The Pharmacology of Sexual Function and Dysfunction
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Neuropeptides, stress and sexuality: towards a new psychopharmacology.

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Studying sexual behaviour: strategies.
The experimental study of sexual behaviour has been highly successful. The use of standardised preparations under carefully controlled conditions has enabled the mechanisms underlying sexual behaviour, as well as other important reproductive events such as ovulation, implantation, and seasonal breeding to be described and, to a degree, understood. Though no-one would argue with the premise that much more needs to be done, nevertheless current information is such that not only are there coherent accounts of these processes, but the applications of this knowledge to the clinic and the community has had immense impact on human affairs. The power of the simplifying approach to these questions is, therefore, vindicated. Sexual behaviour, studied in comparative isolation, has yielded to the powerful experimental techniques currently available. The endocrine requirements for initiating and sustaining sexual behaviour in rodents (and, to a lesser degree, other species) are now understood in some detail.

Sexual behaviour in the real world
But this reductionist approach, though successful in its own terms, has a penalty. Reproduction takes place in the real world, a world in which many other events occur, and is subject to the environmental and social constraints typical of any other activity. Of course, ecologists and population biologists have long recognised this, and the study of such factors occupies a major part of these fields of enquiry. All mammals live in a competitive and hostile environment. The struggle for access to food, water, shelter and a mate, and avoidance of predation or competitive injury, is a major concern. Reproduction is energetically and socially expensive and risky. Every species, therefore, has to maximise its reproductive efficiency - that is, try to ensure that the return (in terms of viable offspring) is maximal for its investment (that is, in terms of energy resources committed, or risks undertaken of damage or death). The precise nature of these risks will depend upon the species concerned. For example, species in which the males have to defend a territory against others during the breeding season will be at risk of injury; the burden on the mother may be less in species in which both parents participate in feeding the young. Species that breed in highly hostile physical environments need to adopt special stratagems to maximise the survival of the young, and so on. All these environmental demands impose constraints upon sexual behaviour (as well as associated reproductive events, such as pregnancy) . The process by which demand is recognised and dealt with is stress management. The problem is to marry our knowledge of the ways that stress regulates sexual behaviour with the detailed accounts of neuroendocrine processes . We must do this, if we are to understand how the basic mechanisms regulating behaviour interact with agents in the social and physical environment that have powerful effects on the success or otherwise of

reproduction in the real world in which animals and man live. There is a considerable literature - much of it anecdotal - on the effects that stress has on sexuality. The effects of stress, and the control of sexual behaviour both involve the brain. We are beginning to know enough about the neural processes of each to try and bring the two sets of neural mechanisms together, and see how they interact.

What is stress?

Before doing so, it is important to consider the contemporary meaning of 'stress' and how our view of this process has altered in recent years. The definition of 'stress' has moved from a single concept to a generic term for a range of processes. It is important to understand the nature of this evolution. Claude Bernard's recognition that maintaining the internal milieu within tolerable limits was an essential property of life carried with it two implications. The first is that there are agents that will tend to displace the milieu from its optimal position, and the second that there must, therefore, be mechanisms that both detect this tendency and counteract them. Though Bernard focused on physical agents, we now know that the environment contains others that can act in similar ways. The notion that responses to such events were unitary derives both from Cannon(1) and Selye (2). Cannon was concerned with acute emergencies, and pointed to the essential role of the autonomic nervous system (ANS) in responses to them. In his view, activation of this system characterised preparation for either 'fight' or 'flight'. It is significant that this concept combined an undifferentiated response (the activation of the ANS) with a differentiated one (the decision on either fight or flight). The latter, of course, involved mechanisms other than the ANS (ie within the brain); but the important point was that, for the theory in its original form, the physiological response did not differentiate between these two very distinct behavioural strategies. A variety of findings now suggest that it is persistent, chronic or repeated stress that is particularly significant in regulating reproductive (and other) events, and which is likely to result in pathological consequences. Selye recognised this. He ascribed these effects not to acute changes in the ANS (and the associated ones in cardiovascular and catecholaminergic function) but to the secretions from the adrenal cortex - in particular, corticoids. His thesis depended upon two principles: that stress (of whatever nature) increased the levels of adrenal corticoids, and secondly, that there was a time-dependent factor in this response. Eventually, he thought, the adrenal response would either wane, or the effects on target tissues of persistently elevated hormone levels would prove damaging. The significant feature, in the context of this discussion, is that Selye also assumed that all 'stresses', of whatever nature, resulted in an undifferentiated endocrine response. Although Selye recognised 'specific' components in the response to a given category of stressor, the significant event in the response to any stress derived from the adrenal cortex and its hormones.

The evolution of concepts of stress

These original, undifferentiated concepts of stress are being replaced with more complex, differentiated, ones. That is not to say that the original findings were incorrect. There is no doubt that activation of the ANS is a feature of a wide variety of acute stresses, though the view that the ANS

responds as a single system is being modified. Increased adrenal corticoid secretion is a consistent element in the response to many, if not all, stresses. But Bernard's fundamental postulate already contains the seed of doubt that undifferentiated models are sufficient. Though current knowledge of the composition of the internal milieu was not available to Bernard, it is clear that the nature of potential disturbances can vary. For example, maintaining temperature, electrolyte composition or blood sugar within tolerable limits involves different mechanisms, and the results of inadequate regulation will have different consequences. There is also recognition that the sources of 'demand' or 'stress' are not only the physical but also the social environment. All mammals live in some sort of social structure; this not only provides advantages in terms of defence of territory, food acquisition or mate selection but also is a source of demands, since there will always be a limit to the availability of resources, and therefore competition for them. So stress in differentiated according to its source and nature. It is also differentiated according to the pattern of response.

There has been much debate over whether the term 'stress' should be applied to an event which by general agreement represents a physiological or psychological demand on (such as, say, extreme heat, or an attack by a conspecific), or to the pattern of response (say, elevated corticoids, or avoidance behaviour). The former assumes that there are events which, inevitably, will be stressors; the latter, that there is a recognisable pattern of response that identifies the presence of a significant stress. Both definitions are too restrictive. Lazarus and colleagues (3), working on humans, and Weiss' work on animals (4) show clearly that there is no simple 'stimulus-response' relation between a stressor and the response to it. In the case of man, there are complex cognitive processes whereby someone presented with a stressful situation apprises the nature, source and significance of the stress, assesses the available resources (both personal and social) , and the likely outcome of the response to the stress. This process, an interactive one, may continue and change during the operation of a prolonged or repeated stress - hence the term 'transactional coping'. Whilst stress responses may differ in animals (and, perhaps equally importantly, in different species or in those with varying degrees of cerebral or social development), there may be similarities. In particular, unpredictable or uncontrollable stress may have particularly powerful effects on both endocrine and psychological function in both man and other animals (5).

The multiple nature of stress responses is also emphasised by more thorough examination of the endocrine changes accompanying them. Mason (6) began this process by showing that hormones other than adrenal corticoids and catecholamines were reliably responsive to stress - and that these changes might occur even in the absence of corticoid hypersecretion. Since that time, a great deal of evidence shows that many endocrine systems, including gonadal hormones, are altered by stress.

A major proposition of this paper is that social structure and its consequent interactions are an important regulator of sexual behaviour, as well as other aspects of reproduction. The second proposition is that this comes about

because social interactions are a major source of stress. Finally, it is proposed that social stress has direct actions on sexual behaviour, and that these come about through the operation of identifiable neural mechanisms, particularly peptidergic systems.

Society and stress

The relation between the social structure and breeding has been recognised for many year. Though, as already pointed out, the form this takes varies, in many species this involves competition between individuals for access to potential mates, or defence of the young against rivals. Losers in this competition will have greatly reduced chances to reproduce. In the majority of socially-living mammalian species (particularly primate) breeding activity is not distributed evenly amongst members of the group. A dominance hierarchy is a consistent feature of primate groups . Dominance is defined as the acquired property of priority of access in competitive situations. It is a form of social learning, in which individual members of the group come to know which other members they are likely to defeat in agonistic encounters. Liaisons and coalitions between group members may complicate the dominance pattern; that is, an individual's rank may depend upon his/her relation with other members of the group as much as his/her own agonistic qualities. The nature of the resource being competed for may also affect dominance hierarchies; for example, competition for food or mates may have somewhat different outcomes. So, although the dominance hierarchy is easily defined and recognised, it is not necessarily linear or simple.

There is little doubt that an animal's position in the social hierarchy can be highly stressful. In monkey groups, the majority of aggressive interactions are directed towards more subordinate animals. This, and the threat of being attacked, seems to represent a potent form of chronic or persistent stress. This state is reflected by both endocrine and behavioural markers. A subordinate monkey shows marked disturbances in the diurnal rhythms of cortisol, with elevated levels throughout the day, most prominently in the evening (when cortisol is usually at its minimum) (7) (see fig 1). There are equally marked differences in behaviour, including high levels of vigilance behaviour by which subordinates constantly monitor the actions of more dominant animals (particularly those of the same sex) (8,9) (fig 2). Subordinate vervet monkeys show stress-typical lesions such as gastric ulcers; there may also be increased neuronal death rate in corticoid-sensitive areas of the brain such as the hippocampus (10). Mortality rates are much higher in subordinate monkeys than more dominant ones (11).

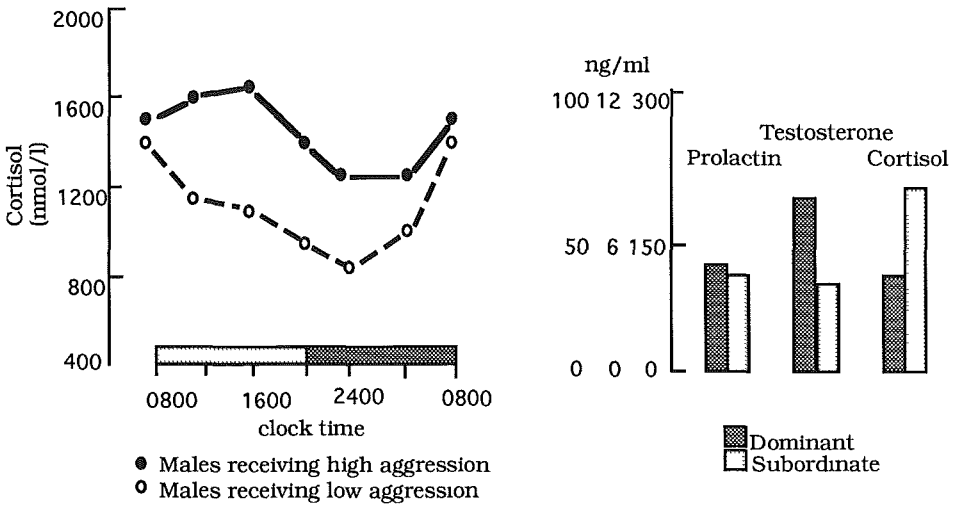

Fig 1. (Left) The effect of receiving high levels of aggression on diurnal levels of cortisol in male talapoin monkeys living in social groups. (Right): Differences in mean levels of prolactin, cortisol and testosterone in dominant or subordinate male talapoin monkeys.

Regulation of reproduction by the physical and social environment.
The social environment regulates reproduction by both behavioural and physiological means (12; 13). For example, only the most dominant male monkeys in captive groups of talapoins copulate with the females (fig 2). Subordinates make few attempts, and are inhibited from sexual interaction for quite long periods even if the more dominant males are removed (14, 15). At the same time, blood levels of testosterone in subordinates are considerably lower than in more dominant animals - an effect that becomes more obvious when the group contains sexually attractive females. However, these behavioural and endocrine stigmata of social subordination are not directly linked, since treating subordinate males with testosterone restores their serum hormone levels but does not reinstate sexual behaviour (16, 14).

There are similar mechanisms in female primates, though it seems that social stress has more marked effects on their physiology. Subordinate females often ovulate less regularly, and in some ovulation may be totally suppressed (17; 18). An extreme example is shown by the New World marmoset, in which the reproductive capacity of young females in their natal group is completely inhibited until they leave the group or the most dominant female (usually their mother) dies (19).

There is continuing discussion over whether an animal's social rank is itself responsible for these effects, or whether the amount of aggressive interaction is the critical factor. The two are not necessarily congruent. For example, in a

stable group, levels of aggression may be quite low, though the dominance hierarchy may be obvious, steep and persistent. However, in more labile groups, in which social relationships are less well established, there may be higher levels of aggression as animals continue to try and establish their rank order. Within a group the same provisos may occur. If the relative rank of two animals is uncertain, there may be more aggression between them. Alternatively, the more dominant male (say) may attack one member of the group more than another. In one study, the negative correlation between serum testosterone and aggression in different male members of a captive talapoin monkey group was more pronounced than that between testosterone and rank (18). This supports the notion that social rank acts as a moderating factor reducing the levels of overt aggression.

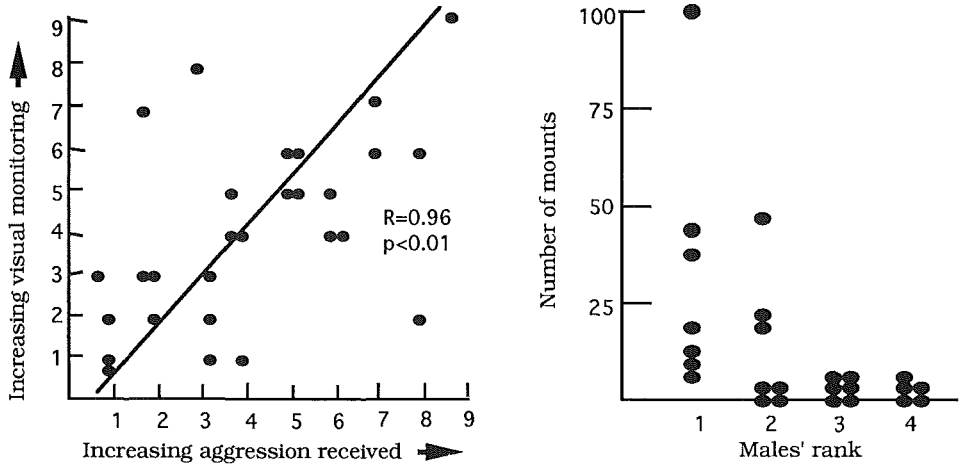

Fig 2. (Left) The relation between vigilance behaviour ('looking at other males') and aggression received in captive groups opf talapoin monkeys. (Right) The effect of decreasing rank on copulation in social groups of talapoin monkeys.

Population density, with its attendant overcrowding, food shortage and increased aggression, has been recognised as an important mechanism for regulating reproduction (see 20). Such conditions result in lower ovulation rates, impaired implantation and increased rates of abortion or resorption. Furthermore, infant mortality increases, and the growth of the young that survive is compromised.

Stress and sexual activity in man.

Is there evidence for similar relations between social structure, stress and sexuality in man? There is no doubt that stress can reduce testosterone levels. Physical danger, such as a military threat, or more psychological stresses, such as the constant vigilance needed by air traffic controllers, both lower serum testosterone in man (21, 22) as do periods of prolonged physical exertion and sleep deprivation (23). Socially dominant men - who are not necessarily

the most aggressive - have been found to have higher serum testosterone than others (24). So-called 'type A' men - who tend to the more dominant members of society because of their assertive and ambitious personalities - also have higher testosterone levels than 'type B', who are more passive. The latter respond to stress by lowering their blood testosterone, whereas in the former it may rise (25). Young men showing high levels of either physical or verbal aggression may also have the highest levels of testosterone (26), though this finding has been questioned (27).

There is a wealth of anecdotal evidence for similar features in women, though reliable data is harder to come by. Physical exertion is thought to be able to interfere with the reproductive cycle (28). Most psychological stressors may also inhibit reproduction, though the evidence is even less secure. During the second world war, it was reported that generalised severe stress, such as that experienced in concentration camps, resulted in amenorrhoea, but these conditions also included food shortage, itself a potent cause of reduced fertility.

Neural mechanisms concerned with stress responses: β–endorphin

There are many different kinds of stresses, and a wide range of stress responses. The neural mechanisms that both recognise and formulate responses to stress are, therefore, equally diverse. However, it is beginning to become evident that there are recognisable parts of the brain, and chemically-identifiable neutral systems that seem particularly concerned with the way that stress modifies reproduction. This is illustrated by the effects of β–endorphin on sexual behaviour and its more general role in reproduction.

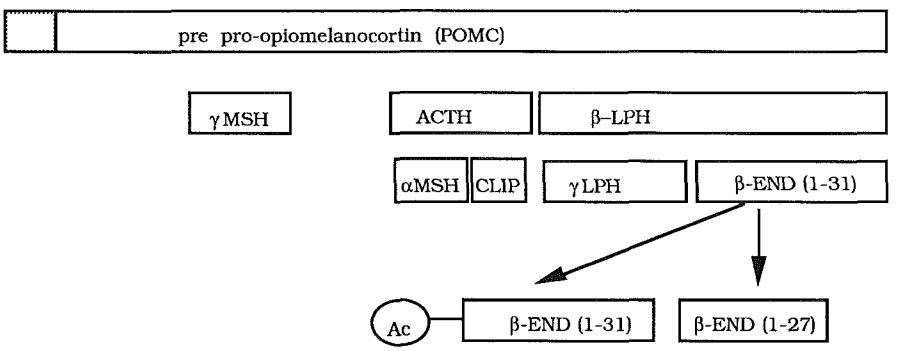

Fig 3. The synthesis of β-endorphin in the brain.

The synthesis of β-endorphin in the brain (Fig 3) is limited to two cell groups, one lying in the hypothalamic arcuate nucleus (a structure implicated in the control of LH secretion), and the other in the brainstem nucleus of the solitary tract (NTS), known to be concerned with autonomic and related functions (29, 30) (Fig 4). It is important to note that β-endorphin is derived from a larger precursor, and is a member of a family of peptides. The action of other members may compete with or complement those of β-endorphin. From the peptide-expressing neurons of the arcuate nucleus, fibres pass anteriorly to other areas of the hypothalamus (including the preoptic area, known to be important in the control of sexual behaviour), and the amygdala (recognised to be concerned with fear and other stress-associated responses). Other fibres run dorsally, towards the hypothalamic paraventricular nucleus (a site for the control of ACTH and hence corticoid levels), and thence to the brainstem, terminating in a number of structures (including the NTS) that have significant functions in the regulation of the autonomic nervous system.

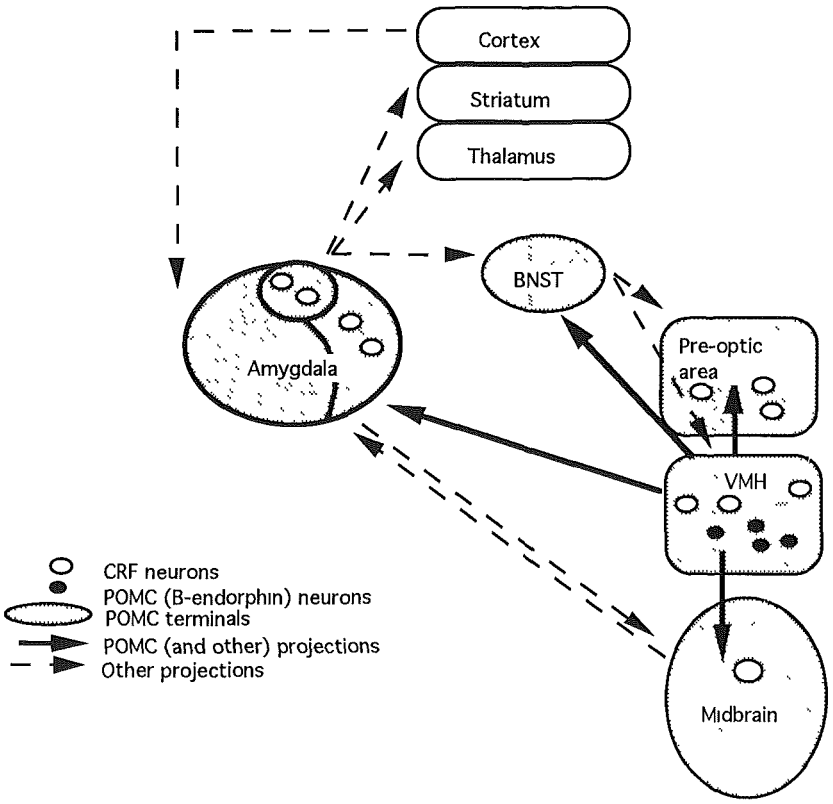

Fig 4. The distribution of β-endorphin-containing pathways in the brain.

β–endorphin and stress

Central β-endorphin seems to be released during various forms of stress (31), including adverse environmental conditions. Though there have been technical problems about measuring the release of β-endorphin under stressful conditions, enough is now known about this peptide to indicate that it is particularly concerned with regulating reproductive physiology, and is part of the mechanism whereby reproduction is controlled by various elements in the external environment, including social and physical stress (32, 33, 34). Much attention has been focused on the mechanisms for inducing reproduction at times or in conditions that are the most propitious for success, and that carry the least risk. Less has been given to equally important mechanisms that ensure that reproduction is inhibited at other times - for example, during periods of increased stress or demand - and yet such mechanisms must exist.

Effects of β-endorphin on sexual behaviour.

Sexual behaviour is attenuated in many species during pregnancy, when β-endorphin levels in the hypothalamus are increased (35). The photoperiod, operating through the pineal gland, acts as a powerful brake on reproduction in some species (eg the hamster, ferret and sheep) preventing birth during hazardous times of the

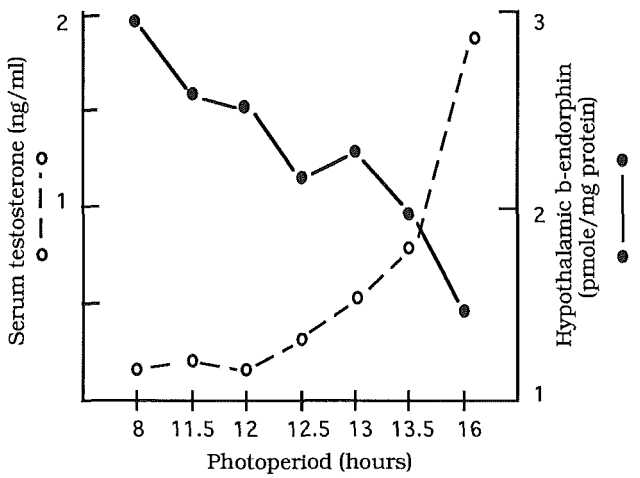

Fig 5. The reciprocal relation between levels of β-endorphin in the hypothalamus of male hamsters and blood levels of testosterone under different photoperiods.

year (36). β-endorphin levels in the hypothalamus of the photoinhibited hamster (that is, a hamster exposed to short photoperiods) are higher than in photostimulated ones (37). The concentration of β-endorphin bears a consistent relation to the duration of the ambient photoperiod: the shorter the photoperiod, the higher the levels of β-endorphin (32) (Fig 5). Behavioural sensitivity to injected steroids is reduced during the non-breeding season. These, and other findings, show that β-endorphin levels are regulated by the duration of the photoperiod, and that this system represents one mechanism whereby reproduction is inhibited under appropriate circumstances (38).

Opiates given peripherally or infused into the hypothalamus and other parts of the limbic system reduce gonadotrophin levels and increase prolactin levels (39, 40). Intra-ventricular β-endorphin has been known for some time to inhibit copulation in male rats (41, 42). These are the typical features of stress-induced reproductive suppression. The conclusion that endogenous opioids may be involved in the process whereby social rank regulates sexual behaviour and reproduction is strengthened by the finding that β-endorphin levels in the CSF of subordinate males is about three times as high as in dominant ones (18) (Fig 6). It is assumed that these levels represent increased release of β-endorphin within some part of the limbic system. Adverse environmental conditions seem to increase the activity of endogenous β-endorphin, and this, it is postulated, represses both sexual behaviour and gonadotrophin secretion.

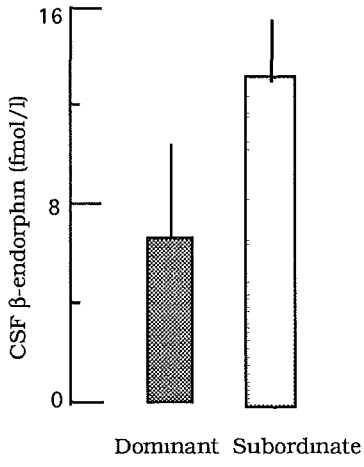

Fig 6. Increased levels of β- endorphin in the CSF of subordinate male talapoin monkeys.

Local infusions of β-endorphin into the brain

A more direct test of the behavioural action of β-endorphin is to infuse the peptide locally into the brain and observe its effects. Various areas of the brain have been implicated in the control of sexual behaviour, but the medial preoptic area and the amygdala are consistently recognised to be critical areas for hormonal action, at least in male rats (43, 44). Both, of course, are also involved in the neural control of gonadotrophin secretion, though the evidence for this is less compelling than for a behavioural role. Local infusions of β-endorphin in these two parts of the limbic system have remarkable effects.

The sexual behaviour of male rats can be studied by pairing the male with an oestrous female. To ensure a relatively consistent behavioural stimulus, an ovariectomised female is treated with a combination of oestrogen and progesterone that induces the full range of oestrous behaviour. Males studied in this way show a characteristic pattern of behaviour. There are two phases. During the first precopulatory stage (sometimes referred to as the 'appetitive' phase), the male explores the cage and begins to investigate the female by exploring her head and flank, paying particular attention to her ano-genital region During all this the female - if she is oestrous and sexually receptive - may begin to display typical hopping and darting runs, accompanied by characteristic vibration of the ears. In some cases, the female seems to be responding to the male; in others, the female's 'proceptive' behaviour (as these actions are collectively termed) occurs even before the male has started to investigate her, and seems to stimulate him to do so. This period of precopulatory behaviour is marked by the male appearing to gather information about the female, and by the female emitting oestrous-dependent behavioural signals to the male. The onset of the second, copulatory phase (the 'consummatory' phase) is signalled by the male mounting the female. This may or may not result in vaginal intromission. A series of such mounts and intromissions then follows, until the male ejaculates. Then there is an interval - the post-ejaculatory refractory period - during which the male seems unresponsive to the female, before another sequence of sexual interaction begins again.

β-endorphin infused into the hypothalamus

Lesion experiments have shown that the preoptic area/anterior hypothalamus (POA) of the male is critical for sexual behaviour. The effects on the sexual behaviour of the male rat of bilateral infusions of β-endorphin into the POA are equally striking and rather specific (Fig 7). After bilateral infusions of as little as 10 or 40 pmoles , male rats continue to pursue and investigate the female in the usual way, vigorously and repeatedly, so that an observer unaware of their treatment would expect that, at any moment, the expected sequence of mounting and intromission would begin. After a while it becomes apparent that mounting does not occur; the animals seem restricted to the precopulatory part of their interaction with the female, and unable to proceed to the next, copulatory, stage of their sequence (45). This behaviour is similar to that following bilateral electrolytic or neurochemical lesions of the POA (46).

One important advantage of infusing peptides over making lesions is that the former is temporary, and can be carried out at different stages in the sequence of sexual behaviour. When this is done, it yields some striking and surprising results . When an the infusion of β-endorphin into the POA was delayed until

the male had made his first intromission - that is, until the copulatory series had begun - than there was no longer any discernible effect (47). The male mounted and ejaculated as if he had received a control infusion. However, the neurochemical state of the POA (ie its content of β-endorphin) was the same as that in which copulation had been prevented provided the infusions were given *before* the male was paired with the female. So β-endorphin in the POA does not inhibit the expression of the consummatory phase of sexual behaviour. It seems to interfere with the process whereby sensory information - obtained during the investigative (or 'appetitive') phase - is processed and leads to the activation of the consummatory response. This disconnection might be one basis of the stress-induced reduction in copulation consistently observed.

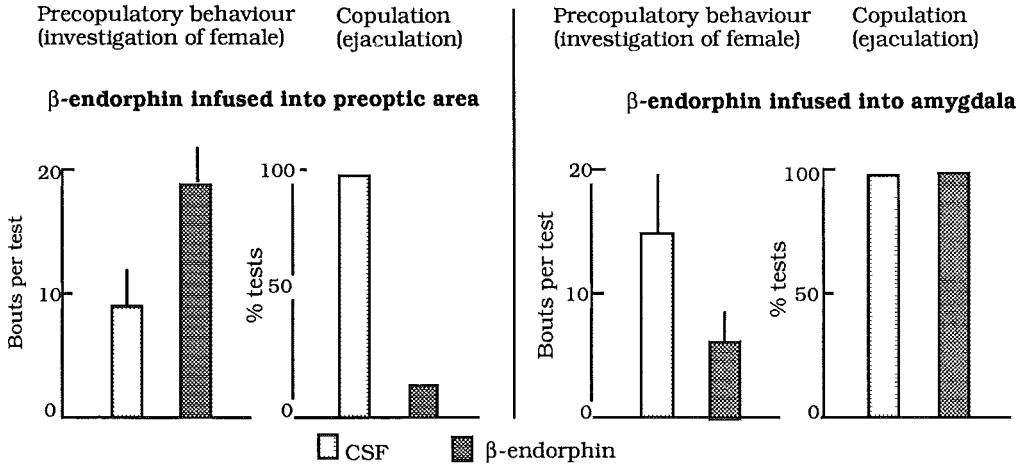

Fig 7. (Left) Suppression of copulation following infusions of β-endorphin into the pre-optic hypothalamus of male rats. Pre-copulatory behaviour is left intact. (Right): Suppression of pre-copulatory behaviour by infusions of β–endorphin into the amygdala.

β–endorphin infused into the amygdala

However, as we have seen, the amygdala - which has major inputs into the hypothalamus - is also implicated in sexual behaviour. Both anatomical and behavioural data suggests that the amygdala is concerned with processing sensory information from the cortex and olfactory system in the context of limbic function - for example, assigning emotional or motivational significance to stimuli. There are extensive inputs to the basolateral amygdala from the neocortex, particularly (but not exclusively) from higher order or 'association' areas (ie the parieto-temporal lobe), and to the corticomedial amygdala from the olfactory tracts (48) (Fig 4). Lesions - particularly in the medial amygdala which receives a plentiful olfactory input - interfere with sexual behaviour in male rats (49). The amygdala also receives a β-endorphin-containing input from the hypothalamus (30). But infusion of β-endorphin into this area have very different effects on sexual behaviour from those into the hypothalamus.

Bilateral infusions of β-endorphin into the amygdala (but not the nearby caudate-putamen) had a consistent and specific effect on the sexual behaviour of male rats. In contrast to the effects of similar infusions into the hypothalamus (which reduce copulation -see above), those into the amygdala inhibit the male's investigation of the female - that is, the initial or 'appetitive' phase of sexual interaction (Fig 7). The onset of copulation is thus much delayed, though when it eventually occurs, it is not impaired. These results show that (i) β-endorphin, a stress-related peptide, has different effects on sexual behaviour when infused into different sites of the limbic system (ii) these effects are on separable components of sexual behaviour, and these components relate to the general function of the neural sites (eg the amygdala is concerned with association of sensory information with motivational states, the hypothalamus with the organisation of behavioural and endocrine responses). So stress can affect separate aspects of reproduction, depending on the site at which stress-related peptides are released (see 50 for a more extensive discussion).

Other peptides implicated in stress.

But β-endorphin is not the only peptide of interest in the context of stress-related alterations in reproduction. There are large number of other peptides in the limbic system and many are involved in different forms of stress (50). As we have seen, social aggression and threat has potent effects on reproductive capacity. Aggression under biologically meaningful conditions is always part of another behaviour (51). For example, the aggressive behaviour of male monkeys or stags towards other males (but not females) during the mating season is part of sexual behaviour, and is thus regulated by testosterone levels and position in the dominance hierarchy, factors that also control sexual behaviour (52). Defence of the young by attacking intruders - in this case, other females - is part of maternal behaviour (53,54) and will have different controls and consequences.

A variety of studies suggest that CRF-containing cerebral systems play an important role in the response to stress. CRF is expressed in neurons and terminals throughout the limbic system, in a number of cell groups in the brainstem associated with autonomic function (such as the parabrachial nucleus, locus coeruleus and dorsal vagal complex) as well as in many areas of the cortex, particularly limbic regions (55, 56). Infusing CRF intraventricularly (icv) invokes a range of autonomic responses, including enhanced catecholamine secretion, alterations in gastrointestinal activity, and increased blood pressure and heart rate - a pattern that resembles the physiological response to a variety of stressors (57, 58; 59). CRF also has behavioural effects. In a familiar environment, icv CRF causes dose-dependent increases in locomotor activity, rearing and grooming, whereas in novel or more stressful contexts these behaviours are inhibited - typical reactions of rats and other small mammals to a fear-inducing or 'arousing' environment (60; 61). CRF has anxiogenic effects in experimental tests of anxiety; it enhances responses both to acoustic startle and conditioned fear, and the behavioural responses of male rats to other, unfamiliar males (62, 63, 64).

Though CRF may form an important part of the intracerebral response to stress (including behavioural and autonomic components, as well as endocrine ones), its effects on sexual behaviour may well be indirect. Infusing

CRF into the male rat's amygdala, for example, increases aggressive behaviour with another male, but has no effect on sexual interaction with an oestrous female (64; 49). Most studies on stress use acute procedures; but chronic or persistent stress is a more physiologically and pathologically meaningful phenomenon. There is clear evidence that persisting or repetitive stress of various sorts can alter the central activity and distribution of peptides. Repeated immobilisation increases the AVP content of CRF-containing neurons and their projections to the medial eminence (65) and might be correlated with a special role for AVP in the regulation of pituitary ACTH in longer-term adaptations (66); the respective roles of CRF and AVP throughout the limbic system under such conditions needs much more intense investigation. It is regrettable that the effects of persistent stress on the brain has yet to be correlated with those on reproductive physiology and behaviour, though it is clear that such an approach might have great interest for those concerned with both animal and human reproduction. In particular, the newer techniques of mapping changes in brain activity resulting from stress (eg using the neuronal expression of immediate-early genes such as *c-fos:* 67 68), and relating this to changes in reproductive capacity might be very fruitful.

Towards the new psychopharmacology

Current psychopharmacology depends almost entirely on drugs that moderate monoamine function, or anxiolytics acting on GABA. Each monoamine is implicated in a wide variety of functions; there is no evidence that they have a preferential action on any category of behaviour. Selective effects are likely to be the consequence of the context in which the behaviour occurs, rather than its pattern. For example, if sexual activity is the predominant behaviour, then modulating monoamines will alter that behaviour. The same may be true for other behaviours (eg eating) under other conditions. Furthermore, monoaminergic drugs do not alter the direction of behaviour - that is, make a particular motivational category of response more or less likely.

Peptides, on the other hand, have been shown by many different methods to change the preferential expression of a particular behaviour (50). Furthermore, they are clearly implicated in formulating specific patterns of behaviour (together with appropriate associated endocrine and autonomic responses). They also have evident roles in the reaction to stressors of various types. However, in contrast to the monoamines, there have been major problems in devising drugs that cross the blood-brain barrier and act selectively on peptide receptors, or alter their expression or release, even though naloxone - a non-peptide drug that blocks opioid receptors - has been known for years. Recently, there are signs that this is being remedied. For example, non-peptide drugs now exist that block angiotensin or CCK. The next few years will reveal many more such compounds. Eventually, we will be able to manipulate selectively the plethora of peptides in the limbic system, and the new age of sexual psychopharmacology will have arrived.

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Discussion - NEUROPEPTIDES, STRESS AND SEXUALITY: TOWARDS A NEW PSYCHOPHARMACOLOGY

J. Stewart

I would like to make a statement and a comment. I would like to extend your analysis of the role of steroid hormones in the regulation of peptides to the role of monoamines in the regulation of peptides. We know for example that the integrity of the dopamine system is important for the regulation of substance P and dynorphin in the striatum and it is possible that these are involved in aspects of sexual behaviour as well as in other motivational effects that we have been talking about. But I would also like to question your absolute statement that peptides have very specific actions. Why do you say that?

J. Herbert

Because all the ones that I know about are characterized by an extraordinary specificity. Let's take for example the NPY. NPY like many other compounds suppresses sexual behaviour. It may be said that this is not specific, since an animal cannot eat and copulate at the same time, but in the real world it will have to make a choice for good reason. What the animal needs is a compound that promotes the correct sort of behaviour and reduces the other. And that is what peptides often do, they have a dual function.

J. Stewart

Well, I am puzzled because it would depend on what part of the brain they are acting.

J. Herbert

Yes, I agree with that. I really simplified the story, you are quite right. I will make another point: some of these peptides are highly localized while others are not. NPY has a large distribution in the cortex but what is it doing there? It should not be there, but it is and I do not know what it is doing there.

K.E. Andersson

And what about the nitric oxide? It coexists with very many peptides for example in the paraventricular nucleus, and that is a new way of discussing the neural transmission within the brain.

J. Herbert

Nitric oxide is a great puzzle of course and a great surprise, but it is there and it does things. The thing I have to say is that it is not receptor-mediated. It acts directly on cGMP and in a completely different way from the peptides. Many peptides cause the release of nitric oxide interneurally so it is very different kind of substance that seems to be a local effector which is used by things like, for example, some of the peptides and other things as well. I do not think you could compare nitric oxide with peptides.

K.E. Andersson

I think you can see there are two functions of nitric oxide. It diffuses and has effects in other neurons but it could have effects within the same neuron and it could facilitate release of, for example, other transmitters.

J.T. Clark

When you injected endorphin did the animals have the choice of drinking and eating and copulating?

J. Herbert

Yes they did.

J.T. Clark

Because what I have seen sometimes with angiotensin II is that if the animal has access to a female and to water at the same time the dose response for drinking is shifted to the right, that is, it takes more angiotensin in stimulating the drink. In the case of NPY if you inject it into the animal, it does mate but he does not eat as equally as if the female was not there: There is some kind of interaction there.

B.J. Everitt

We heard that several peptides when infused into the brain had the ability to inhibit sexual behaviour, but I wonder if we can point to a peptidergic system in the CNS that is either necessary or sufficient for the expression of sexual behaviour in males or females. What I am wondering now particularly, given the attractiveness of the notion that a neuropeptide might have coordinated central and peripheral roles, is which peptidergic systems code for the expression of, rather than the inhibition of, sexual responses?

J. Herbert

I think that there are several reasons why people have not managed to identify peptides which increase sexual behaviour rather than decrease it. The first is that in most situations, in situations under which people normally show sexual behaviour, the behaviour is at high level, and one is not going to see an effect, that is why we are using animal models, and they of course are to pick animals that are suboptimal. Some years ago, we tried to give LHRH to males and saw that nothing happened so we gave up. The second possibility is that we study sexual behaviour experimentally not only at a high level but also under very simple conditions, and I think we have to keep reminding ourselves about that and that many of these things may not be apparent unless we give the animals the opportunity to show the effects of the things we ask. The opposite strategy, of course to giving the peptide which increases the sexual behaviour, in some way a more promising one, is to block the effect in the endogenous peptide to demonstrate that it possibly goes down, and again, the LHRH is the candidate. All the experiments that have been done giving the animal an LHRH antagonists have given highly mixed results. It is certainly not true that there is a profound and regular decrease of sexual behaviour.

B.J. Everitt

I might just comment that the opioid antagonist naloxone infused in the preoptic area does amazing things to the rapidity and frequency of sexual behaviour of male rats who ejaculate several times in 15 minutes or so, suggesting the opposite kind of phenomenon to that which follows infusion of endorphins.

J. Stewart

One approach to this question might be just to study systematically all the peptides that are increased when you give testosterone. We know that vasopressin is increased but we do not know very much about the others.

J.T. Clark

Sometimes, looking at the peptides and seeing what happens with testosterone withdrawal and replacement but also what happens as one changes the behaviour might be critical. If we look at the feeding literature, we see that responses to peptides like NPY are modified by the feeding state: It is increased in food deprivation and decreased with refeeding and those are site specific effects. Can we see the kinds of things for sexual exhaustion? I think the problem with simply using exhausted rats is that the behaviour itself is going to induce changes, both in testosterone and peptides, so when you start getting out to days 1 and 2 you do not have an animal site that is the same, so it may be a context-specific effect. I think this raises new questions.

K.E. Andersson

Could somebody comment upon the observations that both apomorphine-induced erections and oxytocin-induced erections can be blocked by oxytocin antagonists? and also that oxytocin induced-erections can be blocked with the injection of a nitric oxide synthesis inhibitor in the medial preoptic area. To me it is a little bit difficult to find out which is the sequence for producing these erectile responses.

M. Murphy

I think that it has been demonstrated by administering dopamine blockers. Under these circumstances, oxytocin-induced erections still occur after injections of oxytocin into the paraventricular nucleus, but they do not occur after injection of apomorphine. So it seems that oxytocin is acting downstream from apomorphine. As for the nitric oxide part of the question, I don't think it has been answered.