STARLING REVIEW

The endocrinology of sexual arousal

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Abstract

The relevance of testosterone, oestradiol and certain peptides (oxytocin (OT), β-endorphin and prolactin (PRL)) to sexual arousal in humans is reviewed. In addition to behavioural studies, evidence of distribution of gonadal steroid receptors in the brain and the limited evidence from brain imaging are also considered. Testosterone plays a key role in the adult male, with clear, consistent evidence from studies of hypogonadal and eugonadal men. The roles of testosterone in the development of sexual arousability, and in the aging male, are less clear. The relevance of aromatization and of non-sexual effects of testosterone which might indirectly influence sexual arousal are not well understood. Testosterone in the female presents a more complex, less consistent picture. One possible explanation is a much greater variability across women in responsiveness to testosterone. A 'desensitization hypothesis' to account for the striking gender differences is offered. There is limited evidence of a direct effect of oestradiol on sexual arousability in women. The extent to which testosterone in women acts by conversion to oestradiol or by increase of free oestradiol is not yet clear. The role of peptides in sexual arousal remains uncertain, partly because of the multiple roles and sites of action of most peptides. OT and β-endorphin appear to have both excitatory and inhibitory effects. PRL has been proposed as an inhibitory factor via direct inhibition of dopaminergic activity, but the evidence for this is inconclusive. Whereas the traditional concept of 'hormone' continues to apply to the role of testosterone and oestradiol in sexual arousal, peptides present a more complex role.
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Introduction

The term 'sexual arousal' is used with variable meanings. It is commonly equated with genital response; thus the man who has an erection is said to be sexually aroused. As used in this paper, the concept of sexual arousal involves more than genital response (Bancroft 2002*a*), covering a state motivated towards the experience of sexual pleasure and possibly orgasm, and involving (i) information processing of relevant stimuli, (ii) arousal in a general sense, (iii) incentive motivation and (iv) genital response. 'Sexual arousal' applies to the state, and 'sexual arousability' to the capacity for experiencing sexual arousal, which varies across individuals, and within individuals across time. In this paper, sexual interest is conceptualized as an aspect of sexual arousal, when all four components may be involved to some extent, but where at least sexual information processing (e.g. sexual thoughts) is associated with some degree of incentive motivation. Orgasm needs to be considered, both as a goal of the incentive motivation, and as a process associated, at least in males, with a temporary suspension or inhibition of sexual arousability.

This paper will review the role of hormones in influencing sexual arousal, sexual arousability, orgasm and the post-orgasm inhibition of arousability. Its focus will be on the human experience, but reference to the animal literature will be made when helpful in understanding the human condition.

Current concepts

Gonadal steroids

Androgens in the male

Hypogonadal and eugonadal men Most controlled studies of testosterone replacement in hypogonadal men have used a period of withdrawal as a baseline, followed by the administration of testosterone and placebo, using a double-blind cross-over design (for review see Bancroft 2003). Such studies consistently show a reduction in the level of sexual interest during testosterone withdrawal, usually evident within 3 to 4 weeks, consistent with testosterone being necessary for normal levels of sexual interest (and arousability). If testosterone withdrawal lasts

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long enough, seminal emission will eventually be impaired. Typically, in male studies of this kind, placebo has only a modest effect, but testosterone replacement restores sexual interest and arousability. Effects on sexual activity with a partner are less consistent, partly because they depend on partner and relationship characteristics. Frequency of masturbation tends to follow the level of sexual interest, although cultural factors may influence this pattern of sexual expression (Anderson *et al.* 1999).

Psychophysiological studies have been used to assess the effects of testosterone withdrawal and replacement on genital response (erection) to sexual stimuli. Early studies were based on the maximum change in penile circumference as a measure of erectile response; they found little difference between hypogonadal men with and without testosterone replacement. More recently, such assessment has also included penile rigidity as well as duration of penile response. This showed significantly more rigid and longer duration erectile responses with testosterone replacement. Without testosterone, the erectile response was 'stimulus bound', i.e. would recede as soon as the stimulus was switched off. With testosterone replacement, the response would not only show greater rigidity, but would also last beyond the sexual stimulus (Carani *et al.* 1995).

Nocturnal penile tumescence (NPT), the occurrence of spontaneous erections during rapid eye movement (REM) sleep, is relevant. The neurophysiological basis of NPT is still disputed, but one plausible explanation is that REM sleep is associated with a 'switching off' of the noradrenergic cells in the locus coeruleus (l.c.) (Parmeggiana & Morrison 1990) which, via their spinal projections, are probably associated with inhibitory tone in the penis. Thus, the reduction of inhibitory tone during REM permits what can be called 'excitatory tone' to be expressed as erection. NPT is clearly impaired in hypogonadal men, and restored to normal with testosterone replacement. The l.c. has testosterone receptors (Parmeggiana & Morrison 1990), and this putative 'excitatory tone' can be regarded as testosterone dependent. Carani *et al.* (1995) evaluated the effects of exogenous testosterone on NPT in eugonadal men. Intramuscular testosterone enanthate had no effect on sleep parameters, and did not affect frequency, degree or duration of NPT, when assessed as penile circumference, but did increase, modestly but significantly, penile rigidity during NPT.

Testosterone manipulation in eugonadal men has produced results consistent with the earlier hypogonadal studies. Bagatell *et al.* (1994*a*) used the gonadotrophin-releasing hormone (GnRH) antagonist, NalGlu, to suppress testosterone levels in eugonadal men over a 6-week period. This lowered sexual interest and associated sexual activity. An additional feature was the administration of varying doses of exogenous testosterone or placebo during the NalGlu administration. This suggested that the plasma level of testosterone needed to avoid the sexual effects of testosterone withdrawal was substantially lower than the pre-treatment baseline level. This is consistent with most men having more circulating testosterone than they need for the maintenance of normal sexual function.

The exploration of testosterone as a method of male contraception has led to further studies of the effects of increasing circulating testosterone above a normal baseline by means of exogenous testosterone administration. Anderson *et al.* (1992), using weekly injections of either placebo or testosterone enanthate (200 mg) over 8 weeks, found no effect of the exogenous testosterone on sexual activity, either with a partner or as masturbation, but a significant increase in a measure of sexual interest independent of sexual interaction with the partner. Bagatell *et al.* (1994*b*) and Yates *et al.* (1999), in eugonadal men, found no effects of increasing testosterone on frequency of sexual activity, or in the latter study, daily measures of sexual interest.

Buena *et al.* (1993) explored the effect of varying testosterone levels within the normal range. They first suppressed testicular function with a GnRH agonist (Lupron), followed by exogenous testosterone administration in either high or low dosage, to produce testosterone levels that were either at the high end or low end of the normal range. They found no difference in sexual activity, sexual interest or NPT, although the rigidity of NPT was not measured.

Androgens in male sexual development Whereas the importance of testosterone in sexual differentiation, both in early development and around puberty, is beyond dispute, the impact of testosterone on the emergence of sexual arousability is less clear. Udry and colleagues carried out two studies in teenage boys in which testosterone levels were related to various aspects of sexuality. In the first (Udry *et al.* 1985), a cross-sectional study, the free testosterone index was found to be a strong predictor of 'sexual motivation', whereas stage of pubertal development was not predictive. In the second (Halpern *et al.* 1993), a longitudinal study over 3 years, with 6-monthly assessments, they found the reverse; the stage of pubertal development was much more predictive of sexual interest and behaviour than the free testosterone index. One possible explanation for this apparent contradiction is that the impact of testosterone on sexual arousability (and hence behaviour) has to go through stages of development, which may involve changes in receptor numbers or sensitivity, a process which will also be influenced by individual differences in receptor sensitivity. Gooren (1988), in a study of hypogonadal teenage males, found that boys with primary hypogonadism showed less response to testosterone replacement than boys with secondary hypogonadism. Other studies comparing hypergonadotrophic and hypogonadotrophic hypogonadism have not shown such clear differences, but have all

involved males well beyond the age of normal puberty (for review see Bancroft 2003).

Androgens and aging in men Schiavi *et al.* (1990), in a study of healthy, medication-free men aged 45 to 74 years, found a clear decline in sexual interest, arousability and activity with age. The relatively predictable effects of testosterone withdrawal and replacement in younger adult men gives way to a more complex, or at least less well-understood picture in older men. A number of age-related changes may be relevant: altered negative feedback of testosterone and hence less increase in luteinizing hormone (LH) with falling testosterone levels, increased sex hormone binding globulin (SHBG) and hence relatively reduced free testosterone and the likelihood of an age-related decline in testosterone receptor sensitivity. Schiavi *et al.* (1990) also found an age-related decline in NPT. This suggested an age-related decline in testosterone-dependent central arousability (i.e. 'excitatory tone'). It is noteworthy that, as yet, there has been no adequate placebo-controlled evaluation of the effects of testosterone replacement on sexuality in older men (Institute of Medicine 2004).

Clinical studies – relevance of testosterone to low sexual desire and erectile dysfunction (ED) In one small placebo-controlled study of eugonadal men with the primary complaint of low sexual desire, O'Carroll & Bancroft (1984) found a modest but significant increase in sexual desire with testosterone treatment. The limited evidence of the effectiveness of testosterone in treating ED is inconsistent. O'Carroll & Bancroft (1984) found no improvement in erections with testosterone treatment in eugonadal men with ED. In studies of men showing some degree of hypogonadism in association with ED, Carani *et al.* (1990*a*) and Morales *et al.* (1994*a*) found improvement in erectile function in a minority of cases. So far it has been difficult to predict which cases of ED are likely to benefit from testosterone, although low baseline levels of testosterone certainly increase the likelihood. Based on a large clinical series of such cases, Buvat & Lemaire (1997) recommended that in men under 50 years of age, measurement of serum testosterone should only be done when there was an associated loss of sexual interest, whereas in men over 50 years of age with ED, testosterone should be measured in all cases.

Conclusions about the role of testosterone in the male The evidence is fairly clear that in men who have gone through normal puberty and who have not yet been affected by aging, testosterone plays an important role in their sexual interest and associated sexual arousability. The evidence points mainly to the effects of testosterone on central arousal mechanisms; the peripheral effects of testosterone in the human male, relevant to sexual arousal, are as yet unclear. It is also apparent that, in adult eugonadal men, the levels of testosterone in the circulation are substantially higher than required to maintain sexual arousability, suggesting that other effects of testosterone, most probably in the periphery, require higher levels than are needed in the central nervous system (CNS). The role of testosterone in the emerging sexual arousability of the peri-pubertal male is not well understood. In the older male, the picture is complicated by various aging effects, including altered hypothalamo–pituitary feedback, increased testosterone binding and reduced receptor sensitivity.

Androgens in the female In the female, in comparison with the male, we find inconsistent and often contradictory evidence. This is in spite of the fact that we have many more studies in women, usually involving larger samples, than are found in the male literature. This may result from the greater complexity of the reproductive endocrine system in women, who experience menstrual cycles, pregnancy and lactation and a clearly identifiable menopause. At the same time, these endocrine variations offer more opportunities for studying hormone/sexual arousal relationships than is the case with men.

Developmental aspects Increasing levels of testosterone occur in the development of girls as they approach and go through puberty. However, the changes are much less substantial than in the male. Testosterone starts at a lower level in the infant girl, and effectively doubles through pubertal maturation, compared with an 18-fold increase in testosterone for boys. The most substantial evidence of the relationship between testosterone and emerging sexual arousability in females comes again from Udry *et al.* (1986). As with their studies on adolescent boys, they found discrepant results between their cross-sectional study of eighth to tenth grade girls (approximately 13–15 years of age), where they found a relation between testosterone levels and measures of sexual interest and masturbation, but not with the likelihood of having experienced sexual intercourse, and their longitudinal study of girls post-menarche where the reverse relations to testosterone were found (Halpern *et al.* 1997). Similar explanations as discussed for their male studies could apply here, but in addition there is a crucial methodological issue of timing of blood sampling for testosterone in relation to the ovarian cycle (for a fuller discussion of these issues see Bancroft 2003).

The menstrual cycle There is a lack of evidence of testosterone levels during the early cycles of post-menarcheal adolescents, which tend to be irregular and not predictably ovulatory. However, once a woman settles into a pattern of regular ovulatory cycles, testosterone levels typically rise during the follicular phase and are at a maximum approximately for the middle third of the cycle, declining during the final third to reach a nadir during the first few days of the next follicular phase. Given this pattern, if testosterone

is important for sexual arousability in women, we should expect to find related temporal patterns of arousability through the cycle. However, the mid-cycle rise in testosterone is associated with other hormonal changes, and hence correlational studies may not discriminate between direct effects of mid-cycle testosterone levels, and the effects of other mid-cycle changes, such as the rise in oestradiol.

In the substantial literature on the pattern of sexual interest and behaviour through the menstrual cycle there are many inconsistencies, and Hedricks (1994) has discussed various methodological explanations for them. There is a relatively consistent finding that sexual activity is lowest during the menstrual phase. However, this does not necessarily mean that sexual arousability is at its lowest at that stage; there are a number of other non-hormonal explanations for the drop in sexual activity during menstruation. There is also a tendency across studies for indices of sexual interest to be highest during the follicular phase or around ovulation, though with considerable individual variability in this respect. This mid- to late-follicular pattern is compatible with an effect of the rising testosterone during the follicular phase, although one might have expected a continuation of this testosterone effect into the first part of the luteal phase. Clearly, other hormonal explanations have to be considered.

A much more limited literature looks at the correlation between testosterone level and sexuality through the cycle, and it is very inconsistent (for review see Bancroft 2003). In part, there may be methodological reasons for this, especially variability in the aspects of sexuality measured. But these inconsistent findings, involving studies with relatively small numbers of participants, could result from substantial individual variability in testosterone/behaviour relationships.

Only one study addresses the timing of the effects of an increase in testosterone on sexual arousal. Eight healthy women with normal testosterone levels, given sublingual doses of testosterone in a placebo-controlled experiment, showed effects of increased testosterone on genital response to erotic stimuli occurring 3–4 h after the peak increase in plasma testosterone (Tuiten *et al.* 2000). These results suggest that, at least in those women in whom testosterone has an effect on their sexuality, cyclical variation in testosterone levels should be manifested by cyclical patterns of sexual interest and/or responsiveness.

Steroidal contraceptives There is consistent evidence that combined low-dose oral contraceptives (OCs) lower free testosterone (e.g. Bancroft *et al.* 1991). Two principle mechanisms are involved: the mid-cycle rise in testosterone is blocked by suppression of ovulation and the associated pattern of gonadal steroid change and the combined OC increases SHBG levels and hence reduces the free testosterone available. Given this predictable hormonal effect, what happens to sexual arousability in combined OC users? Graham *et al.* (1995), in a placebo-controlled study of women who had been sterilized or whose partners had been sterilized, found that a substantial minority of women on the combined OC reported a decline in sexual interest and enjoyment, an effect not observed with a low-dose progestagen only method. In a subsequent study of women starting on OCs, where a pre-OC baseline was established, negative effects on sexual interest and mood were the best predictors of discontinuation of the OC (Sanders *et al.* 2001). In both of these studies, lowered testosterone levels could be the explanation. As yet, however, we have no direct evidence of the relation between testosterone levels and sexual interest. Other explanations for these adverse sexual effects need to be considered (e.g. progestagenic effects). But if lowered free testosterone is the explanation this illustrates once again that such reduction is only relevant in a proportion of women.

Effects of anti-androgens Cyproterone acetate (CPA) is an anti-androgen with both negative feedback and direct androgen receptor antagonism, and which has been used for the treatment of androgen-dependent conditions such as acne and hirsutism in women. Appelt & Strauss (1986) studied 36 women who had not had sexual problems before starting on CPA, and of these 16 (44%) reported negative effects on their sex life; this rises to 61% if women not in sexual relationships are excluded.

Lactation Reduction in sexual interest and enjoyment is common during the post-partum period, and is more marked in breast-feeding than bottle-feeding mothers (Alder & Bancroft 1988, Hyde & DeLamater 2000). Alder *et al.* (1986) assessed women prospectively for 6 months post-partum. Not surprisingly, given the effects of lactation on ovarian function, bottle feeders had higher testosterone and androstenedione levels than the breast-feeding mothers. Of more relevance, five of the breast feeders reported reduced sexual interest, and their testosterone and androstenedione levels were consistently and significantly lower than the breast feeders who reported no reduction in sexual interest. This finding needs to be replicated.

Aging and the menopause Adrenal androgens have been shown, in a number of studies (Crilly *et al.* 1979, Orentreich *et al.* 1984, Bancroft & Cawood 1996, Sulcová *et al.* 1997, Burger *et al.* 2000) to decline with age over a relatively wide age span. Ovarian androgens start to decline a few years before the menopause, probably due to a reduction in the mid-cycle rise of testosterone (Roger *et al.* 1980, Zumoff *et al.* 1995, Mushayandebvu *et al.* 1996). However, there is no predictable decline in ovarian androgens following the menopause (Bancroft & Cawood 1996, Burger *et al.* 2000). A crucial change in the function of the interstitial cells of the ovary from pre- to

post-menopause complicates the picture. Whereas in pre-menopausal women, gonadotrophic stimulation of the interstitial cells is regulated by the negative feedback of ovarian steroids, the rise in LH that accompanies the menopausal transition, resulting from the reduction in oestrogen-induced negative feedback, may stimulate the interstitial cells to produce testosterone and androstenedione, sometimes excessively. In addition, factors such as body weight and insulin resistance influence this ovarian androgen production (for a brief review of the evidence see Bancroft & Cawood 1996).

A number of behavioural studies have reported a decline in sexual interest in women as they age (see Bancroft 1989, Bancroft *et al.* 2003). Studies have varied in the extent to which the menopause *per se* contributes to this decline, although there is consistent evidence of an increase in vaginal dryness related to the change in oestradiol levels (Dennerstein *et al.* 2003).

Do testosterone levels correlate with measures of sexual interest or activity as women get older? A number of cross-sectional studies, using multivariate methods of analysis, have found no relation between testosterone and changing levels of sexual interest (Cawood & Bancroft 1996, Kirchengast *et al.* 1996, Dennerstein *et al.* 1997). In their longitudinal study of women going through the menopausal transition, assessed over a 9-year period, with an average starting age of 48 years, Dennerstein *et al.* (2003) found no relation between androgen levels and any aspect of sexual functioning. However, in none of these studies was there any assessment of the pre-menopausal testosterone decline. To adequately test the androgen–behaviour relationship during the mid-life period, longitudinal studies are needed in which the baseline testosterone levels are assessed before the pre-menopausal decline.

The effects of ovariectomy and hormone replacement With surgical removal of the ovaries there is an immediate and substantial drop in circulating androgens. Androgen production by the interstitial cells of the post-menopausal ovary is an important source of oestrogen from peripheral conversion. Whether pre- or post-menopausal, therefore, the woman with both ovaries removed is in a state of relative gonadal steroid deficiency.

Most of the literature on hormone replacement, with both natural and surgical menopause, has assessed the effects of testosterone in combination with oestradiol, compared with oestradiol alone or placebo. The evidence from such studies on the role of testosterone in sexual interest and response is inconsistent. Two studies will be considered closely. (For a more comprehensive review of this literature see Bancroft 2003.)

Sherwin *et al.* (1985) investigated women who were about to undergo hysterectomy and bilateral oophorectomy. Post-operatively, women were assigned randomly to one of four 3-month treatment groups: oestrogen only, testosterone only, oestrogen plus testosterone or placebo. All subjects then received 1 month of placebo following which they were crossed-over to one of the other three treatment groups. The oestrogen+testosterone and testosterone only conditions showed significantly higher levels of sexual interest, fantasy and arousal than either the oestrogen only or placebo conditions. They did not differ in measures of sexual activity with a partner or orgasm. This is the only study in which testosterone administration on its own has been evaluated. It is also noteworthy because it focused on the immediate post-operative period in women who were not reporting significant sexual or mood problems pre-operatively. Mood was significantly better with all three hormone regimes (testosterone, oestrogen+testosterone and oestrogen) compared with placebo (Sherwin & Gelfand 1985*a*) and energy level, well-being and appetite were significantly higher in the two groups receiving testosterone than in the oestrogen only or placebo groups (Sherwin & Gelfand 1985*b*).

Shifren *et al.* (2000) studied women who had undergone surgical menopause from 1–10 years previously. In contrast to the previous study, all had impaired sexual function and all had been on Premarin, at least 0·625 mg daily for at least 2 months, when recruited for the study. All subjects continued on the same dose of oral oestrogen throughout the study. After a 4-week baseline assessment, they were all given daily transdermal patches with placebo, or 150μg or 300μg testosterone as the daily dose, each for 12 weeks with the order of presentation randomized. There was a substantial placebo response; however, there was significantly more improvement with the higher testosterone dose than with placebo on measures of frequency of sexual activity, and pleasure/orgasm, though not for sexual desire or arousal (the opposite pattern reported by Sherwin *et al.* 1985). Mood was significantly improved with the higher testosterone dose for ratings of both depression and 'positive well-being'. The transdermal route used in this study has the advantage of producing more physiological and more stable serum testosterone levels than the intramuscular routes used in most other studies, where supra-physiological peaks soon after injection are followed by gradual decline.

A third study also warrants attention. Nathorst-Böös *et al.* (1993) were unusual in this literature in taking a sample of women who had been oophorectomized and reporting the proportion who had experienced loss of sexual interest. Approximately 50% of women came into this category, which suggests that around 50% of women can undergo this depletion of ovarian steroids and not experience loss of sexual interest.

Hormone replacement of adrenal androgens Androstenedione has a substantial capacity for conversion to both oestradiol and testosterone; dehydroepiandrosterone (DHEA) has a very limited capacity for conversion to testosterone. There is little evidence, however, that DHEA is directly relevant to sexuality in either men or women, whereas it may be

relevant to well-being and energy, and hence secondarily to sexual arousability (Cawood & Bancroft 1996). In a placebo-controlled evaluation of DHEA administration to women between 40 and 70 years (Morales *et al.* 1994*b*), there was significant improvement in a somewhat crude measure of well-being, but no effect on 'libido'. In a placebo-controlled study of women with adrenal insufficiency, the addition of DHEA to the corticosteroid replacement improved measures of sexual interest and responsiveness as well as mood and general well-being, although the effects on mood were more substantial (Arlt *et al.* 1999). The sexual effects could therefore have been secondary to improvements in general well-being and energy.

Clinical studies of women with low sexual interest or arousability Stuart *et al.* (1987) and Schreiner-Engel *et al.* (1989) found no difference in testosterone levels between women presenting with low sexual interest and controls; Riley & Riley (2000) found a marginally lower free androgen index (FAI) in women complaining of life-long absence of sexual drive than in controls. Controlled studies of the treatment with testosterone of women presenting with sexual problems have been few. Although Carney *et al.* (1978) found some benefit of testosterone when combined with counselling for couples whose main problem was sexual unresponsiveness of the woman, other comparable studies failed to replicate this effect (Mathews *et al.* 1983, Dow & Gallasher 1989).

In a more experimental study, Tuiten *et al.* (1996) studied eight young amenorrhoeic women with low weight, although none had the diagnosis of anorexia nervosa. They showed lower levels of sexual interest and activity, and lower testosterone levels than a comparison group of normally menstruating aged-matched women. The amenorrhoeic group was given testosterone undecanoate (40 mg) daily for 8 weeks, and placebo for 8 weeks in a double-blind cross-over study. They were evaluated in a psychophysiology laboratory with measurement of vaginal pulse amplitude (VPA) in response to erotic fantasies and erotic films. VPA was significantly greater in response to film in the testosterone-treated condition. However, this effect was not reflected in subjective ratings of arousal. Nor did the two treatments differ in terms of daily ratings of sexuality or mood. This experiment therefore demonstrated an effect of increasing testosterone on physiological response to erotic stimulation, which was not apparent in any subjective or mood measures.

Summary of androgen effects in women Whereas there is evidence that testosterone withdrawal and/or replacement can have effects on women's sexuality, the evidence is inconsistent and sometimes contradictory. One obvious explanation is that women vary in the extent to which their sexuality is influenced by testosterone, and several examples of evidence supporting this have been presented.

It is also becoming increasingly clear that the sexuality of women is powerfully influenced by mood, energy and well-being, as well as by other psychological mechanisms. This may account for why, in several studies of younger women, the relationship between testosterone and sexuality was most apparent in women whose sexuality was unproblematic (e.g. Bancroft *et al.* 1980, Tuiten *et al.* 1996, Riley & Riley 2000). Thus, whereas testosterone may play a role in the sexuality of many women, its effects can easily be obscured by the co-existence of other psychological or affective factors. Testosterone also appears to have a mood and energy-enhancing effect in women. Hence, some of the sexual effects of testosterone may indirectly result from these mood effects.

Where do androgens act in the brain?

Androgen receptor studies For obvious reasons, we are largely dependent on animal studies on this topic, although mainly primate studies will be considered here. Research on the site of action of testosterone in the non-human primate brain has been ongoing for more than 30 years, during which time there have been major changes in the technologies used, and these have to be kept in mind when comparing findings across studies.

Michael *et al.* (1989), using autoradiography in male rhesus monkeys, looked at aspects of both androgenic and oestrogenic activity. They found 5α-reductase activity to be fairly evenly distributed in the brain, whereas, in contrast, aromatase activity was much more localized. They assumed that in areas of high aromatase activity, testosterone was acting by conversion to oestradiol. By identifying brain areas where there was overlap in androgen- and oestrogen-concentrating neurons, they concluded that the medial pre-optic and ventro-medial hypothalamic nuclei, the bed nucleus of the stria terminalis, and the cortical, medial and accessory amygdaloid nuclei were the main sites at which the effects of testosterone are mediated predominantly by oestradiol. In contrast, testosterone activity was thought to be mediated by androgen receptors in the lateral septal, pre-mamillary and intercalated mamillary nuclei.

Roselli *et al.* (2001) used *in situ* hybridization histochemistry to locate cytochrome P450 aromatase mRNA and androgen receptor mRNA (ARmRNA) in the hypothalamus and amygdala of cynomolgus monkeys. Their findings were broadly similar to those of Michael *et al.* (1989). They concluded that testosterone acts through signalling pathways that differ either in specific brain areas, or within different cells from the same area.

Abdelgadir *et al.* (1999) studied the distribution of ARmRNA, using a ribonuclease protection assay, in male rhesus monkeys. Their localization of the ARmRNA was again broadly similar to the distribution of androgen activity reported by Michael *et al.* (1989). In this study, intact animals were compared with castrated animals with and without testosterone replacement. They found little difference between these three groups in the distribution

or concentration of ARmRNA, and concluded that in the monkey brain this androgen receptor is not regulated at the transcriptional level by androgen.

For both non-human primates and humans, the majority of evidence is from males. However, Finley & Kritzer (1999), reporting the presence of androgen receptor protein in the pre-frontal cortex of rhesus monkeys, found no differences between their male and female monkeys in this respect. In a study of humans, Fernandez-Guasti *et al.* (2000) used immunochemical methods to examine the distribution of androgen receptors in the hypothalamus, involving post-mortem samples from five men and five women. In men, intense androgen receptor immunoreactivity was found in neurons of the horizontal limb of the diagonal band of Broca, and of the lateral mamillary and medial mamillary nuclei. Intermediate staining was found in other parts of the diagonal band of Broca, the sexually dimorphic nucleus of the pre-optic area, paraventricular, suprachiasmatic, ventromedial and infundibular nuclei. Weaker staining was found in the bed nucleus of the stria terminalis, medial pre-optic area, dorsal and ventral zones of the periventricular nucleus, supraoptic nucleus and nucleus basalis of Meynert. In most areas, women revealed less staining of receptor protein. This gender difference was particularly marked in the lateral and medial mammillary nuclei. There was also staining in the paraventricular and supra-optic nuclei in the males, which was apparently absent in the females. Overall, there was greater individual variability in the intensity of receptor staining in the women than in the men.

As yet, there are no comparative data on the distribution of aromatase activity in women or female primates, though in the rat greater amounts of aromatase activity are found in the male than the female, in all areas examined except the medial preoptic nucleus (Roselli & Resko 1993). Furthermore, Roselli & Klosterman (1998) concluded from their findings that this male pattern of aromatization in the rat is established perinatally, and probably forms a fundamental component of masculinization.

The limited evidence of androgen receptor distribution in humans includes two studies of the temporal cortex, both of which found substantial amounts of androgen receptor protein (Sarrieau *et al.* 1990, Puy *et al.* 1995). Both studies involved male temporal cortex tissue because it was available from surgical interventions in men with intractable epilepsy, not because the temporal cortex was regarded as a particularly likely site for androgen receptors.

Whereas much of the reported localization is consistent with androgenic effects on sexual and reproductive behaviour, it is important to keep in mind that much of the research has been restricted to the hypothalamus and, where more extensive studies have been done, androgen receptors appear to be widespread in the primate and human brain, including various cortical areas (e.g. pre-frontal cortex: Finley & Kritzer 1999, temporal cortex: Sarrieau *et al.* 1990, Puy *et al.* 1995). What specific role androgens have in these areas is not yet clear, but in addition to more specifically reproductive actions, other relatively non-specific androgen- mediated brain functions need to be considered, including activation or general arousal as well as stimulation of neuronal growth and gender differentiation of brain function (Kelly 1991).

Brain imaging Functional brain imaging promises to throw considerable light on brain activity related to sexual function, but is still at an early stage of development, with methodological inconsistencies across studies making interpretation of the findings more difficult (Sumich *et al.* 2003, Mouras & Stoleru 2005). So far, only two studies provide evidence of direct relevance to testosterone activity. Park *et al.* (2001) reported on two hypogonadal men, assessed with functional magnetic resonance imaging in their response to sexual stimuli, with and without testosterone replacement. In both men, activation of the inferior frontal lobe, cingulate gyrus, insula and corpus callosum was greater with testosterone replacement. Redoute *et al.* (2005) compared positron emission tomography scan evidence of brain activity during response to sexual stimuli in nine hypogonadal men with and without testosterone replacement, and eight eugonadal men. They found greater activation in the controls and the treated hypogonadal men than the untreated, in the right orbito-frontal cortex, insula and claustrum. They also found deactivation of the left inferior frontal gyrus, suggestive of reduced inhibition of sexual arousal, but only in the controls and treated patients. There is some consistency across these two studies, and androgen receptors have been reported in the orbito-frontal cortex of primates (Finley & Kritzer 1999) and to a limited extent, in the cingulate cortex (Abdelgadir *et al.* 1999). As yet, however, there is no evidence of androgen receptors in the insula or claustrum of primates or humans. So far, therefore, there is only limited overlap between localization of testosterone effects in the brain when comparing androgen receptors and functional brain-imaging studies. This may in part reflect methodological limitations of brain imaging; some relevant areas of the brain, especially the hypothalamus, are more difficult to image in this way. But we should also keep in mind that these two techniques are looking at very different markers of brain activity – steroid receptors and localized oxygen uptake. Physiological levels of testosterone may be necessary for a more generalized pattern of interactive brain activity, much of which is not dependent on direct testosterone effects.

Oestrogens and male sexuality Evidence of the effects of oestrogens on the sexuality of the human male, while limited, consistently suggests a negative effect of exogenous oestrogens. Oestradiol appears to play a key role in the negative feedback control of testosterone. In long-term castrated rhesus monkeys, physiological doses of testosterone do not reduce LH unless a small amount of oestradiol is also given (Resko *et al.* 1977). Also, men with aromatase

deficiency or oestrogen resistance show raised LH and follicle-stimulating hormone (see Roselli *et al.* 2001).

In the past, oestrogens were used as a treatment for prostatic carcinoma, based on their assumed anti-androgenic effect, and reduction of sexual interest and response was a typical side-effect. Oestrogens have also been used as a treatment of sexual offenders. Bancroft *et al.* (1974) compared the effects of ethinyl oestradiol (EE) and CPA, an anti-androgen, in 12 incarcerated sexual offenders. Both compounds reduced sexual interest, masturbatory activity and erectile response to erotic fantasies and slides producing a pattern very similar to that found in hypogonadal men. However, although CPA substantially reduced total testosterone, with no change in SHBG, EE substantially increased both total testosterone and SHBG (Murray *et al.* 1975).

How can we reconcile these negative effects with the widespread interaction between testosterone and oestradiol in the male brain? Is it possible that, in addition to interaction between testosterone and oestradiol in negative feedback control of LH, some of the effects of testosterone on sexual interest and arousability are mediated by aromatization of testosterone to oestradiol? Gooren (1985) found that, in eugonadal men, the oestrogen receptor antagonist, tamoxifen, and the aromatase inhibitor, testolactone, had no adverse sexual effects, and that dihydrotestosterone (DHT) was as effective as testosterone in maintaining sexuality in hypogonadal men. He took this to mean that the sexual effects of testosterone within the CNS are mediated by DHT but not by oestradiol.

Whereas in other species, the role of oestradiol in mediating many of the central nervous system effects of testosterone on male sexual behaviour is well established (Lindzey & Korach 2003), its role in human male sexuality remains unclear, with the possibility that exogenous and endogenous sources of oestradiol have fundamentally different effects, particularly when the endogenous oestradiol results from aromatization of testosterone within the brain.

Oestrogens and female sexuality There is consistent evidence of the importance of oestradiol for normal vaginal lubrication. However, whether oestradiol has a direct effect on sexual interest and arousability remains unclear.

A number of studies of the symptoms of either natural or surgical menopause, reviewed above, have either taken women on oestradiol replacement, who continue to have loss of sexual interest or response, and evaluated the effect of adding testosterone, or have compared oestradiol replacement with a combination of oestradiol and testosterone, or testosterone alone. Much less attention has focused on the effects of oestradiol itself on sexual interest and arousal in post-menopausal women.

Dennerstein *et al.* (1980) studied 49 surgically menopausal women, all of whom had stable, satisfying sexual relationships, using a double-blind cross-over design in which they spent 3 months on each of four treatments, EE, l-norgestrel, combination of EE and l-norgestrel, and placebo. The EE only regime was significantly better than the others in improving sexual interest, enjoyment, orgasmic frequency and also mood. Also found were correlations between measures of sexual desire and of mood, particularly 'feelings of well-being'.

Only one study of hormone replacement has incorporated different doses of oestradiol. Sherwin (1991) randomly assigned 'perimenopausal' women to four treatment regimes, involving either a low (0·625 mg) or high (1·25 mg) dose of Premarin, combined with either Provera (5 mg) or placebo. After a baseline month of assessment, each woman took the assigned regime for 12 months, and was assessed with daily ratings during the 3rd, 6th, 9th and 12th months. The main purpose of the study was to evaluate the effects of the progestagen on mood and sexuality, not to compare the different doses of oestradiol. However, apparent from the graphed sexual interest data, women in the high oestradiol+placebo group had substantially lower levels of sexual interest at baseline (i.e. pre-treatment), than the low oestradiol+placebo group, yet by the 6th month of treatment and continuing through the 12th month they were showing noticeably higher levels of sexual interest. This was not commented on in the paper. It would appear to indicate that the effects of oestradiol on sexual interest are dose related.

So to what extent are the effects of testosterone, discussed earlier, the result of aromatization of testosterone to oestradiol or, alternatively, of increased levels of free oestradiol resulting from testosterone-induced reduction in SHBG? Wallen & Parsons (1998) have strongly advocated that the sexual effects of testosterone in women result from the consequent increase in free oestradiol, supporting this conclusion with experimental data from rhesus monkeys. At this stage we should keep an open mind about the role of testosterone and oestradiol in female sexuality.

Mode of action of androgens and oestrogens in the brain The conventional view is that androgens act in the brain via genomic effects (Rommerts 1990). It has been known for some time, however, that oestradiol and progesterone can, in addition, have much more rapid effects directly on the cell membrane (Dufy & Vincent 1980). As yet we have few directly relevant data on the speed of action of androgens in the human, although one study in women, discussed earlier (Tuiten *et al.* 2000), showed an effect on genital response within 3 to 4 h. Caldwell (2002) has proposed a model of steroid-influenced sexual arousability, which depends on membrane-associated receptors linked to a more enduring change in G-protein coupling. However, the evidence he cites is largely restricted to oestradiol and progesterone. It remains a possibility that androgens may produce a relatively rapid membrane-mediated effect by means of aromatization.

Comparison of gonadal steroid effects in men and women As yet, there is little evidence that would allow comparison of the effects of oestradiol on male and female sexuality. With testosterone, there is much more relevant evidence, allowing the following conclusions.

(1) The evidence is more consistent for the male than for the female. Apart from methodological considerations, which are more complex in women than in men, potentially the most important factor accounting for this gender difference is a greater variability of behavioural responsiveness to androgens among women.

(2) Those women who are behaviourally responsive to testosterone respond to levels of testosterone which would be totally ineffective in men. This greater sensitivity to testosterone in women is most apparent in behavioural and other CNS responses and may be less marked in the anabolic and skin effects of testosterone.

(3) In the male, the evidence points to a threshold, below the normal physiological range, above which increased testosterone levels have little behavioural effect, and below which signs of androgen deficiency are likely to occur. This threshold concept does not appear to apply to women. The most convincing behavioural effects of the administration of exogenous androgens to women have involved supra-physiological levels, although in a number of studies sensitivity to these levels appears to decrease over time. On the other hand, it remains possible that signs of androgen deficiency will occur in women if circulating levels of testosterone fall too low, the critical level depending on a particular woman's sensitivity.

(4) A fundamental difference in male and female mechanisms of androgen production needs to be kept in mind. More than 90% of testosterone in the male is produced by the testes. In women, a substantial proportion of androgen production is from the adrenal glands and hence increased adrenal androgens can be expected in states associated with increased adrenal activity, such as anxiety, stress or depression (e.g. Weber *et al.* 2000). Given the strong relationship between mood and sexuality, which has been demonstrated particularly in women (e.g. Bancroft *et al.* 2003), this aspect of testosterone function warrants closer attention.

Peptides

Not only is there a seemingly limitless number of peptides to be found across species, it is apparent that they act in a variety of ways; functioning like classical 'hormones' being released into the circulation to act at a distance, but also acting as neurotransmitters or local regulators, leading Polak & Bloom (1982) to call them 'regulatory peptides'. Although peptides are released in many different parts of the body, neuropeptides are produced in substantial amounts within the CNS. With the evolution of the blood–brain barrier, the mammalian brain has been able to develop peptidergic communication independent of peripheral, classically 'hormonal' effects that may occur. To what extent these intra-cerebral effects involve synaptic transmission, 'parasynaptic' transmission through local diffusion or dissemination via the cerebrospinal fluid is not clear, but all may be involved, together with considerable potential for interaction with other neurotransmitters as well as steroid hormones. The limbic system is characterized by peptidergic neurotransmission, contrasting with the synaptic neuronal structure of the cortex (Herbert 1993) and consistent with the more primitive phylogenetic origins of the brainstem. The specific effect of a peptide may depend on its site of action, or even the context in which it is acting. In this review, attention will be restricted to oxytocin (OT), β-endorphin and prolactin (PRL) as representatives of the main types of peptides relevant to sexual arousal, and most of the cited evidence is from animal studies.

Oxytocin It is generally accepted that OT plays a key role during lactation, facilitating the milk ejection reflex. It may also play a role in facilitating uterine contraction during parturition. For such purposes, OT is produced in the magnocellular neurons of the paraventricular nucleus (PVN) of the hypothalamus, which project axons into the posterior pituitary and thence into the peripheral circulation (Kupfermann 1991). OT has also been proposed as a key factor in affiliative behaviour (Insel 1992). The evidence for OT being important in sexual arousal, response and behaviour is, however, less consistent. In animal studies, centrally administered OT has induced erection, an effect which is apparently testosterone dependent, and OT receptor antagonists can prevent non-contact erections, considered an index of sexual arousal (Argiolas 1999). Dopamine agonists may enhance sexual response by increasing central oxytocinergic transmission (Argiolas 1999). In female rats, studies with OT antagonists indicate that OT facilitates lordosis, an effect apparently dependent on progesterone priming. Less striking effects on proceptive female behaviour (hopping and darting) were also reported. There was also an increase in vocalizations when mounted, consistent with the tactile stimulation leading to lordosis and mounting becoming aversive (Insel 1992). This may be related to the effects of vagino-cervical stimulation (VCS), which has been shown to induce analgesia in rats. Komisaruk & Sansone (2003) have proposed that this analgesic mechanism, which may have a fundamental role in reproduction by making mounting and intromission less noxious for the female, in part involves OT. They also present evidence that VCS results in a release of OT from PVN neurons, which project to the brain stem and spinal cord, activating the sympathetic division of the autonomic nervous system in the process.

Cantor *et al.* (1999) examined the interaction of OT and serotonin. Having demonstrated that fluoxetine, a selective serotonin re-uptake inhibitor, impaired ejaculation in male rats and also reduced appetitive behaviours

(level changing), they found that OT administration reversed the effect of fluoxetine on ejaculation but not on appetitive behaviour. The authors concluded that serotonin suppresses ejaculation by interrupting the action of OT. They suggested that the effects of OT administration could have been mediated by a central stimulation of sympathetic outflow, or peripherally by facilitating smooth muscle contraction in the reproductive tract.

Thus, so far the animal evidence is consistent with both a peripheral and central role for OT; the most obvious peripheral effect being facilitation of smooth muscle contraction – the central role being more as a neuromodulator in a variety of response systems. Both peripheral and central mechanisms, however, appear to be steroid hormone dependent. The enhancement of erections is unlikely to result from the peripheral effects of OT given that they most obviously facilitate muscle contraction (necessary for ejaculation), whereas erection is dependent on muscle relaxation. However, whereas the central role of OT in lactation remains unchallenged, its fundamental role in sexual behaviour is questioned by the effects of OT gene ablation studies. OT knockout mice show clear impairment of milk let-down, but no apparent impairment of either mating or parturition (Nishimori *et al.* 1996, Young *et al.* 1996).

What evidence do we have for humans? Carmichael *et al.* (1987) found that plasma OT increased around the time of orgasm in men and women, remaining raised for at least 5 min after orgasm. The authors postulated that OT has a facilitatory role on sperm and egg transport by increasing smooth muscle contractility in the reproductive tracts. In a recent study of men, OT increased in some subjects following ejaculation, but the individual variability was such that the group effect was not significant (Kruger *et al.* 2003*a*). Murphy *et al.* (1987) reported an increase in OT in men during sexual arousal, which persisted beyond ejaculation, but with no obvious increase at ejaculation. In a study of women, Blaicher *et al.* (1999) found an increase in OT 1 min after orgasm, but levels were close to baseline by 5 min post-orgasm.

It is difficult to draw clear conclusions from this literature on OT and sexual arousal. Whether the increase of OT around orgasm, which has been somewhat inconsistently observed in the human literature, has any specific function, rather than being an epiphenomenon of other changes, remains uncertain, though it is possible that this OT rise will affect the experience of orgasm by influencing uterine and other reproductive tract smooth musculature. The possibility that a peri-orgasmic increase in OT contributes to the post-orgasmic refractory period, at least in males, should also be considered. Caldwell (2002) has proposed that OT is a satiety hormone that acts by de-coupling the G-protein (see above) and hence reducing sexual arousability. The reader is entitled to feel confused.

β-endorphin There has been, for many years, widespread awareness of the negative effects of exogenous opiates, such as morphine and heroin, on the sexuality of male and female drug addicts, reducing sexual interest, impairing genital response and blocking ejaculation and orgasm, with active and spontaneous reversal of such effects often occurring during opiate withdrawal (for review see Pfaus & Gorzalka 1987). In general, the subsequent animal research has shown similar negative effects of both exogenous and endogenous opiate administration, in male and female animals, with confirmatory evidence from blocking such effects with opiate antagonists such as naloxone, as well as withdrawal effects comparable with those in humans. The picture is complicated by the fact that opiates inhibit LH-releasing hormone, and hence reduce LH and testosterone. However, the animal evidence shows that the sexually inhibiting effects are predominantly independent of this reduction of testosterone.

β-endorphin is the endogenous opiate that has received the most research attention. Apart from the anterior pituitary, the synthesis of β-endorphin is limited to two cell groups in the brain, one in the arcuate nucleus of the hypothalamus, the other in the nucleus of the solitary tract in the brainstem. The relevant neurons in the arcuate nucleus project anteriorly to other parts of the hypothalamus, including the medial pre-optic area, and also to the amygdala. Dorsally, neurons run to the PVN of the hypothalamus and then on to the brainstem to structures involved in the autonomic nervous system (Herbert 1995). The sexual inhibiting effects of β-endorphin, and related opiate peptides, are believed to occur mainly through their action on the pre-optic area and the amygdala, the precise inhibiting effect depending on the site of infusion. Thus β-endorphin infused into the medial pre-optic area inhibits consummatory mounting and intromission, providing that mounting has not already started with a particular female; in other words, inhibition is of the activation of the consummatory sequence rather than its completion. On the other hand, infusion of β-endorphin into the medial amygdala inhibits the initial appetitive phase (Herbert 1995). According to Argiolas (1999) the inhibitory effect is dose dependent, with low doses of opiate having facilitatory and high doses inhibitory effects. β-endorphin may facilitate appetitive behaviour by acting on the ventral tegmental area to activate the mesolimbic dopaminergic system. This raises a crucial question, at least about exogenous opiates in humans, which remains largely unanswered. Exogenous opiates can induce an intense feeling of pleasure, which has been likened to an orgasm, followed by a state of relaxation and calm. What are the mechanisms underlying this? Is the activation of the mesolimbic dopaminergic system, which is associated with 'appetite' for a variety of behaviours, including sexual (Hull *et al.* 1998), relevant? 'Appetite', however, is not the same as intense pleasure, the origins of which, and of sexual orgasm also, remain obscure. A fair amount of

attention has been paid to this enigma in the literature, but explanations remain speculative, with conceptual overlap between incentive and reward (e.g. Wise 1996, Robinson & Berridge 2000). Nevertheless, we may be seeing, with the effects of exogenous opiates, a 'deconstruction' of the experience of sexual arousal, with dopamine (DA)-related rewards separated from the other opiate-inhibited components.

Of particular interest are the effects of opiate antagonists, such as naloxone and naltrexone. Whereas the administration of opiate agonists is relevant, it is difficult to relate its effects to those produced by physiological endogenous opiate release, for reasons of dosage, site of action etc. With the antagonist, however, one can expect to interfere with the normal physiological process. Pfaus & Gorzalka (1987) pointed to the potential clinical relevance of such evidence. Is this a way of identifying impaired sexual response which is due to increased endogenous opiate inhibitory tone? And, indeed, to what extent is such inhibitory tone part of the normal physiological picture? The animal research has produced somewhat inconsistent results, although more consistent effects in certain situations (e.g. with sexually inactive or sexually naïve rats) may be relevant (Pfaus & Gorzalka 1987).

In humans, the limited research has also produced inconsistent but in some cases interesting results. A dual dose-related effect was observed in women masturbating to orgasm (Gillman & Lichtigfield 1983); low doses of naloxone enhanced pleasure during orgasm, while higher doses had the opposite effect, reducing sexual arousal as well as orgasmic pleasure. This is consistent with the idea that endogenous opiates have both inhibitory and facilitatory effects, but the precise explanation for the relation to dose remains elusive. In an interesting study of men, Charney & Heninger (1986) assessed the effects of yohimbine (an α2-adrenoreceptor antagonist), naloxone and a combination of the two, compared with placebo. Yohimbine on its own produced no observable effect, whereas naloxone produced partial erection in three of the six men studied. The combination of the two drugs, however, produced a full and prolonged erection in all of the six men.

So far, no changes in plasma levels of β-endorphin have been found during sexual arousal or orgasm in men (Kruger *et al.* 1998) or women (Exton *et al.* 1999). The possible relevance of β-endorphin to the post-ejaculatory refractory state will be considered below, together with PRL.

As with OT, we are left with a complex picture of potentially excitatory and inhibitory effects of endogenous opiates, interacting with gonadal steroids. Although in recent years there has been progress in identifying the different opiate receptors involved (for review see Argiolas 1999) this has added another layer of complexity which as yet has not allowed a clearer picture to emerge.

Prolactin PRL is secreted by the anterior pituitary into the general circulation, showing a diurnal episodic pattern, maximal during sleep. Like OT, it is a peptide hormone with one very clearly established physiological and classically hormonal function, promotion of lactation. There are less well understood, but possibly important effects on ovarian function. With PRL receptors being found in most parts of the body, PRL has been reported as having more than 300 functions across vertebrates, a substantial majority of which relate to reproduction. However, in homozygous PRL receptor knockout mice, the female is infertile, in the heterozygous female lactation is to some extent impaired, the male shows delayed fertility in a minority of animals, but other aspects of male and female reproductive behaviour are apparently unaffected (Bole-Feysot *et al.* 1998).

In the human, low sexual desire is a common symptom of hyperprolactinaemia, often associated, in men, with erectile problems (Franks & Jacobs 1983). Although hyperprolactinaemia is also commonly associated with testosterone deficiency in men and ovarian dysfunction in women, impaired sexual desire can occur in hyperprolactinaemia without obvious gonadal steroid deficiency. This has focused attention on the negative sexual effects of PRL.

In an early study of six married couples engaging in sexual intercourse, blood samples were taken before and at 10, 30 and 60 min following coitus (Stearns *et al.* 1973). In the six women, all of whom reported orgasm during the sexual activity, two showed significant increases in PRL with an apparent peak at 10 min post-coitus. One of these two women reported a heightened orgasmic response, and the other a marked degree of breast stimulation. No changes in PRL were found in the men, all of whom ejaculated.

Studies of sexual arousal and PRL in response to erotic stimuli, not involving direct tactile stimulation or orgasm, have been few, restricted to men and showing inconsistent results. Rowland *et al.* (1987) reported some increase in PRL while watching erotic videos; Carani *et al.* (1990*b*) found no increase. In contrast, in a recent series of studies in which masturbation or sexual activity with a partner led to orgasm or ejaculation, a clear increase in PRL was observed following orgasm in both men (Kruger *et al.* 1998, 2003*a*) and women (Exton *et al.* 1999), with levels still raised after 60 min. This pattern was not found in a parallel study of men who masturbated without ejaculating (Kruger *et al.* 2003*b*).

These apparently consistent recent results have led these researchers to postulate that the post-orgasmic rise in PRL acts as a feedback control of sexual drive, contributing to the post-orgasmic refractory period (Kruger *et al.* 2002). In a comparable fashion, sexual side-effects of DA antagonistic psychotropic drugs, used for the treatment of schizophrenia, and of serotonin re-uptake inhibitors used for the treatment of depression, have been explained as resulting

from the associated, and chronic increase in PRL (e.g. Halbreich *et al.* 2003). Let us consider these claims more closely.

DA in the tubero-infundibular dopaminergic system maintains inhibitory control of PRL release. Thus any reduction of DA activity in this system will result in increased PRL release. Serotonin and thyrotrophin-releasing hormone increase PRL release. An important distinction in the experimental animal literature is between chronic and acute exposure to elevated PRL. The evidence from chronic exposure, typically implemented by means of transplants of pituitary glands, indicates that after a week or longer there is predictable impairment of sexual response with increased intromission and ejaculation latencies, and reduction in reflexive erections in male rats (Meisel & Sachs 1994). The more limited evidence of acute or short-term elevation of PRL indicates either no effect or a facilitatory effect (Melis & Argiolas 1995). A parallel can be drawn with chronic hyperprolactinaemia in humans. In cases of PRL-secreting tumours of the anterior pituitary, there is presumably a continuing release of PRL unaffected by the normal controls, such as DA. In other non-tumour cases, the mechanism underlying the hyperprolactinaemia is not well understood. But in both types of case, given the very high levels of PRL that usually prevail, and the interaction of PRL, DA, serotonin and β-endorphin, and most probably a number of other factors, it is reasonable to expect some more widespread dysregulation. With the transient, and comparatively small increase in PRL observed following orgasm by Kruger and his colleagues, such dysregulation is less likely to be involved. There are therefore alternative explanations to be considered. Thus the increase in PRL following orgasm can be seen as an epiphenomenon of post-orgasmic inhibition of DA activity, and not a hormonal mechanism of functional significance. Kruger *et al.* (2002) postulate that 'PRL forms a negative feedback loop to control its own release, similar to pathways observed for many other pituitary hormones'(p 38). However, for that to be the case PRL would need to increase DA activity, which is incompatible with the postulated function of feedback control of sexual drive. The assumption made by Halbreich *et al.* (2003) that the negative sexual effects of PRL-elevating drugs result from the resulting hyperprolactinaemia is somewhat more valid, because of the sustained hyperprolactinaemia involved. But the case can also be made for the DA antagonistic or the serotonin agonistic drug effect as being the cause of the sexual side-effects, with the raised PRL as an epiphenomenon.

The post-ejaculatory refractory period and 'sexual satiety' What hormonal and neurotransmitter factors are involved? Lorrain *et al.* (1997) showed in male rats that, during the post-ejaculatory interval, serotonin increased in the lateral hypothalamic area. Injecting a serotonin reuptake inhibitor into the lateral hypothalamus produced behavioural effects similar to the post-ejaculatory interval. Serotonin does therefore appear to be involved in the refractory period of the male. Attention is also being paid to a related phenomenon, 'sexual satiety' which, in male rats, occurs after a series of unrestricted access to receptive females. This state of sexual unresponsiveness develops, on average, after seven copulations and return to normal responsiveness takes around 15 days. Rodriguez-Manzo & Fernando-Guasti (1994, 1995) used different types of drug or hormone administration in attempts to shorten this state. They concluded that norepinephric (NE), serotonergic and opiate mechanisms were all involved, but with the NE system playing a key role. Mas *et al.* (1995) concluded that DA blockade was also involved and, because of the interaction between dopaminergic, serotonergic and norepinephric mechanisms, could be the key factor. In humans, the refractory period is more substantial in the male than the female. It is therefore noteworthy that the post-orgasmic rise in PRL was very similar in men and women (Kruger *et al.* 1998, 2003*a*, Exton *et al.* 1999). This would suggest that any reduction of dopaminergic activity is only part of the picture.

Future directions

Given that this article is one in a series celebrating the centenary of the concept of 'hormone' (Henderson 2005), how useful is that concept in understanding sexual arousal? The concept clearly remains relevant to the role of gonadal steroids, in particular testosterone, even though there are a number of uncertainties about how these 'hormonal' effects are mediated at the target organ. With peptides, the picture is different. Some conventional 'hormonal' functions are evident for several of the peptides (e.g. PRL and lactation), but research into the role of peptides confronts us with an ever-increasing complexity which makes 'hormonal' explanations of peptide function less and less helpful. This reflects in part the widespread interaction between peptides and other neuro-mediators, but also the phylogenetically primitive nature of peptides, which could account for their having overlapping functions, in many cases, where one function can be carried out by more than one peptide. The case can therefore be made to shift the emphasis of neuroendocrine peptide research from the study of specific hormonal functions, to the study of conceptual functional systems. The conceptual nervous system, based on functional responses or behaviours, rather than structure or specific mediating mechanisms, was first presented by Hebb (1955). Gray (1987) made good use of this approach with his behavioural activation and behavioural inhibition systems, employing both pharmacological as well as brain lesion methods to identify key factors in each system. We have built on Gray's model with our dual control model of sexual behaviour, which postulates parallel function and interaction of sexual excitatory and

inhibitory systems in the brain (Bancroft 1999, Bancroft & Janssen 2000). From this perspective, inhibition of sexual response, for the majority, is adaptive, preventing sexual arousal in circumstances that are perceived to be dangerous or risky, or in the case of the post-ejaculatory refractory period, ensuring that fertility is not impaired by too frequent ejaculations (all adaptive patterns of obvious relevance across species).

With this conceptual framework in mind, some key issues requiring further research are proposed.

Testosterone

Some key gender differences in the role of testosterone in sexual arousal require research attention. What role does aromatization of testosterone in the male brain play in male sexual arousal, and to what extent do comparable testosterone effects in the female depend on aromatization?

The striking difference in the sensitivity of the female and male brain to testosterone is a crucial issue waiting to be explained. I have proposed the following theory, 'the desensitization hypothesis', to account for this (Bancroft 2002*b*, 2003).

(1) The greater variability in the sensitivity to androgens in women could result from a greater genetic variability in women, on the grounds that in women behavioural responsiveness to gonadal steroids is less crucial to reproduction than is the case with men. However, the mechanism by which a genetically determined sensitivity might be expressed differently in women and in men requires explanation.

(2) Greater levels of testosterone in men are necessary for masculinizing effects, such as increased growth and muscle bulk, dependent on the peripheral anabolic effects of testosterone. It is postulated that if males were as sensitive to the CNS effects of testosterone as females, then the behavioural effects of these masculinizing levels would be maladaptive. Hence there is a need in the male to reduce responsiveness to androgen effects in the brain.

(3) Exposure to substantially higher levels of testosterone during fetal development and also during the first few weeks post-natally could be responsible for desensitizing the CNS to testosterone effects in the male. Given the uncertainty about the principal mechanisms of action of androgens, discussed above, how such desensitization is mediated needs explanation.

(4) Possible consequences of such desensitization in the male include that (i) genetically determined variations in CNS receptor responsiveness to androgens, across individuals, are 'flattened out' and hence less evident and (ii) much higher levels of testosterone from puberty onwards are possible without hyperstimulation of CNS mechanisms.

(5) With no such desensitization in females, the basic genetic variability would be more evident, at much lower levels of testosterone, and manifested as greater variability in behavioural responsiveness, demonstrated from early adolescent development (or adrenarche) onwards.

This hypothesis is open to testing in various ways. Evidence from studies of women with abnormal levels of testosterone in early development may be informative. For example, females with congenital adrenal hyperplasia (CAH), particularly the salt-losing variety which is associated with higher levels of testosterone during fetal development, show not only some degree of masculinization of behaviour, but also low levels of sexual interest and activity associated with low fertility (Meyer-Bahlburg 1999). Although, in such cases there are a number of factors which could impair normal sexual development, this evidence is consistent with there being some degree of desensitization to the high fetal levels of testosterone, which fall and remain low after birth when the CAH is treated.

Studies of testosterone administration to women may also be informative. Evidence of 'tolerance' developing to supra-physiological levels of testosterone was reported in several of the hormone replacement studies reviewed earlier (e.g. Brincat *et al.* 1984, Sherwin & Gelfand 1987). This suggests that desensitization might occur later in life, at least to some extent, and hence not just as an early 'organizing effect'. This is an issue of clinical as well as basic biological importance.

Given the striking variability in the responsiveness of women to testosterone, there is a need to identify markers of testosterone responsiveness. The recent controversy over the use of testosterone patches for low sexual desire in women, and the refusal by the Federal Drug Administration to approve such use, even for post-oophorectomized women, is partly based on the relatively weak treatment effect in the reported studies. If the treatment studies had been restricted to women showing validated indicators of testosterone responsiveness, the results may have been very different.

If support for the desensitization hypothesis is forthcoming, research should be focused on the possible mechanisms underlying the desensitization.

For both men and women, greater understanding is required of the non-sexual effects of testosterone, particularly in the brain. Effects on mood and general arousability may be relevant to sexual arousal indirectly. In addition, physiological levels of testosterone may be necessary for a more generalized pattern of interactive brain activity, much of which is not dependent on direct testosterone effects.

Oestradiol

The issue of whether the effects of testosterone in women result from aromatization to oestradiol, or increase in free oestradiol due to testosterone-induced reduction in SHBG and oestradiol binding, needs to be resolved. Direct comparison of varying levels of oestradiol and the

combination of oestradiol and testosterone is required. Does the addition of testosterone add anything to increasing the level of free oestradiol? This question is researchable in both humans and laboratory animals.

Peptides

The recommendation is that research should be focused on conceptual models of function or behaviour rather than on specific peptide mechanisms. The dual control model is an example. The animal literature is notable for its relative lack of studies on inhibitory mechanisms (Bancroft 1999). It may be informative to distinguish between different patterns of inhibition. For example, do the neurotransmitter/endocrine profiles differ for sexual inhibition in response to an external threat compared with the post-orgasmic/ejaculatory inhibition? To what extent can 'inhibitory tone' be distinguished from reactive increase in inhibition, in terms of the neurotransmitter/endocrine profiles? Many other examples could be given.

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