Steroid control of monoamines in relation to sexual behaviour

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Monoamines are widely distributed in the brain and are involved in arousal and motivational processes as well as motor activity and neuroendocrine control. Interactions between these central monoaminergic systems and steroid hormones play a major role in the integration of reproductive behaviour and gonadal function. This review describes the development of understanding of the relationship between steroids and monoamines, particularly in the control of sexual behaviour.

Steroid control of sexual behaviour

Sexual behaviour can be described in terms of two components. The first, ‘appetitive’ component includes the search for a partner and the display of courtship behaviour that stimulates the partner’s sexual interest. This component is linked to the degree of motivation. The second, ‘consummatory’ component includes the display of behaviour that will lead to mating: adoption of a correct posture by the female and intromission and ejaculation by the male. In males, the intensity of sexual behaviour is most often measured by the latencies and the frequencies with which these behaviours occur. However, these parameters provide only a partial insight into sexual behaviour and, in particular, its motivational aspects. Specific methods have been developed to study particular motivational aspects in males (Everitt, 1990). In females, the term ‘consummatory’ is rarely used and the two components are labelled proceptivity and receptivity after Beach (1976). Proceptive behaviours are the expression of the appetitive component and depend, at least in part, on the motivational state of the animal. Sexual receptivity consists of those behaviours that allow copulation and, in most species, includes immobility. In cats and laboratory rodents, the female adopts a posture called lordosis which is a reflexive arcing of the back. This posture is the most commonly used parameter to quantify female sexual behaviour, but the fact that it is only a sign of receptivity with no obvious motivational component and that it is not necessarily applicable to all species is sometimes ignored.

Although it is simplistic, the view of two distinct components having different neuroendocrine bases has proved to be very useful in our understanding of the mechanisms underlying sexual behaviour (Everitt, 1990).

The probability of sexual behaviour being displayed by an adult animal in response to the appropriate stimulation is modulated by gonadal steroids. The importance of this steroid modulation varies markedly since males and females in several species, including humans and some other primates, show sexual behaviour after gonadectomy (Dixson, 1983). However, even in these species, steroids have been shown to modulate expression of some aspects of sexual behaviour (Bancroft, 1984).

In general, sexual behaviour is sexually dimorphic: males and females have different behavioural repertoires and prefer to engage in sexual behaviour with a partner of the opposite sex. Little is known about the sexual differentiation of partner preference but the development of the sexual behavioural repertoire has been shown, in most species, to depend on the presence of gonadal testosterone, acting directly or through its metabolite oestradiol, during the embryonic or perinatal period (Baum, 1979).

Male sexual behaviour

Male sexual behaviour is generally displayed when testosterone has been present early in life, as in genetic males. In some species, females also display some elements of male behaviour spontaneously, but generally these patterns are expressed only after an exogenous steroid treatment (Baum, 1979). In all species, testosterone induces male sexual behaviour in the adult provided it is present for a prolonged period (Baum, 1992). The link between testosterone concentration and the amount of sexual activity is, however, far from absolute and varies with the behavioural component and the individual (Fabre-Nys et al., 1993). Other factors, such as genetics, previous sexual experience and social context are of major importance. In many species, testosterone does not stimulate sexual behaviour directly but only after being transformed into oestradiol or 5α-dihydrotestosterone (DHT) in the genital tract or within specific brain areas. The active metabolite varies with the species and the behavioural component (Balthazar, 1989). DHT alone is active in rabbits, guinea-pigs, rhesus monkeys and some strains of mice, whereas oestradiol is active in rats, hamsters, ferrets, pigs, sheep and deer. Simultaneous treatment with oestradiol and DHT is often more efficient than either steroid alone, possibly because of a different site of action.

Female sexual behaviour

With the exception of very few species, such as ferrets and pigs, female sexual behaviour is displayed only by genetic females as genetic males have ‘defeminized’ by testosterone early in life. In females, oestradiol and progesterone are the compounds most effective for stimulating sexual activity. They are produced in large quantities by the ovaries so it is unlikely that brain metabolism plays a major role in their
behavioural action. In adults, sexual behaviour is generally displayed by females only for a short period during the oestrous cycle, around the time of ovulation. In all species, expression of female sexual behaviour is preceded by an increase in plasma concentrations of oestradiol, and an acute treatment of ovariectomized animals with oestradiol induces oestrous behaviour within 12–24 h. However, in most cases, progesterone is needed in combination with oestradiol (Morali and Beyer, 1979; Fabre-Nys et al., 1993). In rodents, progesterone is required after at least 24 h of oestradiol priming and is considered to be the hormone that triggers sexual behaviour. In other species, such as sheep, progesterone has to be present for several days and then has to disappear before the increase in oestradiol, and oestradiol is the triggering hormone. In females as in males, sexual behaviour does not necessarily depend closely on steroids. In several species, such as musk shrews, marmosets or rhesus monkeys, only proceptivity varies with the hormonal environment. In others, such as dogs and horses, partner preference is very important and the oestrous female, even with the correct endocrine condition, may actively refuse a partner.

Sites and mechanisms of steroid action and sexual behaviour

Most steroid action on behaviour is genomic and involves specific receptors. In rats and guinea-pigs, correlations have been demonstrated between receptive behaviour and concentrations of steroid receptors in specific brain areas (Blaustein and Olster, 1989). Therefore, the sites of steroid action can be inferred from observations on localization of steroid binding areas or receptors. In all vertebrates studied, and in both sexes, steroid binding is found in the hypothalamus and preoptic area, part of the limbic system and part of the mesencephalon (Fig. 1a). Local administration of steroid in some of these areas restores sexual behaviour in castrated animals (Blaustein and Olster, 1989). Areas vary between male and female but are remarkably similar across species. Female sexual behaviour is most efficiently stimulated by oestradiol administered in the ventrolateral part of the mediobasal hypothalamus (VMH), whereas the medial preoptic area (MPOA) is the most efficient site for stimulating male sexual behaviour. In female rodents, the mesencephalic central grey has been shown to be an important site for progesterone action. Other areas such as the amygdala

Fig. 1. Schematic representation of steroid binding areas (a) and projections of the noradrenergic (b), dopaminergic (c) and serotoninergic (d) systems adapted from Pfaff and Keiner (1973) and Ungerstedt (1971). Acb: nucleus accumbens; Arc: arcuate nucleus; ChO: optic chiasma; HA: anterior hypothalamus; VMH: ventrolateral part of the mediobasal hypothalamus; MPOA: medial preoptic area; MFB: medial forebrain bundle; VTA: ventral tegmental area.
or the septum bind steroids and have been shown to be important in sexual behaviour, but local application of steroids only at these sites has rarely been performed efficiently. In other areas, such as the striatum, activity is altered by steroids, although steroid receptors have not been detected. This could be due to a non-genomic, membrane effect, or to the presence of the recently discovered second type of oestradiol receptor (Shughrue et al., 1996). Finally, other brain structures implicated in general brain functions, such as motor activity, sensory processing or cognitive processes, are not themselves sites of steroid action; however, they have connections with steroid-sensitive areas and their activity can be altered indirectly by steroid action related to sexual behaviour.

Once bound to their receptors, steroids modulate gene expression and protein synthesis in neuronal tissue by functioning as ligand-dependent nuclear transcription factors (McEwen, 1991). Occasionally, they can also regulate gene expression by affecting mRNA stability and translation efficiency. Stimulation of protein synthesis is a major step in steroid action both during development and in adulthood. In rodents, protein synthesis inhibitors administered directly to the brain prevent its steroid-induced sexual differentiation and, in adults, prevent the activation by steroids of male, as well as female, sexual behaviour. Steroids modulate the synthesis of a number of proteins, including receptors, neuropeptides and enzymes implicated in neurotransmitter metabolism. However, the precise nature of the proteins affecting sexual behaviour remain unknown.

Monoaminergic control of sexual behaviour

Monoamines were among the first substances identified as chemical messengers in the brain. They mostly originate in cell bodies localized in the midbrain and the brainstem, which project to telencephalic and diencephalic and lower brain structures (Fig. 1b–d). Central monoamines were first implicated in the regulation of sexual behaviour in the 1960s at the same time as the monoaminergic systems were first described in the brain. These early data suggested that dopamine, noradrenaline and serotonin (5HT) had different behavioural effects and did not act in the same way in males and females. However, because of the lack of specificity of the pharmacological tools available at the time, the relative role of each of them was impossible to evaluate. Research using more specific techniques and a more elaborate behavioural approach has clarified the role of the different monoamines (Meyerson et al., 1988; Crowley et al., 1989; Pfaus and Everitt, 1995). However, an understanding of the role of the recently discovered different receptor subtypes is incomplete (Table 1).

Dopamine

In males, administration of the dopamine agonist apomorphine stimulates male sexual behaviour in intact animals and restores some sexual behaviour in castrated males without any concurrent testosterone treatment (Melis and Argiolas, 1995). In contrast, dopamine antagonists decrease sexual behaviour. Both arousal and consummatory processes are affected, a finding that is consistent with the decrease in sexual desire and activity often reported in humans as a side effect of the use of neuroleptic drugs which act as dopamine antagonists.

The correlation between dopamine concentration in the nucleus accumbens during sexual interactions and steroid-induced effects on sexual arousal suggests an involvement of this area in the facilitatory action of dopamine on sexual motivation. The nucleus accumbens has been implicated in reward-related processes and has been shown to be important during conditioning in mediating reinforcement of the response by sexual interactions (Robbins and Everitt, 1996). This could be one way in which dopamine affects sexual motivation, most likely via D2 receptors. The MPOA may also be implicated in appetitive processes since the dopamine concentration in this area, as in

| Table 1. Summary of monoaminergic effects on sexual behaviour |
|----------------------------------|---------------|----------------------------------|-----------------|
|                                  | Male sexual behaviour | Female sexual behaviour |
|                                  | Arousal component | Consummatory components | Proceptivity | Receptivity |
|                                  | Erection | Ejaculation |                  |
| Dopamine                         |              |            |                  |
| D1                               | 0           | ++ +, 0    | 00, -            | No data | 000, + (via D5) |
| D2                               | 00, + +     | ++ , -     | +++              | + +    | -- , ++ , 0     |
| Noradrenaline                    |              |            |                  |
| α1                               | +           | No data    | ++              | 0      | ++ + , 00 , -   |
| α2                               | -- , +      | -- , 0     | 0 , -            | 0 , -  | 00 , + + , -    |
| β                                | ++          | No data    | +               | 0      | + + , 0 , -     |
| Serotonin                        |              |            |                  |
| 5HT1A                            | ++          | -- , 0     | +++             | 0      | -- --          |
| 5HT1B                            | --          | No data    | --              | No data | +            |
| 5HT2A                            | --          | No data    | --              | No data | + + , 0       |
| 5HT2C                            | --          | ++         | --              | No data | +            |
| 5HT3                             | --          | No data    | --              | No data | -- 0          |

+, behaviour stimulated; --, behaviour inhibited; 0, behaviour not affected.
the nucleus accumbens, increases during the appetitive phase of sexual behaviour. However, this is likely to be indirect and linked to the receptor of sensory cues, especially olfactory ones, from the oestrus female.

In male rats, as well as in monkeys and men, dopamine also has a facilitatory role on some consummatory processes. The paraventricular nucleus of the hypothalamus is implicated, with D1 receptors stimulating erection and D2 receptors stimulating seminal emission. In contrast, dopamine in the spinal cord inhibits copulatory processes. Other brain areas containing dopamine, such as the dorsal striatum implicated in the control of locomotor behaviour and sensory motor co-ordination, may also play a role in the control of sexual behaviour.

The role of dopamine in female sexual behaviour remains controversial, with reports of both inhibitory and facilitatory effects (Melis and Argiolas, 1995). The effect of dopamine varies with the intensity and component of female sexual behaviour. In general, the dopamine agonist apomorphine inhibits lordosis. However, in females with low receptivity, apomorphine given systemically or in the MPOA or VMH has the reverse effect. These contradictory effects have been interpreted as the results of the involvement of both pre- and postsynaptic dopamine receptors, or of the differential involvement of dopamine on proceptivity and receptivity (Caggiula et al., 1979). Consistent with this dual action of dopamine, biphasic changes in the extracellular concentration of dopamine have been observed in the VMH during oestrus in ewes (Fabre-Nys et al., 1994). As in males, dopamine from the nucleus accumbens is probably involved in appetitive processes: introduction of a male induces an increase in extracellular dopamine, measured by microdialysis, in female hamsters (Meisel et al., 1993). However, the role of dopamine in this region seems rather complex since, in rats, the change in dopamine concentration depends partly on the ability of the oestrous females to set the pace of sexual interactions (Mermelstein and Becker, 1995). This could be related to sexual interactions being both rewarding and aversive for females. Dopamine in the dorsal striatum is probably involved in motor components of proceptive responses but the areas involved in the immobility response are not clearly established.

Dopamine effects on female sexual behaviour seem to be mediated mainly by D2 receptors since quinpirole, a D2 agonist, has the same effect as apomorphine. In the VMH, other receptors may also be involved (Power et al., 1991). Apostolakis et al. (1996) suggest that, in the VMH, dopamine acts directly on the progesterone receptors via D5 receptors (a subtype of D1 receptor), but the physiological relevance of their results is questionable since rats were treated with high doses of oestradiol.

Noradrenaline

Manipulation of the noradrenaline system using antagonists indicates that the effects on male sexual behaviour vary with the type of receptor (Crowley et al., 1989; Pfaus and Everitt, 1995). The administration of α1 and β receptor antagonists, either systemically or in the MPOA, decreases male sexual behaviour. In contrast, the α2 antagonist yohimbine stimulates copulatory behaviour in rodents, dogs and men. However, the target of noradrenaline action is not clear. Sexual motivation as well as erection, but not seminal emission, seem to be affected by α2 stimulation. Male sexual behaviour depends largely on sensory feedback from the genital tract for motivational as well as consummatory processes. The role noradrenaline plays in attention mechanisms and sensory processing suggests that its role in male sexual behaviour is to modulate the effect of incoming stimuli so that sexually relevant ones have a higher probability of inducing a response.

In females, the noradrenaline system facilitates sexual behaviour (Crowley et al., 1989). Administration of noradrenaline in the VMH stimulates, and a reduction in noradrenaline activity decreases, lordosis responses. However, manipulation of central noradrenaline does not affect proceptive behaviour. As in males, noradrenaline may alter female behaviour by enhancing responsiveness to somatosensory information. Observations on changes in the extracellular concentration of noradrenaline in the VMH in oestrous female rats or sheep exposed to male behaviour or to pictures of male faces or odours support this hypothesis (Etgen et al., 1992; Fabre-Nys et al., 1997). Pharmacological studies reveal that noradrenaline has different behavioural effects depending on receptor type, brain area and species (Crowley et al., 1989; Etgen et al., 1992). In rats and guinea-pigs, activation of α1 receptors in the VMH, but not the MPOA, increases lordosis responses. Activation of α2 receptors in guinea-pigs also consistently facilitates lordosis but results in rats are contradictory. The intensity of the receptivity and the amount of sensory feedback seem to be important in determining the effect of α2 stimulation. A facilitatory action may be observed when the amount of sensory feedback is limited as in the guinea-pig or in female rats with low receptivity. The role of β receptors is unclear at present, but possibly depends on the amount of concurrent α1 stimulation.

Serotonin

Increased 5HT availability causes a reduction in male sexual behaviour, whereas inhibition of 5HT synthesis by parachlorophenylalanine and selective lesions of 5HT pathways increase the incidence of copulation and ejaculation (Meyerson et al., 1988). TFMPP, a mixed 5HT1B/2C agonist, administered to the nucleus accumbens or the MPOA, mimics the effect of 5HT in decreasing sexual behaviour, suggesting the involvement of these receptors in the inhibitory effect of 5HT (Fernandez-Guasti et al., 1992). However, the strong facilitation of ejaculation by the 5HT1A agonist 8OHDPAT, in intact and spinal rats and in rhesus monkeys, questions the generality of the inhibitory effect of 5HT on sexual behaviour. The specific component of sexual behaviour affected by 5HT transmission has not been clearly established.

An increase in 5HT synthesis in the prefrontal cortex and neostriatum after exposure to an oestrous rat, but not in response to an ovariec-tomized rat or an empty cage, is consistent with an effect on sexual motivation (Vega-Matuszczuk et al., 1993). Facilitation by 8OHDPAT, administered to the nucleus accumbens or the MPOA, of male sexual behaviour in female rats treated with testosterone also indicates a facilitatory action of 5HT on the initiation of sexual behaviour. However, an increase in the concentration of the 5HT metabolite 5HIAA in the nucleus accumbens and the MPOA after ejaculation suggests that 5HT is involved in sexual satiety (Fumero et al., 1994).

Consummatory components are also clearly affected by 5HT. Autoreceptors in the midbrain raphe could be responsible for
the facilitatory effect of 8OHDPAT on ejaculation. In contrast, erection is suppressed by 8OHDPAT but facilitated by MCPP, a 5HT1B/2C agonist (Bagdy et al., 1992).

In rodents primed with oestradiol and progesterone, drugs that increase 5HT activity inhibit lordosis. The same effects are produced by direct administration of 5HT into the MPOA or the VMH. In contrast, decreasing availability of 5HT facilitates sexual receptivity (Mendelson, 1992; Ahlenius, 1993). However, the behavioural effects of 5HT agonists or antagonists are sometimes bimodal, or vary according to dose, type of receptor or species (Gorzalka et al., 1990). Inhibitory effects appear to be mediated by 5HT1A receptors since 8OHDPAT decreases the duration of lordosis in hamsters and the frequency of lordosis in rats, whereas 5HT1B, 5HT2A or 5HT2C receptors facilitate lordosis. However, in ferrets, the lordosis response is stimulated by 8OHDPAT. In several species, 5HT is thought to be involved in anxiety and aggression as well as in nociception. The differences between species could be related to these more general functions of 5HT. The role of 5HT on proceptivity is unclear.

All three monoamines are implicated in the control of male as well as female sexual behaviour. For each of the amines, the effect is facilitatory or inhibitory depending on the type of receptor, the behavioural component and the endocrine milieu. Dopamine modulates the expression of sexual behaviour mainly via D2 receptor. In males, the effect is stimulatory whereas in females both stimulatory and inhibitory effects are observed due to dopamine involvement in the control of motor activity as well as in motivational processes. Noradrenaline has predominantly a stimulatory effect, acting via α1 receptors involved in attention mechanisms and sensory processing. In contrast, α2 receptor activation inhibits sexual behaviour in males, but not in females. Increased 5HT in both sexes predominantly inhibits sexual behaviour. This effect is mediated by 5HT1B/2C receptors in males and 5HT1A receptor in females. Facilitatory effects are also observed and seem to be mediated by 5HT1A receptors in males and 5HT1B/2C receptors in females.

**Relationship between steroids and monoaminergic systems**

**Evidence for a link between the control of sexual behaviour by steroids and monoamines**

In females, as in males, sexual behaviour can be modulated by a number of pharmacological manipulations. In males, the reduction in sexual behaviour after castration can be countered by dopaminergic treatment (Scalaletta and Hull, 1990). In contrast, alterations of male sexual behaviour induced by manipulation of noradrenaline or 5HT systems always depend on the concomitant presence of testosterone. This finding suggests that some motivational components of male sexual behaviour are stimulated by dopamine independently of recent steroid treatment, whereas others depend on steroid–monoamine interactions. In all species studied, in contrast to male behaviour, female sexual behaviour cannot be stimulated, pharmacologically or otherwise, if the animal is totally deprived of oestradiol. The only exception is the stimulation of the lordosis reflex displayed by ovariectomized rats in response to vaginal stimulation, which indicates that the sensory motor reflex does not depend on oestradiol (Komisaruk and Steinman, 1986). This finding suggests that the relationship between monoaminergic systems and steroids is different between the sexes. Variations with sex and steroid in the effectiveness of pharmacological manipulation known to alter one of the monoamines and to induce stereotyped behaviours, such as the ‘serotonin behaviour syndrome’, are consistent with the hypothesis of a strong functional interaction between steroids and monoaminergic systems (Biegon, 1990; Becker, 1992).

Anatomically, there is considerable overlap in brain areas important for sexual behaviour among steroid-binding sites and monoaminergic systems (Fig. 1), although not all of the monoaminergic systems contain steroid receptors. The hypothalamus and the preoptic area, involved both in the control of gonadotrophin secretion and sexual behaviour, bind oestradiol, progesterone, DHT and testosterone. These areas also contain a high density of fibres containing dopamine, noradrenaline or 5HT, coming from the midbrain and the brainstem as well as two local dopamine circuits: the incertohypothalamic and tuberoinfundibular systems. Possible synaptic contacts have been observed in the lateral region of female guinea-pig VMH between cells containing oestradiol or progesterone receptors and punctuate structures containing the enzymes needed for dopamine or noradrenaline synthesis: tyrosine hydroxylase (TH) and dopamine β-hydroxylase (DBH)(Blaustein et al., 1993). For 5HT fibres, synaptic contacts are limited to the lateral hypothalamic area (Brown et al., 1990). In the cell bodies, the proportion of colocalization varies with the structure. Thirty to eighty per cent of noradrenaline neurones in the brain stem concentrate oestradiol (Sar and Stumpf, 1981), whereas, in the hypothalamus, colocalization with TH has been observed in 10–40% of the cells containing oestradiol receptors, depending on the nucleus (Sar, 1984; Batailler et al., 1992). In male hamsters, TH and androgen receptor colocalization has been observed in cells in the amygdala and the bed nucleus of the stria terminalis (up to 79% of the cells positive for TH) but very few in the MPOA (4%, Asmus and Newman, 1993). In contrast, no oestradiol receptor has been observed in dopamine neurones of the ventral tegmental area or the substantia nigra, and no colocalization has been described for 5HT and steroid receptors.

Anatomical data suggest that there are interactions between monoamines and steroids both in cell bodies and at the terminals, but only in specific brain areas.

Changes in neurotransmitter content or turnover after gonadectomy and steroid replacement therapy, or during the oestrous cycle, have been observed in many brain areas (Crowley et al., 1989; Biegon, 1990; Di Paolo, 1994). The results are often contradictory, probably as a result of differences in methodology. In females, most studies show a decrease in dopamine and 5HT activity in the VMH and a decrease in 5HT in the mesencephalic central grey during proestrus or after progesterone and oestradiol treatment. In other structures, such as the dorsal striatum, the nucleus accumbens and the zona incerta (Wilson et al., 1991; Gereau et al., 1993; Di Paolo, 1994), an increase in dopamine activity is generally found, possibly in relation to the stimulatory control of motor and proceptive behaviour by these areas. However, biphasic changes in monoaminergic activity are observed in some cases, for example, dopamine in the VMH in ewes (Fabre-Nys et al., 1994), indicating that steroid–monoamine interactions are time-dependent. As is the case for induction of female sexual behaviour, combined
treatments with progesterone and oestradiol generally modulate neurotransmitter content or turnover more efficiently than treatment with each steroid separately.

Changes in noradrenaline content and turnover in females after steroid treatment in the hypothalamo-preoptic complex are probably more related to their action on the LH surge than on sexual receptivity (Herbison, 1997).

In males, 5HT and noradrenaline activity do not seem to be affected by castration and steroid treatment (Crowley et al., 1989). In contrast, dopamine content decreases 4 weeks after castration in the nucleus accumbens, and this is reversed by treatment with testosterone or its metabolites concomitant with the induction of male sexual behaviour (Melis and Argiolas, 1995). A decrease in the number of cells containing TH is also observed in the zona incerta after castration. In contrast, dopamine content increases in the MPOA after castration and decreases after testosterone treatment, a result that is difficult to interpret in terms of the control of sexual behaviour.

In summary, brain monoamine content and turnover studies support the view that there is an interaction between steroids and monoamines but it is not known whether these interactions are related to the control of sexual behaviour.

Effect of steroids on the development and plasticity of monoaminergic systems

Steroids, and in particular oestradiol, formed locally after testosterone aromatization, affect neuronal growth, survival, differentiation and dendritic branching, as well as synaptogenesis (Toran-Allerand et al., 1984). This ‘organizational effect’ of steroids permanently changes brain structures and results in differences in brain anatomy between males and females. In the MPOA and the VMH, synaptic connectivity, size and shape of neuroanatomical nuclei are sexually dimorphic and are modified by neonatal steroids (reviewed in Gorski, 1990; Tobet and Fox, 1992). In some cases, monoaminergic systems are involved (DeVries, 1990), for example, 5HT in the VMN (Borisova et al., 1996), and catecholamines in the periventricular nucleus of the preoptic area, or the locus coeruleus. In these areas, but not in the A1 noradrenaline cell group, the number of cells and fibres containing TH is higher in female rats than in males or in females treated neonatally by androgen. Similarly, in the frontal cortex, concentrations of catecholamines increase earlier in development in females than in males and testosterone slows the development of catecholaminergic projections to these brain areas (Stewart and Rajabi, 1994). The relationship between these changes in brain structure under the influence of steroids and the adult behavioural dimorphism has not been clearly demonstrated.

Brain structures are also modified by steroids in adults (Frankfurt, 1994; Garcia-Segura et al., 1994). In the VMH, dendritic spine density fluctuates during the rat oestrous cycle and is higher during proestrus than dioestrus. Ovariectomy decreases dendritic spine density, an effect which is reversed by the administration of oestradiol alone or in combination with progesterone at doses generally used to induce sexual behaviour (Frankfurt, 1994). Lesion of 5HT afferents to the VMH, which facilitates female sexual behaviour, also increases dendritic spine density both in males and females. Oestradiol treatment further increases dendritic spine density in females but not in males. Frankfurt (1994) suggests that these changes in dendritic spine density in the VMH possibly result in increased neurotransmission and may be one of the mechanisms through which oestradiol activates female sexual behaviour. The absence of these cyclic changes in males may be related both to the inability of males to show female sexual behaviour and to their continuous sexual activity.

Effect of steroids on the function of monoaminergic systems

In the presynaptic compartment, neural transmission is controlled by the availability of the neurotransmitter, which is modulated by biosynthesis, degradation and reuptake. In the postsynaptic compartment, the most important events in neurotransmission are release and binding (Fig. 2; Table 2).

Metabolism. Neurotransmission depends largely on the availability of newly synthesized transmitter. As a consequence, activity of TH, the rate-limiting enzyme in the biosynthesis pathways for noradrenaline and dopamine, is of crucial importance (Crowley et al., 1989; Jones and Naftolin, 1990; Etgen et al., 1992; Yuri and Kawata, 1994). Steroid effects on TH activity depend on the structure, the dose and the duration of exposure to steroid. In the VMH, TH activity decreases during proestrus or after oestradiol and progesterone treatment. This decrease is only transient (Etgen et al., 1992) but may explain the low dopamine concentration observed in the VMH. This may be necessary for the display of sexual receptivity. However, in the striatum, oestradiol treatment increases TH activity and this results in an increase in newly synthesized dopamine (Pasqualini et al., 1995). This is consistent with the increase in dopamine metabolism in the nucleus accumbens after oestradiol and progesterone treatment (Shimizu and Bray, 1993) and may be related to the stimulation by dopamine of motor activity and proceptivity. In contrast, steroid treatments do not affect dopamine metabolism in the brainstem.

Synthesis of 5HT seems less affected by steroids (Biegon, 1990). Consistent with the changes in 5HT concentration in the VMH during proestrus, sequential treatment of rats with oestradiol and progesterone decreases the concentration of 5HT that accumulates in the VMH, after the monoamine catalysis has been blocked, and increases it in the MPOA. However, oestradiol alone has the opposite effect. In male rats, 5HT synthesis in dorsal and medial raphe is reduced after castration, while in the lateral septum and central amygdala, 5HT synthesis is reduced after testosterone treatment (Crowley et al., 1989).

In summary, steroid modulation of TH activity in the VMH and the striatum seems to be one of the ways in which oestradiol and progesterone modulate dopamine transmission and influence the expression of sexual behaviour.

Release and receptors. Steroids also affect the amounts of monoamines released in response to a stimulus and this could be one of the ways they affect female sexual behaviour (Crowley et al., 1989). The release of dopamine from the striatum, induced in vitro by amphetamine or KCl, is sexually dimorphic (Becker, 1990). Castration has no effect on the release of dopamine from the striatum in males but decreases it in females. In females, the steroid effects vary with the dose and the timing of administration of steroids: small doses of oestradiol, or oestradiol or progesterone given in a pulsatile manner, increase dopamine
release, whereas high doses of oestradiol decrease dopamine release. Continuous progesterone administration has no effect on the release of dopamine from the striatum in females. It is not known whether steroid-induced changes in striatal dopamine release are important in the control of sexual behaviour, but similar increases in KCl-induced dopamine release have been observed in the nucleus accumbens after oestradiol administration (Thompson and Moss, 1994). Furthermore, after contact with a male, the dopamine concentration increases in the nucleus accumbens only in female rats pretreated with steroids to induce oestrous behaviour (Mermelstein and Becker, 1995). Treatment with oestradiol and progesterone also increases noradrenaline release in the VMH. This has been observed in the rat after KCl stimulation or exposure to a male (Etgen et al. 1992) and in sheep after exposure to a male as well as exposure to pictures of male faces or to male odour (Fabre-Nys et al., 1997). Oestradiol or progesterone alone, however, have no effect on dopamine or noradrenaline release in the VMH in response to male cues (Etgen et al. 1992; Fabre-Nys et al., 1994) or, as in the mouse hypothalamus, decrease dopamine release (Dluzen et al., 1994). These effects are consistent with an increased sensitivity of VMH neurones to incoming stimuli as a result of steroid treatment. In contrast, 5HT release in rats is reduced by progesterone treatment after oestradiol priming in the VMH as well as in the mesencephalic central grey (Farmer et al., 1996). This is consistent with a decrease in sensitivity to stimuli that inhibit sexual behaviour and with the inhibitory role of 5HT observed in pharmacological studies. This effect is rapid (20 min in mesencephalic central grey; 60 min in VMH) which suggests it is a non-genomic effect, as Becker (1990) and Thompson and Moss (1994) have suggested for the action of oestradiol on dopamine release in the striatum and the nucleus accumbens.

The number and affinity of monoamine receptors are also altered by steroid treatment. Studies in the striatum show that dopamine receptor concentration, as well as the relative proportion of high and low affinity binding sites, is altered by steroid treatment, and that the effect varies with the dose and duration of treatment (Di Paolo, 1994). No systematic study of steroid effects on dopamine receptors has been performed in relation to the control of sexual behaviour by the VMH, MPOA or nucleus accumbens. Treatment with oestradiol and progesterone also affects noradrenaline receptors. The effect differs with the steroid, the brain area, and the type of receptor (reviewed in Crowley et al., 1989 and Etgen et al., 1992). The concentration of the dopamine a1B receptor increases in the MPOA and the VMH 24 h after administration of a low dose of oestradiol, with no change in binding affinity and no change in the dopamine

**Fig. 2.** Schematic representation of (a) dopaminergic, (b) noradrenergic and (c) serotonergic synapses indicating the sites of steroid modulation. As is shown by the presence of more than one symbol at a given site, steroid action can be multiple and may vary with time, brain area or steroid priming. COMT: catechol-O-methyltransferase; DA: dopamine; DBH: dopamine β-hydroxylase; Dopac: dihydroxyphenylacetic acid; 5HIAA: 5-hydroxyindolacetic acid; 5HT: serotonin; HVA: homovanillic acid; MAO: monoamine oxidase; MHPG: 3-methoxy-4-hydroxyphenylethylenglycol; NA: noradrenaline; TrpOH: tryptophan hydroxylase; TH: tyrosine hydroxylase.
creases high-affinity diol increases a receptor concentration in the cortex. In the MPOA, oestradiol increases after castration and this effect is reversed by oestradiol. This effect is non-genomic because it still occurs when progesterone is administered conjugated to bovine serum albumin (BSA). Progesterone administered in this way cannot penetrate the cell membrane.

In many areas of the brain, 5HT1 binding differs markedly between the sexes and changes during the oestrous cycle (Biegon, 1990). In ovariectomized females, oestrogen treatment results in an acute reduction in the density of 5HT1 receptors in the whole brain, followed by a selective increase in the number of 5HT1 receptors in the preoptic area, the anterior hypothalamus and the lateral septum. These latter areas are thought to mediate the inhibition of female sexual behaviour. In the VMH, 5HT1 binding is not significantly different between males and females and oestriadiol treatment does not have any significant effect on this binding. In castrated males, an increase in 5HT1 binding is seen after oestriadiol treatment in the anterior hypothalamus and the dorsal raphe but nowhere else in the brain. In the midbrain, the number of 5HT1 receptors decreases after castration and this effect is reversed by oestriadiol treatment.

In summary, one of the ways steroids affect monoaminergic systems is by altering the function of monoamine receptors. At present there is not sufficient information to explain how steroid action on a given type of receptor in a specific area of the brain controls any particular aspect of sexual behaviour.

Non-genomic action of steroids

Steroids also affects brain function via direct interaction with the neuronal membrane through a non-genomic mechanism. For example, oestriadiol treatment alters neuronal firing in the hypothalamus, hippocampus, cerebellum and cortex within seconds (McEwen, 1991). The relevance of these short-term actions of oestriadiol for sexual behaviour is questionable because in all species several hours are needed for oestriadiol to affect sexual behaviour. This is not the case for progesterone which, when administered intravenously, facilitates lordosis in oestrogen-primed rats within minutes. Because of the short latency, this is suspected to be a membrane effect. In hamsters, injection of 3-hydroxydihydroprogesterone bound to BSA into the ventral tegmental area facilitates lordosis in animals in which oestriadiol and progesterone have been previously injected into the VMH (Frye and DeBold, 1993). In this case, the steroid does not act on monoamine neurons, but by opening the chloride channel of the γ-aminobutyric acid-benzodiazepine receptor (Frye and DeBold, 1993). However, monoaminergic neurons can also be the target of progesterone membrane

<table>
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<th>Table 2. Major steroid effects on monoaminergic systems in relation to sexual behaviour</th>
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<tr>
<td><strong>Oestradiol and progesterone</strong></td>
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<tr>
<td><strong>Content or turnover</strong></td>
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<tr>
<td>Dopamine</td>
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<td>Noradrenaline</td>
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<td>Serotonin</td>
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<tr>
<td><strong>Metabolism</strong></td>
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<td>TH activity</td>
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<td>Dopamine</td>
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<td>Noradrenaline</td>
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<td>Serotonin</td>
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<tr>
<td><strong>Receptors</strong></td>
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<tr>
<td>Dopamine D1</td>
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<td>Dopamine D2</td>
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<td>Noradrenaline α1</td>
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<tr>
<td>Noradrenaline β</td>
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<tr>
<td>Serotonin 5HT1</td>
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<td>Serotonin 5HT2</td>
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</table>

Acb: nucleus accumbens; MCG: mesencephalic central grey; MPOA: medial preoptic area; TH: tyrosine hydroxylase; VMH: ventromedial hypothalamus; ZI: zona incerta.
effects, for example, in the striatum, where a progesterone injection produces an increase in dopamine release after amphetamine treatment within 15 min (Becker, 1990) or, in the VMH, where progesterone decreases second messenger formation in response to noradrenaline stimulation by means of a membrane effect (Etgen et al., 1992). In many cases, the steroid acts simultaneously via the genomic and nongenomic mechanisms.

Oestradiol or its metabolites, catecholoestrogens, interact directly with monoamine receptors (reviewed by McEwen, 1991). However, the physiological role of this interaction is uncertain.

**Effects of neurotransmitters on steroid action in the brain**

Monoaminergic input on steroid concentrating neurones affects the way these cells respond to steroids in a number of ways (Montemayor et al., 1990; Table 3).

Steroid metabolism is a limiting factor in the effect of steroids on behaviour. This has been described in birds, in which changes in steroid metabolizing enzymes account for different ratios between testosterone metabolites and, therefore, stimulation of different phases of courtship behaviour (Balthazart, 1989). In many mammals, the hypothalamus is regulated by noradrenaline (Montemayor et al., 1990; Blaustein et al., 1993). In male rats and guinea-pigs, administration of noradrenaline antagonist also decreases androgen receptor concentration in the hypothalamus (Montemayor et al., 1990). Anatomical data using immunological labelling of oestriol receptors and dopamine β-hydroxylase and measurement of oestriol receptor and noradrenaline content suggest that the quantity of oestriol receptor in the hypothalamus is regulated by noradrenaline (Montemayor et al., 1990; Blaustein et al., 1993). In female, but not male, rats dopamine increases oestradiol binding in the VMH by 60% and has a slight effect on oestradiol binding in the anterior hypothalamus–preoptic area, but no effect in the cortex. This increase in binding is blocked by perphenazine, a dopamine antagonist. D2 receptors are responsible for this effect, which may involve an increase in steroid retention as well as in steroid uptake (Wooley et al., 1994).

Noradrenaline transmission is involved in both progesterone and oestradiol binding (Blaustein and Olster, 1989; Crowley et al., 1989). Inhibition of noradrenaline synthesis or blockade of α1 receptors in guinea-pigs decreases cytosolic progesterone receptor in the VMH by about 30%, and stimulation of α1 receptors reverses this effect (Blaustein and Olster, 1989). Receptors in the preoptic area are not affected. Curiously, the quantity of nuclear progesterone receptors in the hypothalamus, unlike cytosolic progesterone receptors, are increased by treatment with a noradrenaline antagonist. This observation suggests that noradrenaline affects the strength of the association between progesterone receptors and nuclear elements. Alternatively, noradrenaline may act by increasing the transfer of the receptor from the cytoplasm to the nucleus. Oestradiol receptors are also affected by noradrenaline. Lesion of the lateral tegmental area or the A1 noradrenaline cell group in the brainstem decreases the concentration of oestradiol receptor in the hypothalamus (Montemayor et al., 1990). Anatomical data using immunological labelling of oestriol receptors and dopamine β-hydroxylase and measurement of oestriol receptor and noradrenaline content suggest that the quantity of oestriol receptor in the hypothalamus is regulated by noradrenaline (Montemayor et al., 1990; Blaustein et al., 1993). In male rats and guinea-pigs, administration of noradrenaline antagonist also decreases androgen receptor concentration in the hypothalamus (Crowley et al., 1989). However, the type of noradrenaline receptor involved in mediating changes in hypothalamic steroid receptor in either males or females is unclear.

As opposed to dopamine and noradrenaline transmission, 5HT does not seem to affect steroid binding. Depletion of 5HT in the VMH by 5,7HT lesioning does not affect oestriol or progesterone binding, despite the fact that it increases lordosis behaviour (Luine et al., 1987). According to Frankfurt (1994), this facilitatory effect of the VMH 5HT lesion on lordosis may be explained by a stimulation of the density of dendritic spines that increases sensitivity to oestriol.

Neurotransmitters also activate steroid receptors directly without the presence of their steroid ligand (Power et al., 1991). Activation by progesterone of lordosis behaviour in rats pretreated with oestriol is mimicked by D1 agonist. This
effect is blocked by the progesterone antagonist RU486, or by administration of an antisense oligonucleotide to the progesterone receptor, which demonstrates that the activation occurs via the progesterone receptor (Mani et al., 1994). The physiological role of such a direct action of the neurotransmitter on gene activation by steroid receptor is not known. However, O’Malley et al. (1995) proposed that a suboptimal amount of steroid and of neurotransmitter has a synergistic effect on gene transcription resulting, therefore, in a decrease in the threshold for steroid action. This could be of major importance not only in sexual behaviour but in all steroid-dependent functions or diseases.

Concluding remarks

Steroids play a major role in the control of sexual behaviour. Many demonstrations of the involvement of the monoaminergic systems in this steroid control have been gathered over the years. However, none of these systems is specific to sexual behaviour. Steroids alter the way these systems function and do so in such a manner that the probability of sexual behaviour being displayed is changed. In this respect, changes in neurotransmitter release and receptor function seems to be particularly important. But, measurements of c-fos expression (Ohkura et al., 1997) suggest that steroids also indirectly alter the activity of several brain areas and, thereby, change the way the animal reacts to changes in its environment. In adults, the regulatory role of steroids seems more marked in females than in males. This could be related to the cyclic organization of female reproduction as opposed to the continuous organization of males, which increases the requirement in females for a close coordination of behavioural and endocrine changes. It is also possible that the different processes implicated in sexual behaviour, for example, those related to reward, have differential importance in males and females.

Understanding the way in which steroid interactions with monoaminergic systems regulate sexual behaviour is far from complete. The control of the lordosis posture through interactions between oestradiol, progesterone and noradrenaline is well understood. But the roles of dopamine and 5HT are less well-documented, and information concerning the motivational aspects of female sexual behaviour are scarce. Data on the control of sexual motivation in males are more abundant than in females and there is a growing understanding of how the cortex, limbic system, striatum and MPOA interact. However, there remains a lack of information on the mechanisms by which steroids modulate these systems. Furthermore, sexual behaviour and other aspects of reproduction are regulated in a coordinated way and are affected by many factors such as experience or stress. Little is known about how this coordination is achieved or about the specific roles of steroids, monoamines and other neurotransmitters or neuromodulators. One of the challenges for the next few years will be to refine our patchy understanding of the way in which central monoaminergic systems integrate hormonal and environmental information to control the expression of reproductive behaviour.

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Steroid control of monoamines in relation to sexual behaviour 41