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EDITORIAL

Monoamines and the control of sexual behaviour[1]

The availability of large numbers of drugs in the 1960s and 1970s resulted in an explosion of psychopharmacological studies of motivated behaviour, including sexual behaviour. The effects of some drugs, particularly those affecting serotonin and dopamine, on patterns of sexual activity in males and females of a number of non-human species were impressive and encouraged the belief, held by many, that these cerebral monoamines were of special importance in regulating the expression of sexual motivation. Before summarizing the major consequences of manipulating monoaminergic activity in the brain, it is important to point out that such experimental investigations were undertaken within a conceptual framework which acknowledged that sexual behaviour is hormone-dependent. Thus, it was well known that gonadal steroids critically determine whether or not a male or female displays sexual activity in the presence of an appropriate stimulus. That the hypothalamus is a major target for these behavioural effects of sex steroids was similarly widely accepted, but the precise mechanism of action remained largely a mystery. It was the latter problem which the consequences of aminergic manipulations appeared to address although, as we shall see, the narrow interpretation of the results of many of these psychopharmacological experiments was, in retrospect, misleading.

It was Meyerson, in a series of innovative experiments, who first showed that inhibiting serotonin (5-HT) synthesis enhanced the display of 'heat' in female rats (Meyerson, 1964). Indeed, the effect was so great that progesterone, the hormone which together with oestradiol controls oestrous behaviour in this species, could be replaced by drugs causing 5-HT depletion. Conversely, elevating 5-HT levels prevented the display of oestrus normally induced by the ovarian hormones. These results have been confirmed subsequently in a number of species and have been extended to include the male – for example, castrated male rats treated with doses of testosterone too low to restore their sexual behaviour can be rendered sexually active by injection of 5-HT-depleting drugs or receptor antagonists (Malmnäs, 1973). The interpretation of these data, still held by many, was that hormones induce changes in sexual behaviour by depressing 5-HT transmission – indeed, Meyerson spoke of 5-HT neurones as a 'heat inhibition system' and continues to present experimental evidence directly linking progesterone and 5-HT in female rats. There is no doubt that decreasing 5-HT concentrations in the brain can have profound effects on sexual behaviour and not only in rodents.

Thus, treatment of female rhesus monkeys made unreceptive by hormone withdrawal with para-chlorophenylalanine (PCPA), an inhibitor of tryptophan hydroxylase and hence 5-HT synthesis, greatly increases their receptivity, an effect prevented by restoring 5-HT levels by treatment with 5-hydroxytryptophan (Gradwell *et al.* 1975). Indeed, there have also been reports that PCPA or another 5-HT-depleting compound, para-chloromethamphetamine, increases 'libido' in men, although the behavioural analysis and rationale for such drastic treatments leave much to be desired (see Everitt, 1976).

Manipulating dopamine (DA) transmission profoundly alters the expression of sexual behaviour. The availability of an array of relatively specific DA receptor agonists and antagonists has allowed an exploration of dopaminergic functions to proceed more rapidly than is the case for 5-HT. In the male DA receptor blockade virtually abolishes sexual behaviour: ejaculation, intromission and mounting patterns are decreased by doses of drugs which do not markedly interfere with locomotor activity and which are much lower than those inducing catalepsy (Malmnäs, 1973: Baum & Starr,

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1980). Conversely, DA agonists (e.g. apomorphine, amphetamine) enhance sexual activity (Paglietti *et al.* 1978). Thus, ejaculation occurs after fewer intromitted mounts, post-ejaculatory refractory periods are said to decrease, and mounting activity is in general greatly increased. It has even been reported that so-called 'sexually sluggish' rats, who rarely if ever copulate, can be made sexually potent by treatment with these drugs. There have been some attempts to relate improved sexual performance in men to enhanced DA activity. For example, in the late 1960s and early 1970s it was claimed that patients with Parkinson's disease receiving *l*-dopa showed a marked recrudescence of their sexual interest and capacity. More careful analysis, however, revealed that this effect was only a reflection of the reversal of akinesia and their generally improved motor performance and not a specific action of *l*-dopa on sexual behaviour alone (see Everitt, 1976). This, as we shall see, was an important and often missed conclusion.

In the female, the situation is slightly complicated by the fact that, in most species, sexual behaviour comprises active and inactive (immobile) patterns which serve to incite the male's interest and then allow intromission, respectively. These patterns have been termed proceptive (an expression of the female's readiness to mate – her 'motivation') and receptive (the ease with which she assumes the receptive posture, lordosis, and hence allows the male to intromit). Drugs which enhance DA activity enhance proceptive patterns – as they do, by analogy, in the male – but diminish receptive patterns probably because the attendant motor activation is inconsistent with immobility (Everitt *et al.* 1974, 1975; Caggiula *et al.* 1979). Conversely, DA receptor blockade markedly attenuates proceptivity but enhances the display of lordosis. Indeed, female rats, for example, will remain immobile in the lordosis posture for 30–60 s instead of the normal 1 s necessary for an intromitted mount to occur (Everitt *et al.* 1974, 1975; Caggiula *et al.* 1979).

These, then, are major effects of DA manipulations on sexual behaviour. Initially it was largely ignored that the same drug treatments also markedly affected the expression of all other forms of goal-directed behaviour (e.g. eating, drinking, aggression, etc.). Hence, rather specific hypotheses concerning dopamine systems and sexual behaviour were proposed (as they were for other forms of behaviour) and it was some time before more broadly based views of dopaminergic function in the control of behaviour were aired. I return to this below.

In contrast to the success of psychopharmacological experiments on DA and 5-HT, those involving noradrenergic (NA) manipulations have been difficult to interpret. This may be largely because many of the drugs have severe effects on the periphery via the autonomic nervous system – for example, alpha-Na receptor acting drugs – which make any possible central actions difficult to define. The advent of neurotoxins with which to lesion central NA neurones has been of major importance, therefore, in revealing their behavioural functions (see below).

The problem facing psychopharmacologists armed with so much data on the effects of drugs on sexual behaviour was interpretation. Specifically, it is necessary to define the relationship between monoaminergic neurones in the brain (which, presumably, are affected by aminergic drugs) and the hypothalamic hormone-dependent mechanisms known to regulate sexual behaviour. Much was, and still is, made of the fact that the hypothalamus receives a rich monoaminergic innervation. Furthermore, castration and subsequent treatment with sex steroids (oestradiol, testosterone, progesterone) results in substantial changes in the levels and turnover of DA, NA and 5-HT. These correlations between steroid hormones and hypothalamic amines form in large measure the basis of assertions that the two are causally linked in the context of sexual behaviour. Indeed, it has recently been shown that sex steroids can induce alterations in the binding of NA, 5-HT and DA in the hypothalamus and elsewhere (see Everitt *et al.* 1983). Thus, these hormones may alter the expression of sexual behaviour by a direct action on amine receptors thereby indirectly modulating NA, DA and 5-HT transmission.

This remains an area of intense research effort, and it is a particularly interesting one since it may explain how widespread and diffusely projecting systems of neurones, which NA, DA and 5-HT neurones undoubtedly are, may have their actions channelled specifically at some points in time. In this case, only those axons terminating in areas which are addressed by steroid hormones would have the consequences of transmitter release modified and only at those times when steroid hormone

secretion is optimal. Axons terminating elsewhere (and these may even arise from the same neurones, since the axons of monoamine neurones branch widely) would, presumably, be unaffected by this process. However, a problem for this view is that few reports have convincingly demonstrated that aminergic drugs exert their behavioural actions within hormone-sensitive areas of the brain. Indeed, if we focus our attention on the preoptic area (in males) and the ventromedial nucleus (in females) there are few data to suggest that aminergic manipulations here affect sexual behaviour. Conversely, aminergic manipulations elsewhere do, particularly with regard to the DA system.

It is the advent of neurochemical neurotoxins and accurate information on the distribution of monoamine neurones which has allowed a more refined investigation of their behavioural importance. The neurotoxins include: 6-hydroxydopamine (6-OHDA) which may be used to destroy either NA or DA neurones or both, depending on where it is placed; 5,6- and 5,7-dihydroxytryptamine which may be used more or less specifically to destroy 5-HT neurones; and, more recently, excitotoxic amino acids such as ibotenic acid or aspartate which have the unique property of destroying neuronal cell bodies when injected intracerebrally but leaving axons passing through the area unaffected. These compounds have made it possible to make neurochemically specified lesions in the brain, a distinct improvement over the 'burn and run' of electrolytic and related lesion techniques. But neurochemical neurotoxins are not without their drawbacks – for example, it has proved difficult to make specific lesions in terminal areas receiving a mixed innervation, while local plasticity changes following such lesions make interpretation of behavioural effects problematical, particularly in the long term. However, selective lesions to ascending (and descending) axons may be achieved in the brainstem to yield neurochemically specific denervation of relatively restricted structures, and these have resulted in valuable behavioural data.

Before considering some of these data it is pertinent to mention briefly the organization of monoaminergic neurones in the brain (see Hökfelt *et al.* 1983; Steinbusch, 1981; Lindvall & Björklund, 1978). Dopaminergic neurones lie largely in the midbrain within the substantia nigra and adjacent ventral tegmental area. The forebrain areas receiving the densest innervation from these cells are the neostriatum, including the nucleus accumbens, septal nuclei, amygdala and frontal cortex. The hypothalamus has intrinsic DA neurones lying periventricularly, particularly in the arcuate nucleus, while the preoptic area receives a DA input from cells in the zona incerta. Noradrenergic (and adrenergic) neurones lie in the ventro-lateral reticular formation of the medulla and, within the dorsal vagal complex, they innervate largely sub-cortical structures, especially the hypothalamus, and also septal nuclei and amygdala. Noradrenergic cells in the pontine locus coeruleus also innervate similar sub-cortical structures but, in addition, they uniquely provide the hippocampus and neocortex with NA terminals. Both groups of NA neurones branch widely, such that relatively few cells innervate virtually the entire neuraxis. This characteristic is shared with 5-HT neurones which lie in the raphé nuclei of medulla, pons and midbrain. Only cells in the latter (dorsal and median raphé) contribute substantially to ascending systems which provide the hypothalamus (particularly suprachiasmatic nuclei), thalamus (particularly lateral geniculate nuclei), striatum, septum, hippocampus and neocortex with a 5-HT innervation. The question to be answered here, then, is how such widespread ascending reticular formation-like projections are involved with the expression of sexual behaviour. It seems unlikely at present that sub-divisions of these systems are specifically involved with sexual behaviour *per se*. They are more likely to subserve much more general or fundamental functions since this would explain why single monoaminergic manipulations affect the expression of so many forms of behaviour, as well as endocrine and physiological processes. The real challenge, then, is to define the nature of these amine-dependent processes and how they interface, if they do, with the hormone-dependent events which are specifically related to the expression of sexual behaviour.

Ungerstedt's demonstration that many features of the lateral hypothalamic syndrome of adipsia, aphagia and akinesia could be produced by 6-OHDA lesions of the nigrostriatal DA pathway has been of seminal importance in revealing the behavioural functions of DA (Ungerstedt, 1971). Both types of lesion also impair, not surprisingly in retrospect, sexual behaviour – particularly in the male. Here we see then, quite clearly, what was often not taken into account in psychopharmacological

experiments: the depression of central DA levels/transmission, especially in the striatum, markedly impairs the expression of virtually all forms of goal-directed behaviour and not just sexual behaviour (see Robbins & Everitt, 1982). With respect to the latter, it is important to note that the striatum is not a hormone-sensitive structure and, thus, we must come to terms with the fact that dopaminergic manipulations can affect the expression of sexual behaviour without *directly* affecting its hormonal determinants. Much has been written about the nature of DA-dependent functions of the striatum and these have been variously described as such fundamental processes as 'sensory–motor integration' and 'activation'. Space precludes a detailed discussion of these views (but see Robbins & Everitt, 1982), but if we accept, as it is reasonable to do, that DA-depleted animals cannot respond to environmental cues (whether due to sensory, motor or activational impairments) then the problem of DA function in the control of sexual behaviour is easier to define. Thus, the expression of sexual behaviour depends critically on exposure of the hypothalamus to sex steroids. It also depends, as do all other forms of motivated behaviour, on the integrity of the DA system and, hereby, upon the integrity of striatal processes. Is there a relationship between the two? For example, are the sensory–motor functions of the striatum biased towards sexual patterns when the hypothalamus is exposed optimally to sex hormones and the animal is in the presence of appropriate environmental cues (e.g. an individual of the opposite sex)? Little is known about where such interactions between these two systems might occur, although the abundant preoptic and hypothalamic projections to the limbic midbrain area, where many DA neurones lie, would appear to be a natural focus. Some data do suggest that hypothalamic and DA mechanisms interact: thus, the marked decline in sexual performance following preoptic area lesions in male rats can be reversed by systemic treatment with the DA agonist lisuride (Hansen *et al.* 1982). Exact interpretation of this result requires more experimentation, but it is consistent with the possibility that recruitment of the DA system might be impaired after hypothalamic lesion, so preventing the sex hormone-related bias in response priorities, and that this was essentially circumvented by direct activation of the DA system by the DA agonist. The possibility of interactions between hypothalamic and striatal DA-dependent mechanisms should undoubtedly be explored experimentally. However, it should not detract from the possibility of more direct DA-steroid hormone interactions occurring intrahypothalamically. Changes in DA receptor sensitivity attendant upon oestradiol or testosterone treatment in both steroid and non-steroid target areas of the brain emphasize that both interactions might occur and that the story is not a simple one.

Noradrenergic neurones in the brainstem appear from electrophysiological studies to be concerned with sensory events. Those within the dorsal vagal (solitary) complex seem especially to receive visceral afferent inputs and those in the ventro-lateral medulla may receive somatosensory information from fibres running in the anterolateral columns. These groups, rather than locus coeruleus neurones, are mentioned here because of their dominant projections to the hypothalamus and limbic forebrain. Furthermore, a number of these NA neurones appear to be targets for sex steroids, notably oestradiol (Heritage *et al.* 1977). Selective lesions of the lateral tegmental NA neurones by 6-OHDA in female rats results in a dissociation of proceptivity and receptivity which reveals their possible importance in sensory processing (Hansen *et al.* 1981). Thus, proceptive responses (which probably reflect the female's sexual 'motivation') are unimpaired by the lesion. By contrast, receptive responses (lordosis) which depend exclusively on tactile stimulation of the perineum and vagina by the male during a mount are much reduced. Hence, it would appear that these NA neurones are important in enabling behavioural responses to tactile cues associated with coitus. Indeed, the same lesions disrupt the induction of pseudopregnancy following cervical stimulation in this species, so emphasizing how different types of response, though both dependent on the same types of sensory information, are equally impaired by damage to a single system (Hansen *et al.* 1981). This principle is an extremely important one since it helps to explain how a diffusely projecting system of neurones can affect different behavioural and other processes rather selectively, provided that they have in common dependence, for example, on a particular category of sensory stimulus. Thus, 6-OHDA lesions to NA terminals in the main and accessory olfactory bulbs profoundly affect the selective processing of olfactory cues following coitus in the mouse (which

determines the olfactory block to pregnancy – the 'Bruce effect') and following parturition/cervical stimulation in the sheep (which determines subsequent mother–infant bonding) (Keverne & de la Riva, 1982; Keverne *et al.* 1982). The brainstem noradrenergic systems, then, can modify the expression of at least sexual and maternal behaviour as well as endocrine responses to coital events by mediating, in some way yet to be defined, the consequences of somatic and/or visceral sensory stimulation. It will be intriguing to discern whether noradrenergic influences on feeding, aggression and other forms of behaviour can also be viewed in a similar context.

If we come full circle to discuss, finally, 5-HT mechanisms in the control of sexual behaviour we see that this system of neurones remains an enigma. The advent of 5-HT neurotoxins has not, to any great extent, revealed more clearly the functions of 5-HT-containing neural systems. There is no doubt, however, that animals bearing 5-HT denervations of the hypothalamus and limbic forebrain generally display increased levels of sexual behaviour (and also aggressive and ingestive behaviour) (Everitt, 1978). Much interest has focused on the dense 5-HT innervation of the suprachiasmatic nuclei since they are very much involved in the genesis of circadian rhythms. Recently, a circadian rhythm in oestradiol sensitivity and hence sexual activity has been demonstrated in the female rat, with peak levels occurring at night (Hansen *et al.* 1978). Lesions of the suprachiasmatic nuclei abolish this rhythm and result in high levels of sexual receptivity both during the day and night – a situation also seen after systemic 5-HT-depleting treatments (e.g. with PCPA) (Hansen *et al.* 1978). It may be, then, that one way in which 5-HT neurones may affect the display of sexual behaviour is by contributing to the regulation of circadian rhythms in steroid sensitivity. However, this has not been demonstrated directly, and it is entirely possible that these neurones are more involved with regulating the responsiveness of several areas of the brain to sensory inputs arriving through more direct channels – as has been suggested, for example, for the responsiveness of lateral geniculate neurones to visual inputs.

To summarize a field of research where so little is definite is impossible. It is probably more pertinent to re-emphasize that the widespread systems of monoamine neurones are of fundamental importance in regulating the selection (NA and perhaps 5-HT) and expression (DA) of goal-directed behaviour. Defining the neural processes they subserve is a task that has only just begun, although real advances have been made with respect to the functions of dopaminergic and noradrenergic neurones. When considering sexual behaviour itself, it is clear that the dominant question to be answered is how the unique, hormone-dependent mechanisms are related to the processes subserved by the monoamine systems and here, indeed, is a fertile area of research. It has recently been suggested that hypothalamic gonadotrophin releasing hormone (GnRH) containing neurones may represent a steroid hormone-sensitive link between the two, since their cell bodies lie in a region (the preoptic area) highly responsive to sex steroids and their axons project to the midbrain, where aminergic and/or descending neural systems may be influenced (Kawano & Daikoku, 1981). Certainly, intracerebral infusion of GnRH seems quite specifically to activate sexual behaviour, at least in female rats (Sakuma & Pfaff, 1983). This trilogy of amine, peptide and steroid has long been the focus of functional studies of the control of anterior pituitary function and may, it seems, have its counterparts in the brain (see Everitt *et al.* 1983).

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