; 50: 627-646.
45   Pfaus JG, Phillips AG. Behavioral Neuroscience, 1991; 105: 727-743.
46   Pfaus JG, Everitt BJ. In: Bloom FE, Kupfer DJ eds. Psychopharmacology:
     The Fourth Generation of Progress. Raven Press New York. 1994 (in press)
47   Bitran D, Hull EM. Neurosci Biobehav Rev 1987; 11: 365-389.
48   Everitt BJ, Cador M, Robbins TW. Neuroscience 1989; 30: 63-75.
49   Everitt BJ, Fuxe K, Hokfelt T, Jonsson G. J comp Physiol Psychol 1975; 89:
     556-572.
50   Pfaus JG, Damsma G, Nomikos GG, Wenkstern DG, Blaha CD, Phillips
     AG, Fibiger HC. Brain Res 1990; 530: 345-348.
51   Damsma G, Pfaus J.G, Wenkster D. Phillips AG, Fibiger HC. Behav
     Neurosci 1992; 106: 181-191.
52   Mas M, Gonzalez-Mora J, Louilot A, Sole C, Guadalupe T. Neurosci Lett
     1990; 110: 303-308.
53   Mas M, Neurosci Biobehav Rev 1994 (in press).
54   Wenkstern D, Pfaus JG, Fibiger HC. Brain Res 1993; 618: 41-46.
55   Fibiger HC. Sem Neurosci 1993; 5: 321-328.
56   Phillips AG, Pfaus JG, Blaha CD. In: Willner P, Scheel-Kruger J, eds. The
     mesolimbic dopamine system: From motivation to action, London: Wiley.
     1991; 199-224.
57   Mitchell JB, Gratton A.. Brain Res 1991; 551: 20-27.
58   Lal S, Ackman D, Tharundayil JX, Kiely ME, Etienne P. Progress in
     Neuropsychopharmacology and Biological Psychiatry 1984; 8: 695-699.
59   Rosen RC. In: Bancroft J, Davis C.M, Ruppel H.J Jr, eds. Annual Review of
     Sex Research. Vol. II. Society for the Scientific Study of Sex 1991; 119-180.
60   Alheid GF, Heimer L. Neuroscience 1988; 27: 1-39.
61   Heimer L, Wilson RD. In: Santini M, ed. Golgi Centennial Symposium.
     New York: Raven Press. 1975; 177-192.
62   Kelley A.E, Domesick VB, Nauta WJH. Neuroscience 1982; 7: 615-630.
63   Groenewegen HJ, Berendse HW, Wolters JG, Lohman AHM. In: Uylings
     HBM, Van Eden CG, De Bruin JPC, Corner MA, Feenstra MPG, eds. The
     Prefrontal Cortex: its structure, function and pathology. Progr Brain Res
     1990; 85: 95-118
64   Everitt BJ, Robbins TW. In: Aggleton J P, ed. The Amygdala:
     neurobiological aspects of emotion, memory and mental dysfunction. John
     Wiley & Sons Inc:New York. 1992: 401-430
65   Cador M, Robbins TW, Everitt BJ. Neuroscience 1989; 30: 77-86.
66   Robbins TW, Cador M, Taylor J.R, Everitt BJ. Neurosci. Biobehav. Rev.
     1989; 13: 155-162.

Discussion - NEUROENDOCRINE MECHANISMS UNDERLYING APPETITIVE AND
CONSUMMATORY ELEMENTS OF MASCULINE SEXUAL BEHAVIOUR

J.G. Pfaus

Obviously, there is a lot of cross talk between the mPOA and the VTA and there are pathways that connect the VTA to the mPOA and both regions contain androgen receptors. How do you think they might talk to each other?

B.J. Everitt

This has been studied, for example, in the context of maternal behaviour with an asymmetric lesion procedure, which is a rather powerful paradigm for looking to see whether there is seriality of connections between distinct neural structures, and indeed one can show that asymmetric lesions of the preoptic area on one side of the brain and in the region of dopamine neurons in the ventrotegmental area on the other will together produce a combined deficit in maternal behaviour similar to a bilateral lesion of either structure alone. In those experiments the midbrain manipulation was not selective for dopamine neurons, but perhaps one can consider the attractive possibility that the processing of incentive cues by limbic-striatal structures and the responsiveness of the dopamine system to these cues can address, by direct interactions, a system that is concerned with the reflexive and integrated actions associated with copulation. But I don't know of any really direct evidence that puts those two things together, do you?

M. Baum

I wanted to ask whether there are data on the dopamine response in mPOA-lesioned animals. You also said that if you allow males to experience the inability to copulate long enough after a mPOA lesion, you do start to see changes in performance.

B.J. Everitt

As far as the dopamine response in mPOA lesioned males is concerned, my strong prediction is that it would not be changed. Concerning performance, it seems

that at least part of that response depends upon the feedback that comes from copulation itself so, a priori, there is no effect of the neural manipulation or indeed the endocrine manipulation on the approach response, for example, to cues previously associated with copulation. But if you repeatedly let the male learn about the fact that he can no longer copulate then that response will extinguish. Indeed, the same thing happens without any neural manipulation; if one prevents a male from actually intromitting by pairing him with a female that has her vagina taped over so he can't intromit, his place preference will extinguish at approximately the same rate as in the male that is experiencing a failure to copulate as a result of a preoptic area lesion, or indeed, castration.

G. Wagner

I have a question about one of your last experiments where you actually thought that you were able to tell that you could manipulate the male behaviour through manipulation with the female. How could you be certain that you are not interfering with some pheromones or creating others?

B.J. Everitt

Data from social interaction tests show that dopamine receptor blocking drugs don't affect the odour qualities of rats, but this has not specifically been studied with females in heat. So one answer to that question is that I can't deny absolutely that systemic treatment with a neuroleptic prevents the vagina from smelling in an oestrous way, but I would be very surprised if that would have happened within 15 minutes of the injection of the neuroleptic under any circumstances. I think one of the dramatic observations in that experiment is that you have males that become completely incapacitated in terms of their sexual behaviour by treating the female with a neuroleptic. If one just takes her out and puts an untreated female in, the sexual behaviour of the male resumes as soon as she starts running under his nose, hopping, darting and soliciting his interest.

J. Stewart

It has been shown that the normal rat male can perfectly well distinguish an

oestrous female from an ovariectomized one when both are given the dopamine antagonist.

B.J. Everitt

Well certainly, the control males in the study I mentioned copulated readily with immobile receptive, but not proceptive females; the neuroleptic-treated females go into lordosis and stay there for long periods, the male mounts at will and is not impaired at all in his response in that regard.

J.T. Clark

I think it is really clear that changes in second order operant responding can be interpreted as changes in motivation, but I am not so sure that you can say that if the animal doesn't copulate it is because he is not able to. An animal with a preoptic lesion can have an erection. If he doesn't copulate that doesn't mean that he cannot. I think that may be what is happening is that the link between arousal and performance is disappearing but that both are, in fact, intact.

J. Herbert

I think you raised three main issues in your talk, Barry, which I would like to go back to. One is the use of c-fos as a mark of sex activation that has to be talked about because there are reservations about that which we should speak too but we have not got time to clear this point. The second is the problem of dopamine which we come back to again and again. The point to make there is the point that has just been made about lesions. Now, the message of your paper is that males with preoptic lesions cannot copulate. It depends on how you make the lesion. If you make a large neural damaging lesion before the male copulates, that is what you get: the male never copulates. But if you do a chemical lesion, which is reversible, that is not the case and I think we should actually be very cautious about concluding that the consummatory responses, by which I guess you mean the ability of a male to copulate, are dependant on an intact mPOA.

B.J. Everitt

Yes, but if you are referring to infusing, for example, beta-endorphin in the medial preoptic area, then that is not a lesion; it is selectively removing one particular chemical address system in the preoptic area which has clearly different effects to removing the intrinsic neurons there. One would not expect the effects of such different manipulations necessarily to be the same.