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Central inhibition of sexual response in the male: a theoretical perspective

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Abstract

A theoretical model for central inhibition of sexual response is proposed, postulating individual variability in the propensity for such inhibition. Whereas such inhibition is typically adaptive, individuals with high propensity may be vulnerable to sexual dysfunction, and those with low propensity to high risk sexual behavior. Evidence of the existence and localization of such inhibitory mechanisms from both the animal and human literature is reviewed. Evidence of central neurotransmitters with sexual inhibitory effects is substantial, though in most cases the inhibition is not specific to sexual response or behavior. Recent studies have identified centers in the brain stem and lateral hypothalamus which appear to have specific inhibitory effects on sexual response. A variety of adaptive mechanisms involving inhibition of sexual response are considered, some involving perception of threat, others occurring more directly as consequences of previous sexual activity. These different adaptive functions may well involve different inhibitory mechanisms. This theoretical model opens a new agenda for experimental research into adaptive sexual behavior, both human and animal.

Keywords: Sexual response; Neurophysiological inhibition; Serotonin; Dopamine; Norepinephrine; β-Endorphin; Nucleus paragigantocellularis

1. Introduction

The purpose of this paper is to consider a theoretical model for the central control of male sexual response, and to review the evidence, both from the animal and the human literature, which may be relevant. The model postulates the existence in the central nervous system (CNS) of both excitatory and inhibitory systems, which together provide a 'dual control' over sexual response and consequently, sexual behavior. The emphasis in this paper is on the inhibitory component, as hitherto considerable attention has been paid to excitatory mechanisms. The existence of the capacity for inhibition of sexual response is assumed to be adaptive, providing the degree of control which enables the individual to avoid danger or other disadvantages that might ensue from a sexual response. The propensity for this 'central inhibition' to be invoked is assumed to vary across individuals, and whereas in the majority this propensity is adaptive, helping individuals to keep out of trouble, there will be those whose propensity for inhibition is unduly high, resulting in an impairment of the capacity for sexual function (in the human, referred to as sexual dysfunction) and, at the other end of the scale, those whose propensity for inhibition is low, increasing the likelihood of engaging in risky sexual behavior. This theoretical model will be elaborated at the end of this paper after first considering the possible functions of such central inhibition of sexual response, together with the evidence for the existence of central inhibitory mechanisms and how they might be organized.

The concept of a balance between excitation and inhibition is fundamental to neurophysiology, although in most respects at the neuronal level; i.e. each neurone, at least within the CNS, has both excitatory and inhibitory neurones acting on it. But at that level, the interplay between positive and negative inputs can have a wide variety of outcomes—e.g. an inhibitory signal can have a disinhibiting effect by acting on an inhibitory neurone. The issue becomes more relevant to our purpose when we consider excitatory and inhibitory *systems* within the CNS. It has been assumed for some time that an interaction between excitatory and inhibitory mechanisms determines the species-specific pattern of sexual behavior [1–3] although evidence for such inhibitory mechanisms has been largely indirect and has received much less research attention than the excitatory mechanisms. Such paired systems are very familiar in neurophysiology, although they vary in complexity and in the type of purpose they serve. There are purely homeostatic systems, such as those which control body temperature, or blood pressure, where the interplay between positive and negative feedback signals is designed to maintain a steady state, within relatively narrow limits. Control of food intake

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is a further interesting example, more complex than temperature regulation, and having some features in common with control of sexual behavior. This can also be seen as a feedback system maintaining a steady state, in this case body weight, although in contrast to temperature the system can be set to achieve widely differing body weights across individuals, and even within the same individual over time. When we consider the control of sexual behavior, there is no direct individual-based 'homeostatic' parallel. The occurrence of sexual activity carries a cost, at least in terms of risk, whereas the absence of sexual activity has no cost to the individual (apart from the lack of reward from sexual interaction). However, the fact that sexual activity may result in reproduction, and inhibition of sexual activity avoids reproduction, raises the issue of homeostatic control of population density (i.e. a 'homeostat' for the group rather than the individual). For most mammals studied in this respect, there is maintenance of a fairly stable population density, which is only destabilized by major environmental changes. For some reason not as yet understood, this does not appear to apply to humans. The mechanisms by which population density may be controlled will be discussed below, but, as we shall see, they include inhibition of sexual behavior.

2. What are the possible purposes of central inhibition of sexual response?

Bjorklund and Kipp [4] make the persuasive case that inhibitory mechanisms became necessary in small groups of hominids for the purposes of cooperation, group cohesion and individual political success. The two response patterns which are most in need of inhibition for these purposes, they suggest, are sexual and aggressive behavior. The comparison of these two is of interest. Whereas, with aggression, inhibition is beneficial in many social situations, in other situations lack of aggression is dangerous. Inhibition of sex is not quite like that, although it can be linked to the inhibition of aggressive behavior. Certainly, in many social primates there is evidence of inhibition of sexual behavior organized around the dominance hierarchy [5, p. 61]. It is potentially dangerous for a low dominance animal to be sexually active in the presence of a high dominance member of the group. There are no obvious risks from avoiding sexual activity, apart from the aggressive response it might induce in a potential partner whose sexual needs are thwarted. Furthermore, beyond the social context, engagement in sexual activity reduces vigilance and therefore may increase vulnerability to a variety of threats, and if pursued excessively, may maladaptively reduce attention to other important adaptive functions.

Fertility is also dependent on inhibition of sexual response in a variety of ways. The simplest example is the restriction of sexual arousal following ejaculation to avoid excessive sexual activity and repeated ejaculations which, over a short time period, would result in lowering of the available sperm store. More complex is the organization of sexual behavior, by hormonal mechanisms, to occur around the time of ovulation, the oestrous pattern, which maximizes the chance of fertile mating. It has been proposed that the main effect of reproductive hormones on sexual behavior is to reduce inhibition of sexual responses in a permissive fashion [1]. This is of particular relevance to the female who, in most species, has to expose herself to mounting and penetration by another animal, a situation which in other circumstances would be threatening and potentially dangerous. More subtle is the inhibition of male sexual behavior that allows the pacing of group sexual interactions in some rodents [6].

A threat to fertility, and in some cases survival, is sexual transmission of disease. This is an issue of paramount importance to humans. Sexually transmitted diseases are also common in animals, and are of particular importance in agricultural breeding as a cause of infertility and abortion [7]. The possibility that such infections in other species may have evolutionary significance, influencing for example mating patterns, is receiving increasing attention (e.g. [8]). The role of inhibition of sexual response as an adaptive mechanism to avoid such risks has, as far as I am aware, not been considered or studied in other species, but obviously forms a large part of the relevance of this theoretical model to humans.

The biological benefits of incest avoidance may also rely on inhibition of sexual response. Keverne and Vellucci [9] described the family groups of the marmoset which appear to involve some form of incest 'taboo'. The father will not mate with his daughter until she has been living outside the family group for several months.

The threat of population overcrowding, as already mentioned, is important. How do different species deal with problems of population density? Mechanisms which have been studied include 'migration outwards', increased mortality in some individuals, reduction of fertility and actual suppression of sexual behavior [10–13]. Most if not all of these mechanisms are often manifested via the dominance hierarchy, with the low dominance animal being more susceptible to the stress-related increase in mortality, reduction of fertility and suppression of sexual behavior. The likelihood that such mechanisms are, at least in part, genetically determined, poses a problem for evolutionary biologists which as yet remains unresolved. If a genetically determined susceptibility to overcrowding is involved, then such genes would soon disappear. The best attempt to get round this dilemma is the concept of 'coupled genetic oscillators' discussed by Wilson [12] which proposes that there are more than one genetically determined mechanism, so that as one begins to be 'non-bred' out of existence, another mechanism takes over allowing the first to reappear.

This fundamentally important notion of inhibition of sexual behavior or suppression of fertility as a method of controlling population density does not translate easily into

human terms [14]. Furthermore, it confronts us with an apparent paradox, the existence of two contradictory adaptive goals, maintaining fertility and, in situations of overcrowding, reducing fertility or at least reducing reproduction. Yet this paradox, ironically, is captured by two of the principal threats facing the human race at the present time—overpopulation and the threat of sexually transmitted diseases to both fertility and survival.

It is therefore relatively easy to make the case for the adaptive function of inhibition of sexual response and behavior, and furthermore, to regard it as having a fundamental cross-species role. Thus we might expect to find physiological mechanisms involved, of relevance across species.

At this stage we can recognize five situations in which inhibition of male sexual activity may be adaptive; (i) when sexual activity carries some threat or danger (e.g. attack from other more dominant males, or risk of sexually transmitted disease); (ii) where a non-sexual threat exists, and inhibition of otherwise distracting response patterns, including sexual, is necessary for focussing on the appropriate avoidance response; (iii) when excessive involvement in the pursuit of sexual pleasure distracts from other important adaptive functions; (iv) when the consequences of continued 'excessive' sexual behavior includes reduction of fertility due to excessive ejaculation; (v) when social or environmental pressures result in suppression of reproductive behavior and reduction of population density. We should keep in mind that these five different needs for inhibition of sexual behavior may involve different inhibitory mechanisms or systems.

3. Is the inhibition specific to sexual behavior?

A fundamental question is whether inhibition of sexual response and behavior involves mechanisms which are specific to sexual response or are part of a more general inhibitory system. Bjorklund and Kipp [4] address this question and conclude from their review of the evidence that the relevant inhibitory mechanisms are probably 'domain-specific' and not 'domain-general'. Certainly with mechanisms such as the post-ejaculatory refractory period, a mechanism specific to sexual response, and even to ejaculation, seems likely.

A different, less specific perspective is provided by Gray [11] with his conceptual nervous system for avoidance behavior and his dual model of behavioral activation and behavioral inhibition. His Behavioral Inhibition System (BIS), is designed to 'switch off' or immobilize behavior when confronted by a signal that punishment is likely to occur. This is in contrast to the Behavioral Activation System (BAS) which drives rewarded behavior. Gray uses the term anxiety to describe the 'emotional state' associated with function of the BIS, and his model has been painstakingly built on experiments with rats in which effects of both antianxiety drugs and brain lesions on avoidance behavior have been studied. Gray sees anxiety as in opposition to sex, which is expressed more via the BAS. This idea of the opposition of anxiety and sex is widespread in the human literature as well, though as we shall see, the term anxiety is often used somewhat differently to the specific meaning given it by Gray, and this accounts for some of the inconsistencies in the human evidence. Although Gray does not really tackle the relationship between his form of anxiety and sexual behavior in any detail, by implication he postulates that, when faced with the threat of punishment, sexual behavior and/or response is inhibited by the BIS.

This paper is focusing on the role of central inhibition in males, and some justification for this is required. It is distinctly possible that there are important differences between males and females in the role of inhibitory mechanisms. Gray [11] reviews the evidence from the rat and other rodents that fearful behavior, in particular, is more a characteristic of the male than the female. Selective breeding to discriminate between reactive and non-reactive strains of rat produces differences which are similar to differences between male and female, the female being more like the non-reactive male rat. Gray acknowledges, however, that this pattern is, if anything, in the reverse direction in primates and humans. Bjorklund and Kipp [4] argue the case that inhibitory mechanisms are better developed in women than in men and they offer an evolutionary explanation for why that might be so. That would suggest that women are less variable in their capacity for inhibition than men. As it happens, we have more evidence relevant to the male to consider at this point in time. The important issue of how males and females compare in this respect deserves a paper on its own.

The relevant evidence of central mechanisms of inhibition is mainly from animal experimentation. This evidence will be reviewed first. No attempt has been made to review exhaustively the literature of potential relevance. The purpose here is limited to exploring to what extent evidence for central inhibitory mechanisms exists and can be seen to be organized into anatomically discrete or functionally organized systems. A variety of types of evidence consistent with central inhibition of sexual response in the human will be also considered, including drug effects and brain lesions. Finally, the theoretical model will be revisited in the light of this review.

4. Possible mechanisms of central inhibition of sexual response—the animal evidence

The limbic system clearly plays a central role in the organization and implementation of sexual behavior. This includes the hypothalamus, amygdala, septum and ventral striatum, with additional cortical components in the hippocampus, cingulate gyrus and orbital parts of the frontal cortex. Sexual behavior, as one of the behaviors organized in the limbic system, requires coordination of endocrine and

autonomic responses together with the specific behavior. The neurochemistry of the limbic system has three components to it; neuropeptides, which act within the limbic system; steroids, which because of the concentration of steroid receptors in the limbic system, are particularly in evidence; and monoamines. Most of the monoaminergic innervation of the limbic system comes from three fiber systems ascending from the brain stem to influence the limbic system but also the cortex and other brain areas.

In considering possible inhibitory mechanisms, we need to consider neuropeptide effects within the limbic system and the impact of the three ascending monoaminergic systems on the limbic system, in addition to steroid hormones and the role of inhibitory neurotransmitters such as GABA.

4.1. Neuropeptides

There is a substantial body of evidence showing that opioid agonists including morphine and β-endorphin produce inhibition of sexual behavior in a variety of male mammals, reversible by naloxone, an opiate antagonist, and at doses which do not disrupt other aspects of motor or social behavior [15]. Herbert [16] emphasizes the importance of neuropeptides in the control of sexual behavior, and regards the principal candidate for an inhibitory effect on sexual behavior and other aspects of reproduction to be β-endorphin. This is synthesized by only two cell groups within the brain, the principal source being from in and around the arcuate nucleus of the hypothalamus. This cell group projects widely within the limbic system; anterior fibers terminate in the dorsomedial and anterior hypothalamus, preoptic area, bed nucleus of the stria terminalis, the septum and part of the nucleus accumbens. Lateral fibers enter the central and medial nuclei of the amygdala, and other fibers are directed towards the brain stem ending in the reticular formation and structures associated with autonomic function [17].

Studies of infusions of β-endorphin in specific sites indicate that the consequences of its inhibitory action depend on where it is acting. Infusion of minute amounts of β-endorphin into the male rat pre-optic area disrupts copulatory behavior without affecting pre-copulatory exploration of the female by the male [18]. The complexity of this effect, however, was demonstrated in a further experiment; if the infusion was given before the first mount had occurred, no copulatory behavior followed; if the infusion was given after the male had made the first mount, further mounting behavior and intromission proceeded normally. Furthermore, if after one mount, the infusion was given and then another female was presented, the block on copulatory behavior was still apparent [19]. This would appear to indicate some disruption of the information processing which links pre-copulatory signals to copulation. It is difficult, on the basis of this highly artificial experimental situation, to interpret this inhibitory effect in 'real life' terms. However, infusion of β-endorphin into the amygdala had a very different effect; here it was the pre-copulatory explorations which were disrupted. Once copulation started it proceeded normally [20]. In general, the amygdala is implicated in learning when information from different sensory modalities are coordinated, and in the association of a stimulus with an emotional response, which, with feedback to the prefrontal cortex results in a conscious emotional experience [21, p. 739, 747]. This inhibitory effect of β-endorphin is consistent with the amygdala identifying a stimulus as sexual, upstream from the hypothalamic regulated consummatory responses.

4.2. The cerebral monoamines

In order to make sense of the evidence concerning inhibitory effects of the monoamine neurotransmitters, it is helpful to have a picture of how the monoamine neurons are organized in the CNS.[1]

The three major monoaminergic systems in the brain stem are the noradrenergic (NE), dopaminergic (DA) and serotonergic (5HT) systems [22].

(i) The NE system, which in terms of numbers of neurons is the smallest, originates in two brain stem nuclei, the locus coeruleus (l.c.) and the lateral tegmental nucleus (l.t.n.). Each nucleus has neurons with ascending and descending projections. The ascending projections of the l.c. terminate, quite widely, in the dorsal thalamus, hypothalamus, basal forebrain, including hippocampus, and the frontal cortex. The descending projections from the l.c. go to the spinal cord (mainly ventral horn) and to sensory nuclei in the brain stem. The l.c. receives only two major inputs; from the nucleus paragigantocellularis and the nucleus hypoglossi prepositus, both situated in the brain stem.

The neurons from the l.t.n. are more diffusely distributed and project to three major sites, spinal cord, brain stem, and thalamus and cerebellar and cerebral cortices.

There is relatively little overlap between the targets of these two NE systems. The l.c. is activated by novel sensory input, with a role in orienting and attending to sudden contrasting or aversive sensory input. The NE neurons from the l.c. have both excitatory (e.g. in the hippocampus[2]) and inhibitory effects (in other cortical areas). The l.t.n NE system is involved in integration of autonomic function in brain stem and spinal cord nuclei. Direct activation of these neurons reduces blood pressure and heart rate.

Drugs which increase central NE transmission or availability at α-receptors increase various aspects of male rat sexual behavior consistent with an enhancing effect on central sexual arousal [24,25]. By contrast, α-receptor

[1] The description of the anatomical organization that follows is largely dependent on chapter by Role and Kelly [22].

[2] The 'exciting' effect of NE on the hippocampus is probably the result of its reducing the spontaneous firing rate of the hippocampal neurons, and hence, by increasing the 'signal to noise' ratio, increase the response to afferent stimulation [23].

activation in the periphery blocks genital response [26]. Evidence of effects on β-receptors is inconclusive. Central α-effects, however, appear to be complex. Sala et al. [27] demonstrated an inverted U dose–response curve, with middle range doses producing maximal enhancing effects and high doses inhibitory effects. Administration of the NE-synthesis inhibitor DDC produces a dramatic lengthening of the post-ejaculatory refractory period and intromission latencies as negative effects, and facilitation of copulation, with reduction in the number of intromissions preceding ejaculation and ejaculation latency as positive effects [28]. These authors refer to the concept, usually attributed to Beach [29], that sexual arousal and copulatory mechanisms are two independent processes involving separate control systems, and also suggest that the NE system may have very complex interrelationships with the DA and 5HT systems accounting for these apparently inconsistent effects.

Perhaps as a result of this complexity, much less attention has been paid to the central role of NE transmission in relation to sexual behavior, compared with other neurotransmitters.

(ii) The DA system contains three to four times as many neurons as the NE systems, but is less diffuse, being highly organized topographically into five subsystems; the meso-striatal system (projecting from the substantia nigra and ventral tegmentum to the striatum), the meso-limbic and meso-cortical systems (from the ventral tegmentum to limbic and cortical areas [22]), and two smaller and more localized DA systems, the incerto-hypothalamic (or A14) periventricular (which projects to the medial pre-optic area (MPOA)), and the tubero-infundibular (from the arcuate nucleus of the hypothalamus to the pituitary stalk), which are important for reproductive behavior and neuro-endocrine control respectively [22].

There is a substantial body of evidence showing that DA agonists enhance and DA antagonists impair male sexual behavior [24]. Experiments in which specific D1 or D2 DA receptors are selectively involved, or where local infusion of drugs or dialysis have allowed investigation of DA action in discrete areas of the brain, have contributed to a more complex picture of DA activity as it relates to male sexual behavior [23,30]. Hull et al. [31] concluded that there are three parts of the DA system that impact on sexual behavior, two of them relatively non-specific and one more specifically sexual. First, the nigro-striatal tract (from the substantia nigra to the dorsal striatum), degeneration of which causes Parkinson's disease; this is involved in the organization of motor behavior, particularly initiation of motor responses and 'readiness to respond' which includes copulatory but also many other integrated motor patterns. Second, the meso-limbic tract (from the ventral tegmentum to the ventral striatum, and other parts of the limbic system); this promotes 'appetite' for a variety of appetitive behaviors, including sexual. Third, the dopaminergic input to the MPOA from the A14 periventricular system; the MPOA receives sensory input from many parts of the brain, and serving a more specifically sexual function, helps to orchestrate genital responses and stereotyped sexual motor patterns such as mounting or thrusting. Whereas there is a remarkable consistency across species in the role that the MPOA plays in the orchestration of consummatory responses, there is less agreement about its possible role in appetitive responses (e.g. [32,33] and the following discussion). If the MPOA does have a role in sexual motivation, then its DA activity may be relevant to this [34].

DA therefore plays an excitatory role, though its effects on the MPOA may depend on disinhibition of inhibitory tone [31].

(iii) In terms of numbers of neurons, the 5HT system is the most extensive of the three. The majority of neurons are located within the raphe nuclei (named because of their midline position near the raphe or seam of the brainstem). The more caudal of these nuclei provide the descending serotonergic projections to the spinal cord, whereas the upper raphe nuclei project rostrally through the median forebrain bundle to a variety of target sites, the dorsal raphe nucleus mainly to the frontal cortex and striatum, the median raphe nucleus mainly to the septum and hippocampus. These neurons are mainly inhibitory in their effects.

There is now a substantial body of evidence from studies of the male rat that drugs which increase serotonergic transmission inhibit and those which disrupt serotonergic transmission enhance male sexual behavior (see reviews by Bitran and Hull [24] and Wilson [25]). However there are a number of complexities that have to be born in mind. First, most such drugs also effect a variety of other behaviors such as eating, aggression and general motor activity [23]. Hence we are considering serotonergic inhibition of a non-specific kind. Second, there are a variety of 5HT receptors; central inhibition of behavior, including sexual, is most clearly related to the 5HT2 receptor whereas, by contrast, the 5HT1A variety is predominantly an auto-receptor on the cell body and dendrites, activation of which reduces 5HT transmission through that neuron. Third, drug effects are often complex and apparently contradictory depending on their site of action or dose. Thus, 8-OH-DPAT in addition to decreasing 5HT release by its 5HT1a agonist effect, also increases 5HT in the MPOA [35]. Also, experiments with lysergic acid diethylamide (LSD), a 5HT1A agonist indicate a U shaped dose–response curve, with low doses facilitating, and high doses inhibiting behavior. This complex picture can be explained by low doses preferentially affecting the auto-receptors and high doses predominantly affecting post-synaptic receptors [24].

A recent attempt to locate the specifically sexual inhibitory effects of 5HT produced evidence that 5HT does have an inhibitory role in the lateral hypothalamic area, but not in the MPOA, as had been previously suggested [36].

4.3. γ-Aminobutyric acid

γ-Aminobutyric acid (GABA) is an inhibitory neurotransmitter widely though unevenly distributed in the mammalian CNS. Because of its ubiquitous nature it can be expected to play a role in inhibiting inhibitory as well as excitatory processes. This is well demonstrated by Gray's [11] BIS, the effects of which can be reversed by drugs such as benzodiazepines which amplify effects of GABA by their action on the $GABA_A$–benzodiazepine receptor complex. However, there is a consistent body of evidence showing that GABA and drugs with GABAergic effects, have an inhibitory effect on male sexual behavior in the rat [24] and this may be particularly significant during the post-ejaculatory refractory period when levels of GABA in the CSF are raised [25]. Stimulation of presumed $GABA_A$ receptors in the MPOA decreases the number of animals mounting and intromitting whereas blockade of $GABA_A$ sites decreases the post-ejaculatory interval (reviewed in Bitran and Hull [24]). $GABA_B$ agonists injected intrathecally around the lumbo-sacral cord inhibit ex-copula reflexive erections without apparently interfering with mounting and intromission [37].

4.4. Steroids

The role of androgens in permitting and maintaining male sexual behavior is well established. This is shown most clearly by the effects of castration and their reversal by androgen replacement, though the gradual decline and changing pattern of sexual behavior following castration in the rat suggests that androgens are affecting a number of mechanisms relevant to sexual behavior with different time relationships to androgen withdrawal [23,38]. Clearly, among those various mechanisms is an effect of testosterone (T) on the MPOA [39] and recent evidence suggests this might be via its enhancement of DA release, an effect which involves up-regulation of nitric oxide [40].

The possibility that testosterone might be necessary for the development of central arousal associated with sexual response is suggested by the findings of Davidson's group that sexual behavior can be at least partially restored by administration of α-2 antagonists such as yohimbine [41]. It is also true that manipulation of other neurotransmitter systems can elicit sexual behavior in male castrates; e.g. dopaminergic agents [42] and PCPA, a 5HT synthesis inhibitor [43]. But these effects appeared to be restricted to relatively early in the post-castration period (around 30 days post-castration), when some effects of testosterone may still have been evident, whereas yohimbine was effective both at the earlier time period and as late as 91 days post-castration [41] suggesting that at least part of testosterone's effect may actually be mediated by NE mechanisms. Clark et al. [41] also showed that the sexually enhancing effect of yohimbine was independent of any direct effect on erection, leading them to conclude that the drug's principal effect was on central arousal. Thus we can tentatively conclude that part of testosterone's relevance to male sexual behavior is through its NE-mediated effects on central arousal.

Beach [1] considered the possibility that gonadal hormones promote sexual behavior by reducing central inhibitory mechanisms. However, in his 1967 review, Beach presented only limited evidence supporting this concept for the female mammal, and virtually no evidence for the male. Since then, no clear evidence that T reduces central inhibition in the male has been forthcoming, except via its effect of increasing the release of DA which itself could be considered a dis-inhibitor. The contrary possibility that T may be involved in promoting inhibitory mechanisms, in addition to its undoubted role in activatory mechanisms, will be considered with the human evidence.

4.5. The search for a sexual inhibitory system

Given the striking success with lesion experiments in identifying the MPOA as having a crucial role in sexual activation (i.e. consummatory and possibly appetitive behavior), comparable attempts have been made to locate inhibitory centers or systems. A series of studies in the 1960s and 1970s investigated the effects of lesions at the juncture of the diencephalon and mesencephalon leading to inconsistent and inconclusive results. Some studies reported evidence of an increase in sexual behavior or response following lesioning, consistent with partial or complete destruction of an inhibitory centre or tract [44–48]; others failed to replicate these findings [49,50]. Clark et al. [45] reported that bilateral destruction of an area within the rostral midbrain (at the level of the interpeduncular nucleus), through which the dorsal noradrenergic (DNE) bundle projects, resulted in a shortening of the post-ejaculatory interval and significant depletion of NE levels (though not 5HT levels) in the telencephalon. In a later study, Walker and Gerall [51] found further support for a disinhibiting effect of rostral mid-brain lesions, but concluded that this was probably not due to damage to the DNE bundle. Electrolytic lesions of the locus coeruleus, the origin of the DNE bundle, resulted in increase in the post-ejaculatory refractory period [28]. To add to the confusion, Clark [52] found that neurotoxic lesions of the DNE bundle had no effects on sexual responses even though they caused a major reduction of NE in the cortex. Taken together with the pharmacological evidence considered earlier, it is reasonable to conclude that the role of the NE system in male rat sexual behavior remains unclear, though it is likely to be involved with arousal in some way.

A decade later attention became focussed on the nucleus para-gigantocellularis (nPGi) in the brain stem. Anatomical studies have shown a direct projection from this nucleus to sympathetic and parasympathetic neurons involved in penile reflexes [53]. Lesions of the nPGi produced facilitation (i.e. disinhibition) of ex-copular reflexive erections in

the male rat [54] and a more generalized increase in copulatory efficiency consistent with a role for the intact nucleus in behavioral inhibition [54,55]. Yells et al. [56] then explored the possible role of 5HT in mediating this inhibitory effect and were able to show that the well-established inhibitory effects of fluoxetine, a 5HT re-uptake inhibitor (SSRI), on male sexual responses were partially negated by lesions of the nPGi (for a useful review of this and related evidence see McKenna [57]). Most recent has been the demonstration that 5HT increases in the lateral hypothalamic area (LHA) during the post-ejaculatory interval although no increases were observed at any other time during copulation or during a pre-copulatory exposure to an estrous female [36]. In addition, these workers found that an SSRI, microinjected into the LHA produced an increase in extracellular 5HT associated with an increased latency to mount, intromit and ejaculate [36].

A possible role for descending neurons of the l.c. in the rat, is suggested by transneuronal labeling with the pseudorabies virus which demonstrated a clear link between neurons in the penis and the l.c. However, these studies also showed a link between other somatic and autonomic, non-sexual neurons and the l.c., indicating that the l.c. has more downstream functions than sexual [57].

4.6. The role of the spinal cord and peripheral autonomic nervous system

Beach's [1] proposition that reflexive genital responses in mammals can function independently of the brain and are predominantly under inhibitory control from higher centers, has been supported by experiments involving spinal transection in rats. Thus Hart [58] found a drastic reduction of erectile reflex latency and increase in number of reflexive erectile responses following mid-thoracic spinal transection. Meisel and Sachs [59] further showed acceleration of the development of these reflexes in 25 day old rats by spinal transection. They concluded that the effect was probably due to the surgical removal of supraspinal inhibition which, in the intact animal, would otherwise decrease more gradually with age.

Whereas supraspinal inhibition of genital reflexive response is likely to result from direct inhibition of the spinal reflex centers, (probably mediated by 5HT), inhibitory influences on erectile response are also implemented by an anti-erectile sympathetic outflow, originating in the caudal sympathetic chain, though the precise anatomic localization of these inhibiting fibers as they descend to the erectile tissues has not yet been clarified and may be variable. The evidence also suggests that there may be two sets of such fibers, one acting on the arterial blood supply to the penis, the other on the sinusoidal smooth muscle in the corpora cavernosa [60]. It is likely that both sets involve NE neurotransmission.

4.7. Experimental induction of inhibition of sexual behavior

Although some early studies [61–63] used an electric shock as a barrier between the male and the female, to provide a measure of sexual motivation (i.e. how much shock is the animal prepared to tolerate in order to gain access to the female) it was Beach et al. [64] who more deliberately set out to inhibit sexual response by associating electric shock to the male with the process of mounting the female. Low levels of shock did not appear to inhibit mounting. High levels of shock, on the other hand, predictably resulted in 'sexual inhibition' defined as two successive tests with no attempts to mount the female. The number of high level shocks needed to induce this inhibition, and the number of unreinforced tests required before sexual behavior resumed varied across animals.

Since this early study, a number of studies involving administration of electric shock to the male during sexual activity have been reported (reviewed in Sachs and Barfield [3]). These have predominantly shown an excitatory or arousing effect of low levels of shock during the pre-ejaculatory phase (e.g. Sachs et al. [65]) and variable effects post-ejaculation depending on whether the shock was delivered during the absolute refractory period (which was consequently prolonged) or later, when the total refractory period appeared to be shortened [66].

An interesting extension of the 'post-ejaculatory inhibition' model is the 'sexual satiation' or 'sexual exhaustion' of male rats. The unrestricted exposure of male rats to receptive females results in repeated copulation until a state of sexual satiation is established. The average number of such copulations required to establish this state is seven, and complete recovery takes around 15 days [67,68]. The assumption that this state involves a specific inhibition of sexual responsiveness is supported by the otherwise normal behavior shown by the sexually sated animal.

Although first described more than 40 years ago, only recently has this state been subjected to experimental evaluation. Rodriguez-Manzo and Fernando-Guasti [69,70] showed that the 5HT1A agonist, 8-OH-DPAT, which typically facilitates ejaculation by its reduction in serotonergic transmission, the α-2 adrenoceptor antagonist, yohimbine, which also typically has sexually enhancing effects by increasing NE at the synapse, and the opioid antagonists (naloxone and naltrexone), when given individually, all partially restore sexual behavior in the sated rat. Furthermore, the positive effects of 8-OH-DPAT and the opioid antagonists were largely eliminated by neurotoxic lesioning of the central noradrenergic system, although the positive effects of yohimbine were not affected [71], suggesting that the anti-opioid and anti-serotonergic effects were dependent on an intact central NE system. Taking a different experimental approach, Mas et al. [72], using voltametry and micro-dialysis, reported an increase in the metabolites of DA (dihydroxyphenylacetic acid or DOPAC, and homovanillic acid or HVA) in the MPOA of sexually

sated rats. They interpreted this as evidence of a blockade of DA neurotransmission resulting in an increase in DA turnover and DA metabolite levels. They found further support for this explanation by demonstrating a positive effect of apomorphine on sexual responsivity of the sated rat, and postulated that the mediator of the DA blockade could be prolactin, which is known to increase in male rats following ejaculation [73], and possibly in humans also [74]. Fiorino et al. [75] found further evidence of the role of DA in sexual satiation, reporting an increase in DA transmission in the nucleus accumbens as exposure to a novel receptive female resulted in re-initiation of sexual behavior.

With 'sexual satiation' we therefore have an experimental model of probable relevance to normal adaptive sexual behavior in rats, which demonstrates the involvement of most of the principal excitatory and inhibitory mediators that are currently known about (with the apparent exception of GABA), and that also appears to depend on the integrity of the NE arousal system. Experimental use of this model is still at an early stage, and the complexity so far revealed may be clarified with further research. But it is consistent with the idea that both inhibitory and excitatory mechanisms affecting sexual behavior depend on complex interactions between different neurotransmitters and neuromodulators, and that experimental manipulation of single parts of this complex system is likely to produce an incomplete or inconsistent picture.

4.8. The effects of chronic stress on sexual behavior

The neuroendocrine pattern of response to chronic stress is highly complex (see Whitnall [76] for review), although increase production of corticotrophin releasing factor (CRF) and increased activity of the hypothalamo-adrenocortical axis is central to what was first described by Selye [77] as the 'general adaptation syndrome' (GAS), the organism's response to chronic stress.

Gray [11] draws our attention to the substantial effect that the GAS has in suppressing sexual and reproductive behavior, summarizing the principal effects as follows. "In the male there is a fall in the production of spermatazoa, a reduction in the secretion by the testes of testosterone,…and delay or complete suppression of puberty. In the female there is disruption or suppression of the menstrual cycle in primate species or of the equivalent estrous cycle in subprimates; a decrease in the weight of the uterus; failure to ovulate and failure of the fertilized ovum to become implanted in the uterus; an increase in the number of spontaneous abortions; and a failure of lactation, which can result in the death or slowed growth of the young." [11, p. 87]. He points out that how these changes are brought about is still not clear. But he argues the case that the GAS is an ideal mechanism to regulate population density and maintain optimum population numbers, as discussed earlier. His main points in support of this conclusion are: (1) GAS is set into operation by chronic stress; (2) the degree to which it is activated is proportional to the intensity of the density stress; (3) it includes a large reduction in fertility and increase in mortality; (4) the signals activating the process arise from social interaction; and (5) the individuals most affected by density stress are usually low in the dominance hierarchy.

An experimental model of chronic stress in the laboratory rat is the use of housing in mixed-sex groups which quickly establish dominance hierarchies in which the subordinate animals are severely stressed. Using this model, McKittrick et al. [78] found not only that some of the low dominance animals had elevated cortisol levels with blunted cortisol response to additional acute stressors, but those animals also had increased 5HT2 receptor binding in the parietal cortex, as well as decreased 5HT1a binding in the hippocampus. They drew parallels between this pattern and depressive illness in humans. Brotto et al. [79] used individual housing as a stressor and found that increased 5HT2a receptor activity was associated with decreased sexual behavior, suggesting a functional interaction between the HPA axis, 5HT2a receptor activity and sexual behavior.

The role of gonadal steroids may also be important in modulating the effects of chronic stress on reproductive function. In the rat, testosterone inhibits the HPA axis response to stress, whereas estrogen enhances it [80]. Subordination in the dominance hierarchy is also likely to lower testosterone levels. This has been shown in several primates [9] although manipulating the testosterone levels only partially alters the effects of the dominance hierarchy on sexual behavior. Also the relationship between dominance, testosterone levels and the response of the HPA axis seems to be variable across primates studied [9].

Herbert [16] has proposed that it is the CRF induced increase in β-endorphin (e.g. Almeida et al. [81]) which is the principal mechanism mediating between environmental stress, such as density stress, and the impairment of reproductive and sexual behavior. As yet the most important mechanisms that lead from chronic stress to inhibition of sexual behavior remain to be established, but it is once again likely that more than one mechanism is involved, and there may be important species differences.

4.9. Evidence for a non-specific behavioral inhibition system

Gray's [11] principal contribution to the subject of this paper is his model of behavioral inhibition. Following Hebb [82], he makes the distinction between a 'conceptual nervous system', which is inferred by psychologists from behavioral data, and the physiological CNS. His model of behavioral activation (BAS) and behavioral inhibition (BIS) is of the conceptual variety, and he has pursued its physiological basis in two particular ways, first by demonstrating how antianxiety drugs counteract the behavioral inhibition induced by threat of punishment, and then by comparing these drug effects with the behavioral effects of specific

brain lesions. As considerable overlap has been demonstrated between the behavioral effects of anti-anxiety drugs and the behavioral effects of hippocampal and septal lesions, he regards an integrated septo-hippocampal system as involved in the manifestations of BIS. He postulates that the hippocampus functions as a comparator which, in this context, involves assessing discordance between actual and expected stimuli. When such discordance is recognized, the septo-hippocampal system takes over direct control of behavior, which, in effect, is the output of the BIS. A crucial feature of this system is the noradrenergic (NE) input to the septo-hippocampal system from the dorsal NE bundle projecting upwards from the locus coeruleus in the brainstem. This input is likened to an 'alarm bell', producing the arousal which characterizes BIS activity, and which Gray describes as 'anxiety'. He suggests that the most likely site of action of anti-anxiety drugs (such as benzodiazepines and barbiturates) in counteracting BIS and the anxiety associated with it, is on this ascending NE bundle. The cell bodies of the l.c. have many GABA receptors [83]. GABA interacts with their terminals [84] and the assumption is that the drug promotes GABAergic inhibition of NE release in the septo-hippocampal system. This is consistent with the human evidence that α-2 noradrenergic agonists and antagonists produce anxiety reduction and increase respectively, associated with reduction and increase in NE release [85].

An obvious question is whether the central inhibition of sexual response may result from mobilization of this non-specific BIS. The down-stream projections from the locus coeruleus have received much less attention than the up-stream projections, and probably include neurones imposing inhibitory control on those peripheral autonomic responses which are not a useful or necessary part of the BIS activated state (such as genital responses which are not likely to help an animal confronted with threat of punishment). It is therefore of some significance that GABAergic drugs, such as benzodiazepines, counteract the BIS; as stated above, these drugs predictably impair sexual behavior in animal studies. On the face of it, this makes it unlikely that the BIS is relevant to inhibition of sexual behavior. However, we should not be too simplistic in interpreting the behavioral effects of GABA action, given the wide distribution of GABA receptors. It is distinctly possible that the predominant effect of administration of GABAergic drugs will depend on the context in which they are given. In other words, their effects on sexual response when given to an animal facing no threat but rather the prospect of a sexual reward, may be different to the situation where the animal has perceived threat of punishment and is motivated towards avoidance. As yet, it appears that no experiment reported in the literature has attempted to explore this possibility.

For the present, therefore, it may be sensible to keep an open mind about the relevance of the BIS to sexual behavior. Its most obvious relevance is to the second of our five functions of sexual inhibition; where inhibition of sexual behavior, as well as other potentially distracting behaviors, is part of the process of focussing on coping with some immediate (non-sexual) threat. Gray [11] has also suggested that the BIS may be involved in mediating the suppressing effect of chronic stress on sexual behavior. But as yet there is no clear evidence on that point.

4.10. Conclusions from the animal evidence

Although the evidence convincingly indicates that inhibitory mechanisms affecting sexual response exist in the central nervous system, with a variety of neurotransmitters involved, the organization of such mechanisms into functional systems, with identifiable anatomical localization, has so far largely eluded us. The exception is the nPGi in the brain stem which could well be playing a crucial role linking higher inhibitory processes to the peripheral manifestations of inhibited genital response. The excitatory system(s), by comparison, though complex and highly interactive, is more clearly localized, most obviously in the MPOA and its connections. This may reflect the greater degree of topographical organization of the various DA systems, compared with the much more diffuse distribution of the NE and 5HT systems.

The role of the NE system(s) in both sexual excitation and inhibition remains unclear. Centrally, this system appears to be involved in arousal. However that arousal may be associated with positive response patterns such as sexual behavior and more negative patterns such as fear and avoidance. What is particularly unclear is how this 'arousal system' is selected to serve one or other relatively specific behavioral pattern. Testosterone may well be relevant to this recruitment of central arousal to sexual purposes. In ways which have not yet been clearly conceptualized, the superimposition of such arousal on to the relatively specific excitatory mechanisms serving sexual response appears to be necessary as if to 'drive' or energize the behavioral pattern. We will return to this issue when considering the human evidence and the potential for 'excitation transfer' (i.e. the 'transfer' of arousal elicited by non-sexual (even aversive) stimuli to sexual response patterns).

In the absence of any physiologically discrete inhibitory 'systems' in the CNS, we should turn our attention, as Gray did in relation to general behavioral inhibition, to 'conceptual inhibitory systems' defined in terms not of their anatomical or pharmacological characteristics but of their behavioral manifestations and purposes.

Although most of the experimental literature on sexual activation in male rats has involved laboratory paradigms of appetitive and consummatory sexual behavior which may be only crudely comparable to such behavior in the animals' natural habitat, they nevertheless are based on biologically meaningful behavioral objectives—in particular gaining access to and mounting receptive females. In the case of Gray's BIS, a common theme of avoidance when confronted by threat of punishment guides the research. In contrast, the

sexual inhibition literature lacks a model of inhibited sexual behavior which has adaptive significance, which can provide a focus for the experimental work. A possible exception is the 'sexual satiation' model of central inhibition, which does have potential adaptive relevance. It may prove to be of crucial theoretical relevance that this 'satiation' model appears to depend on the NE arousal system for its effects. For the remainder of the 'inhibition' literature, it is not clear to what extent the inhibitory mechanisms in question are selectively involved in the manifestation of biologically meaningful behavioral paradigms, beyond the basic role of inhibitory tone in the normal balancing of neural systems. If we are to further our understanding of central inhibition of sexual response, and test our theoretical model based on it, we will need behavioral paradigms of adaptive significance, possibly following the five categories of inhibitory function listed earlier, that can provide the focus for experimental studies. Such paradigms will probably be more difficult to design and implement than their 'excitatory' counterparts. Interestingly, Beach et al.'s study [67] with electric shock provided an early model which has not been built on, in spite of the interest in inhibitory mechanisms that surfaced in the 1970s [2,3]. But before launching into a new phase of such experimental paradigms we should ask whether the laboratory rat is the best animal for the purpose. As Richter [86] pointed out a long time ago, more than a hundred years of selective breeding of the Norway rat for laboratory research has resulted in genetically similar strains most of which are low in fear and aggression, with comparatively meager hypothalamic–adrenocortical systems, and strong in their propensity for sexual behavior in the laboratory situation. If there existed a trait measure of the propensities for sexual excitation and inhibition, suitable for rats, we would probably find the laboratory strains high on the first and low on the second.

5. The human evidence

Evidence from the human is less systematic, often anecdotal, fragmented and in some cases, of a different kind.

5.1. The physiology of erection

Although various theories to explain penile erection have been proposed over the years [87], there is a fairly widespread consensus now about the key mechanisms involved, although still some uncertainty about how the mechanisms are mediated. A crucial part of the process is seen to be reversal of tonic contraction of the smooth muscle that forms the walls of the sinusoidal spaces in the erectile tissues [88]. The consequence of this smooth muscle relaxation is the filling of the sinusoidal spaces with blood and a resulting compression of the venous drainage between the sinusoidal spaces leading eventually to cessation of venous outflow. This process, accompanied by increased arterial inflow leads to an increase in pressure within the corpus cavernosum which, contained by a non-distensible fibrous capsule, the tunica albuginea, thus becomes rigid. Although a number of neurotransmitters have been implicated in this smooth muscle relaxation, recent evidence points to nitric oxide as playing an important role [89,90]. The physiological process probably depends on a reduction of the tonic inhibition as well as a direct relaxation mechanism. The aspect of this explanatory model which is of particular relevance to our inhibition concept is therefore the idea that the non-erect penis involves a relatively high level of inhibitory tone in the smooth muscle, which is required to relax for an erection to develop. Consistent with this model is the fact that the penis can shrink in size in cold situations, and, at least in some individuals, in anxiety provoking situations. This may particularly be the case when the anxiety is about the size of one's penis. Paradoxically, because of the potential for varying the basal inhibitory tone, the size of the fully erect penis is more predictable than the size of the flaccid penis.

The discovery that injection of smooth muscle relaxants into the corpus cavernosum produces erection [91,92] has provided an important new approach to studying the penile manifestations of the central inhibitory process. Various drugs have been injected in this way—some of them specific noradrenergic α-1 antagonists, others pharmacologically different, such as prostaglandin E1 or papaverine. They all have in common the ability to relax the smooth muscle of the sinusoidal spaces of the corpus cavernosum. Although there was initially a widespread tendency amongst clinicians to see this as a peripheral target organ effect, independent of the CNS, a substantial proportion of men with assumed psychogenic erectile dysfunction respond poorly to these injections [93]. In our series [94], between 40 and 50% of dysfunctional men with normal erections during sleep, and hence assumed to have psychogenic dysfunction, responded poorly to intracavernosal drugs. Buvat et al. [93] postulated that this impaired response is a result of increased circulating levels of norepinephrine that result from anxiety induced by the injection. Such an explanation is consistent with the traditional model of the relationship between anxiety and sexual response—that anxiety leads to activation of the peripheral sympathetic NS which in turn, by means of increased circulating NE, inhibits sexual response. An alternative explanation is that some central inhibitory process is counteracting the peripheral effects of the smooth muscle relaxant.

Kim and Oh [95] compared men with assumed psychogenic erectile dysfunction with poor response to intracavernosal injections (ICI) of papaverine to men without evidence of psychogenic ED, who showed full responses to the injection. They measured NE in the penile blood and found this to be significantly higher in the first group. This is consistent with an increased inhibitory tone in the erectile tissues being mediated, at least in part, by NE. Granata et al. [96] reported on 59 men with erectile dysfunction of various types who had their nocturnal penile

tumescence (NPT) responses monitored, followed by systematic evaluation of responses to intracavernosal prostaglandin E1 (10 μg). The men were divided into two groups (high and low inhibition) on the basis of the difference in the maximum erection occurring during sleep (NPT) and during response to the ICI. It was assumed that, as the NPT response should be relatively free from inhibitory effects, the more the NPT response exceeded the ICI response, the greater the level of 'inhibition' of the ICI response. Psychometric measures and serial plasma samples for assaying catecholamines, were taken on two occasions, one of which also involved the ICI. Both state and trait anxiety measures were higher in the high inhibition group but this was not dependent on the injection. Furthermore, the high inhibition group showed significantly lower levels of plasma NE in the periphery. Thus there was no support for Buvat et al.'s [93] hypothesis, and further support for the idea that the erectile response is inhibited by a signal focussed specifically on the genitalia, presumably originating in the brain, and if the animal evidence is relevant to the human, probably involving the nPGi. Given that this inhibitory signal is set higher in at least some men with psychogenic erectile dysfunction, then this could be regarded as a peripheral manifestation of a propensity to high central inhibition, associated with a greater vulnerability to erectile dysfunction, as postulated in the opening section. What this evidence does not tell us is whether such a propensity is manifested by a more or less stable 'high inhibitory tone' or is determined by response to some threatening stimulus. This crucial but conceptually difficult distinction will be considered further later in the paper.

5.2. Ejaculation and the post-ejaculatory refractory period

The refractory period, as mentioned earlier, is probably the clearest sexual example of central inhibitory processes at work. Where does the refractory period come from, in the developmental process? There have been a few case reports of men who appear to lack normal post-ejaculatory refractoriness and are similar to women in their capacity for multiple orgasms (e.g. Dunn and Trost [97]). Kinsey et al. [98] presented evidence that a number of pre-adolescent boys were capable of multiple orgasms. This evidence came largely from the observations of one man who had been involved in sexual activity with or observing sexual activity in a large number of boys (see Kinsey et al. [98, Tables 31–34]). This evidence has become the focus for recent attacks on Kinsey, with allegations that he engaged in or at least promoted child sexual abuse (see Bancroft [99] for discussion of this controversy). Whereas such allegations are unfounded, one has to raise questions about the scientific validity of these observations. Yet if they are valid they raise theoretical issues of considerable interest. In the main Kinsey study, 35% of men recalling their childhoods reported pre-pubertal experience of orgasm [100]. Careful inquiries of adolescents and young adults about their pre-pubertal orgasmic experiences are required to throw light on this issue. If it is the case that some such boys are capable of multiple orgasm, with minimal or no refractory period, when they are pre-pubertal, it strongly suggests that something happens, developmentally, with the onset of puberty, to bring the refractory process into play. This presumably happens at the same time as ejaculation starts to accompany orgasm, and raises the question of whether androgenic effects are promoting this inhibitory mechanism as well as having obvious effects on the arousal mechanisms. Although at this point in time this must be regarded as speculative, the idea that changes in gonadal steroids around puberty play a role in the organization and expression of central mechanisms for inhibiting sexual response in the male as well as their obvious role in activation, deserves consideration.

A further characteristic of the post-ejaculatory refractory period which is widely accepted is that it typically increases with age (e.g. Kolodny et al. [101]). Interestingly, it is difficult to find any systematic evidence to that effect, which is unfortunate because the explanation for this age effect could be of considerable theoretical interest. Is it due, for example, to an age related decline in excitability? The commonly reported reduction in refractory period together with a general increase in arousability that older men may experience with a new partner is consistent with that explanation. Is there an age related increase in inhibitory response post-ejaculation, and if so why? Are both types of change involved, and if so, is the age related decline in responsiveness to testosterone relevant in any way?

Whatever the underlying mechanisms, the refractory period, in both men and male rats, can be seen to play an obvious role in relation to functions (iii) and (iv) described earlier. It is also conceivable that if we see 'sexual satiation' as an extension of the 'refractory period' then the complex underlying mechanisms may play a part in certain types of 'loss of sexual desire' in the human, as suggested by Mas et al. [72]. If this state can be produced by 'sexual satiation', similar outcomes might result from more complex and continuing psychological states, or alternatively, endogenous changes in the interactive neurochemical substrate, analogous to the neurochemical basis of affective disorders which are not simply reactions to circumstances.

5.3. Neurological lesions

Early and extensive clinical studies of men with spinal cord injuries, particularly during the period following the second world war, have demonstrated that provided the lumbosacral part of the cord which contains the reflexive centers for penile erection is not damaged, reflexive erections occur in many cases, often requiring minimal tactile stimulation to be elicited (e.g. Riddoch [102]; Kuhn [103]; Talbot [104]; Bors and Comarr [105]; see Higgins [106] for review). This evidence suggests the reduction or absence of inhibitory signals from the brain which are unable to get

past the cord lesion to reach the reflexive centers in the cord, and is entirely consistent with the animal evidence from spinal transection discussed earlier. What this evidence does not tell us is whether the level of inhibitory tone disrupted by the lesions varies across individuals in a manner reflecting variable 'propensities for central inhibition'. Once we have established methods for measuring such propensities, then this question could be addressed in future clinical studies. For example, does the propensity for inhibition of sexual response prior to the injury, predict in any way degrees of 'disinhibition' of spinal reflexes following spinal cord damage?

Lesions in the brain, whether traumatic or due to cerebrovascular accidents, tumors or other pathologies, are commonly associated with a decline in sexual interest and response, more so when certain brain areas, such as the temporal lobes or limbic system, are involved. Increased sexual responsiveness or interest following brain lesions, however, is rare [107]. This is consistent with the difficulty in disinhibiting male sexual behavior in animals by means of localized lesions, as considered earlier. Although episodes of apparently disinhibited sexual behavior are reported in men with dementia, a careful study found such inappropriate sexual behavior to be uncommon [108].

5.4. Nocturnal penile tumescence

It has been known for more than 30 years that spontaneous erections occurring during sleep, so called nocturnal penile tumescence or NPT, are largely confined to REM or 'paradoxical' sleep. This has also been demonstrated in the rat [109]. Until recently, however, little attention has been paid to why there should be this particular temporal association between erection and REM. A characteristic of REM, in animal studies, is that NE neurons in the locus coeruleus (l.c.) are effectively switched off as if to allow REM to occur [110]. As mentioned earlier, the ascending NE neurons from the l.c. have both excitatory and inhibitory effects, and descending neurons are linked to a range of peripheral structures, including the penis. There is also animal evidence that during REM peripheral sympathetic activity decreases in the renal and splanchnic (which would include genital) circulation, while increasing in the vasculature of skeletal muscles. Much less is known about REM sleep in the human, although it is known that so called 'autonomic storms' occur during REM sleep in humans with bursts of increased heart rate, blood pressure and respiratory rate [111,112]. As yet we have no evidence of what happens to NPT during such bursts of peripheral sympathetic activity, although typically erection during NPT is well sustained. However, it is distinctly possible that 'switching off' of the l.c. during REM is part of a wider reorganization of peripheral autonomic activity which includes decreased sympathetic activity in the splanchnic (and penile) vessels, and which therefore results in reduction or cessation of the inhibitory tone in the smooth muscle of the erectile tissue. If so, that would have a permissive effect on erection during REM but would not be a sufficient explanation for why erections occur at that time.

Testosterone (T) is necessary for normal NPT. Hypogonadal men show erections during REM, but they are much less strong (in terms of both circumference and rigidity) and of shorter duration than those in eugonadal men, a difference which is corrected by T replacement [113–118]. As mentioned earlier, it is possible that T is responsible for a level of central arousability, or 'excitatory tone', mediated by the NE system, and this may account for the occurrence of spontaneous erections when the inhibitory tone is 'switched off' during REM. Central effects of NE are probably best shown pharmacologically by α-2 adrenoceptor antagonists, which increase NE at the synapse by blocking re-uptake. The NE cell bodies in the l.c., as well as their presynaptic terminals throughout the brain, are populated with α-2 receptors [119, p. 159]. In a recent study the effects on NPT of intravenous infusion through the night of a specific α-2 antagonist, RS 15385, which would be expected to have an excitatory effect on the NE arousal system, were studied in both sexually functional and dysfunctional men [120]. As α-2 antagonists (e.g. idazoxan) injected into the corpora cavernosa have little or no effect on erection, either positive or negative [121], it is reasonable to assume that any effects of such drugs when given intravenously are centrally rather than peripherally mediated. The results in this study were complex, as might be expected from the complex picture of NE effects in the animal literature, presented earlier. In the functional men, there was a curvilinear dose–response curve; in comparison with placebo, the lower dose produced an increase in erection *outside REM sleep*, whereas the higher dose produced a reduction of erection *during REM*. In the dysfunctional men, who received the same dosages, the positive effect of the drug on non-REM erection was apparent, but only with the higher dose, the lower dose had no effect and the disruptive effect on REM-related erection was not apparent. This complex picture was interpreted as follows: the curvilinear dose–response curve in the functional men, which is reminiscent of that reported by Sala et al. [27] on rat sexual behavior (see above), was seen as an example of a dose-related shift of maximum receptor impact, with the higher dose having an disruptive effect on the REM related 'switch off' of l.c. NE neurons, and the lower dose producing a T-like arousal effect which was apparent only during non-REM (It is also of interest that the higher dose produced an increase in spontaneous erection in the 'lights out' period preceding sleep onset). The pattern observed in the dysfunctional men was seen as a shift in the dose-response curve to the right, consistent with a higher degree of α-2 inhibitory tone in the dysfunctional subjects [122]. If that interpretation is correct, then we would predict a similar curvilinear dose–response curve in the dysfunctional men when higher doses are used. As suggested by the animal evidence, it appears that we cannot expect a simple response pattern to central

NE activation because it has both excitatory and inhibitory effects.

The relationship between REM sleep and NPT is clearly a researchable issue which deserved further attention. It may well provide an illuminating model of central inhibitory mechanisms which can be studied in both the human and the rat. The difficulty of distinguishing between a high level of basal 'inhibitory tone' and an inhibitory response to a perceived threatening stimulus was raised earlier. The evidence from this study suggests that response to drugs during sleep may be one way of assessing inhibitory tone, in this case of a specifically α-2 adrenoceptor type.

5.5. Other pharmacological evidence

α-2 Antagonists have also been studied in the waking state. Yohimbine is the drug in this category which has received the most attention. A series of studies of its effects in treating erectile dysfunction, while limited by methodological shortcomings, consistently showed an average modest positive effect on erectile function [26]. More experimental evidence was obtained from a placebo-controlled acute dosage study in which the specific α-2 antagonist RS15385 was infused intravenously into both functional and dysfunctional men while responding to erotic stimuli [123,124]. The dysfunctional men had significantly smaller erectile responses than the functional men during the placebo condition. Of particular interest was the finding that in younger dysfunctional men, blood pressure and heart rate responses to erotic stimuli were also blunted during placebo administration and normalized by the α-2 antagonist. This evidence, together with that from the sleep study mentioned earlier [120] suggest that, in psychogenic erectile dysfunction, there is central inhibition of autonomic response to erotic stimuli, involving both erection and cardiovascular responses, which is based, at least in part, on increased central α-2 tone. The partial normalization of the erectile response by the drug in the dysfunctional subjects was consistent with this explanation. The lack of such effects in the older dysfunctional subjects raises the interesting possibility that these central inhibitory mechanisms (and presumably their excitatory counterparts) decline with advancing age.

In view of the clear inhibitory role of serotonin indicated by the animal evidence, the sexual effects of serotonergic agents used therapeutically are of obvious interest. There is now a wealth of anecdotal evidence that serotonin re-uptake inhibitors (SSRIs), such as fluoxetine, which increase serotonin at the synapse, have adverse sexual effects in a substantial proportion of cases [125]. The most predictable of these effects are delayed or blocked ejaculation in men and orgasmic difficulty in women. Negative effects on sexual interest are reported but are more difficult to evaluate because of the confounding effects of the mood disturbance for which the drug is taken. As yet there are no methodologically sound studies of these adverse serotonergic effects. The effect of delaying ejaculation is being used as a pharmacological treatment for premature ejaculation [126].

The inhibitory role of certain neuropeptides, considered with the animal evidence above, is also suggested by evidence obtained from narcotic addicts [15,127]. Once again there is a lack of well-controlled human studies, and the potential confounding factors in this group of subjects are considerable, but there seems little doubt that chronic opiate use is associated with a diminution of both sexual desire and sexual arousability, including ejaculation and orgasm. There is also well documented anecdotal evidence of a phase of 'rebound hypersexuality' during opiate withdrawal, sometimes with spontaneous orgasms.

An interesting experimental study was reported by Charney and Heninger [128]. In a group of six 'normal' men, effects were monitored of the opiate antagonist, naloxone, the α-2 antagonist yohimbine, and placebo, with each drug being administered separately and together. The combination of naloxone and yohimbine resulted in spontaneous and full penile erection lasting at least 60 min, an effect which was not reported when either drug was used alone. In addition, the drug combination produced increased anxiety and nausea. These results suggest an interaction between the two drugs which may reflect a balance between the inhibitory effects of neuropeptides and the arousing effects of NE. These authors drew attention to the fact that increased activity of the l.c. may be associated with anxiety and that the l.c. is regulated by both α-2-adrenergic and opiate receptors. It is difficult to reconcile the idea that increased activity of the l.c. was contributing to the erection with the evidence, discussed earlier, that 'switching off' of l.c. NE neurons during REM is associated with spontaneous erection. Further studies are required to provide an explanation for this theoretically interesting phenomenon.

Given the central role that benzodiazepines have played in the development of Gray's 'conceptual nervous system', and in particular their capacity for blocking behavioral inhibition in response to threat of punishment in animal studies, their effects on human sexual response is of some interest. If, for example, central inhibition of sexual response was a part of the general BIS then benzodiazepines might be expected to block or reduce central inhibition of sexual response. Unfortunately there is no evidence with which to address that question. There are no adequate controlled studies of the effects of benzodiazepines on sexual response in men, and the anecdotal clinical evidence suggests that negative effects are more likely than positive [125]. However, as suggested earlier, the effects may depend on the context in which the drug is administered. If, for example, the BIS is involved in suppressing sexual behavior as part of a general suppression of competing response patterns, then with some examples of erectile dysfunction, where the problem is part of a more generalized stress response, benzodiazepines might be helpful. Careful double-blind placebo controlled evaluation of

benzodiazepines as a treatment for such carefully selected cases is warranted.

5.6. Psychophysiological evidence

Over a number of years, the author has been involved in studies which have, by chance, resulted in observations of possible relevance to the central inhibition concept. These have been reviewed more fully elsewhere [129]. The earliest observations occurred during experimental evaluation of aversive procedures used for modifying deviant sexual interest, which in those days included homosexual interest [130]. The aversive procedure which was most used involved monitoring penile erection in response to the deviant stimulus (image or fantasy) and delivering a mild but unpleasant electric shock to the arm whenever the erectile response reached a certain criterion. A common occurrence was a 'rebound' increase in penile circumference which occurred as soon as the threat of shock was removed. This looked like an example of the 'rebound phenomenon' described by Sherrington [131] as the concurrence of both excitation and inhibition during the presentation of a stimulus, with the excitation outlasting the inhibition once the stimulus was removed. A more striking phenomenon, possibly related to this rebound effect, was labeled 'paradoxical facilitation'. Two methods of modifying homosexual interest were compared. The aversive method, as described above, was preceded during each treatment session by measurement of erectile response to both homosexual and heterosexual stimuli in the absence of any shock threat. This same assessment was repeated at the end of each aversive conditioning session. The other procedure involved systematic desensitization of heterosexual anxiety, based on the rationale that homosexual interest may be reinforced by a fear of heterosexuality. In this procedure fantasy images were combined with relaxation; there were no aversive stimuli involved. But the same assessments were carried out at the start and end of each treatment session as described for the aversive method. Remarkably, and quite unexpectedly, in those men undergoing the aversive procedure there was a significant increase in the erectile response to the heterosexual stimuli at the end of the session, compared with the response at the start of the session. No such effect occurred with the non-aversive procedure [130]. One explanation for this phenomenon was that throughout the aversive procedure, inhibition invoked by the threat of shock while looking at homosexual stimuli may have co-existed with and overwhelmed excitation, whereas at the end of the session, when the possibility of further shock was gone, the excitation, in rebound fashion, carried over to facilitate the response to the heterosexual stimuli. The use of hetero and homosexual stimuli per se was probably less important in explaining this phenomenon, than the fact that contrasting categories of sexual stimuli were involved.

In the early 1980s the author, together with Christopher Bell, an autonomic physiologist, investigated the measurement of pulse amplitude (PA) from the dorsal artery of the penis and compared changes in PA to circumference change during development of erection [132]. The dorsal artery of the penis contributes little to the erection in the corpus cavernosum, whereas it supplies much of the blood to the glans and corpus spongiosum. The advantage of this fact is that, whereas blood flow in the deep penile artery is reduced as pressure builds up in the corpus cavernosum with the development of erection, there is no such impediment to flow in the dorsal artery, and variations of PA in the dorsal artery can therefore be seen as variations in neural control of blood flow to the penis. The typical pattern in normal subjects was for PA to increase during the development of an erection, although often the increase started after circumference increase was already underway. Also the PA increase often continued beyond the 'offset' of the erotic stimulus, whereas circumference change would be much more closely linked to stimulus onset and offset. A strikingly different pattern was observed in a proportion of men with psychogenic erectile dysfunction [133]. In such cases, the PA would reduce in parallel with a modest increase in penile circumference, and often, once the erotic stimulus was withdrawn, there would be a rebound increase in PA lasting for some minutes. One possible explanation for this phenomenon was that, in men with psychogenic erectile dysfunction, presentation of an erotic stimulus elicited an increase in inhibition of vascular response which was reflected in a decrease of PA in the dorsal artery. In typical rebound fashion, once the stimulus was off, the inhibitory increase ceased abruptly whereas the parallel excitation continued for a short time. A further striking example of this phenomenon was reported in a single case study of a man with psychogenic erectile dysfunction, in which an erection had been induced by papaverine [129]. During the course of the papaverine induced erection, an erotic stimulus was switched on and off at 5 min intervals. Although the papaverine injection was followed by a large increase in PA as well as penile circumference, as soon as the erotic stimulus came on, the PA went right down, to return with erotic stimulus offset; this happened repeatedly. This was in contrast to the penile circumference which remained largely unaffected. It remains an interesting possibility that this PA phenomenon is an indicator of varying levels of peripheral inhibition. However, measuring PA from the penis is methodologically difficult and little additional attention has been paid to this phenomenon. More recently, Wagner et al. [134] reported the measurement of electrical activity from the smooth muscle within the corpus cavernosum (CC-EMG). This showed a decrease of the signal during the development of the erection consistent with a reduction in inhibitory tone. A technique of this kind may provide a better way to measure directly the inhibitory process in the penis, although further studies of CC-EMG are producing a complex picture (e.g. Sasso et al. [135]) and its precise physiological significance remains to be elucidated.

While we must be tentative about interpreting this type of data, it could be related to a more 'stimulus-bound' pattern of central inhibition, of potential relevance to erectile failure in presumably threatening situations.

A further important series of experiments was carried out principally by Barlow and his colleagues in the United States (see Cranston-Cuebas and Barlow [136] for review), and Everaerd's group in Amsterdam (see Janssen and Everaerd [137] for review), using a cognitive or information processing approach involving measurement of erectile response to erotic stimuli in men with and without erectile dysfunction, in conditions which manipulated specific cognitive or affective aspects of the experience. Their key results can be summarized as follows:

1. By inducing states of anxiety with threat of shock, sexual response can be enhanced in functional and impaired in dysfunctional subjects.
2. Imposing 'performance demand', requiring the subject to respond to an erotic stimulus with an erection, and measuring the response, can again enhance the response in functional and impair it in dysfunctional subjects.
3. By contrast, distraction with some non-erotic cue impairs response in the functional subjects and may have no effect or even enhance response in the dysfunctional subjects.

Barlow [138] has focussed on two particular aspects of these findings. First the distraction; the negative effect of distraction in the functional men he sees as evidence of the fundamental importance of 'attention to the sexual cues' for normal sexual response. The paradoxical effect of distraction in the dysfunctional men, he suggests, is because they are otherwise distracted by non-erotic cues which are even more negative in their effects on sexual response than the experimental ones. Secondly he draws attention to the amplifying effect of arousal, whether it be negative, such as that associated with anxiety, or otherwise non-specific. Thus arousal will enhance the focus of the information processing—if it is focussed on sexual cues, then the sexual response will be enhanced, whereas if it is focussed on non-erotic or anti-erotic cues, such as worrying thoughts about failure, then the anti-erotic effect will be enhanced. In these ways he explains the discrepancy between the functional and dysfunctional men in his experiments.

It is the difference between the functional and dysfunctional men that is of particularly interest to this review. Are the dysfunctional men showing activation of our putative central inhibitory mechanisms, based on previous learning? Does their different response result from previous experiences of punishment or frustration in circumstances that they regard as comparable i.e., sexual failure? The question of how typical the 'functional' men are is also of interest. In general the numbers in such experiments were small and, although the 'functional' subjects were presented as representative of normally functional men, we must assume considerable volunteer bias. Might they represent the 'low inhibition' group postulated in the opening paragraph? Or alternatively, was there variance amongst the 'functional' men that might be consistent with this concept? This possibility is also relevant to the paradoxical effects of anxiety in augmenting sexual response in some subjects. Whereas Barlow explains this effect in information processing terms, it can also be seen as an example of 'excitation transfer' [139] where arousal from one source becomes employed as arousal for another response pattern (i.e. sexual), but only in those individuals where the cause of the anxiety has not also inhibited sexual response i.e. in low inhibition men. This issue will be reconsidered in the final theoretical conclusions.

There is some additional experimental evidence that raises questions about the adequacy of the Barlow model, in particular its reliance on distraction as the key mediator. The most interesting examples are, in fact, from Everaerd and Barlow's groups. Janssen and Everaerd [137] compared the erectile response, in functional and dysfunctional men, to two types of stimulation, vibration applied to the penis, and an erotic film, both separately and in combination. With the vibration alone, the dysfunctional men showed significantly less response than the functional men. But when the vibration was combined with the film, and when the films were shown alone, the two groups did not differ. Once again information processing must have been involved; but how does one explain the lack of response to tactile vibration in terms of information processing alone? Vibration alone may well be capable of producing erection without any specific cognitive mediation, but in this case, the processing of the information in the dysfunctional men receiving vibration alone, with the connotation of 'need to respond to this direct stimulus', may have invoked an inhibitory mechanism which reduced the erectile response. The effect of adding the erotic film was to distract the dysfunctional man from this anti-erotic thinking and hence switch off (or reduce) the inhibitory mechanism.

The second example involves the use of mis-attribution. The principle is to give the subject a pill, which in fact is inactive, but tell him that it will increase his sexual response whilst he looks at erotic stimuli. He will attribute any response that occurs to the pill and consequently minimize his own arousal. Conversely, if you give him an inactive pill and tell him that it will *decrease* his response, he will be impressed by any response that does occur and hence report greater subjective sexual arousal. Cranston-Cuebas and Barlow [136] examined this possibility and to their surprise demonstrated the effect strikingly in functional men, but with the effect showing itself in the actual erectile responses and not in their report of subjective arousal. With dysfunctional men, however, the findings were different. When told that the pill would decrease their response, that is what in fact happened, again in the erectile and not in their subjective responses. The response-enhancing pill, on the other hand, was no different to placebo for the dysfunctional group. Janssen and Everaerd [137] went on to replicate

these findings, although they looked only at functional and not dysfunctional men. They commented, however, on the remarkable difference between the clear effect of the mis-attribution procedure on the physiological response, the erection, and the lack of effect on the subjective response, the self-rating of arousal.

Whilst information processing was undoubtedly involved in these procedures also, if it was the only relevant mechanism it is difficult to account for the lack of effect on the subjective experience. An alternative explanation is that the altered expectation produced by the mis-attribution effect was associated, in the functional men, with a reduction in the usual level of inhibitory tone, an effect of which the subject was presumably unaware and which did not lead to any revision of his subjective state. In contrast, the dysfunctional men processed the information differently and in a way which either did not reduce inhibitory tone, or actually increased it.

These experiments provide evidence which may well be relevant to inhibition *in response to perception of some threat*. Clearly, the central inhibitory process is being influenced, either positively or negatively, by the information processing that is taking place. The interface between information processing and central inhibition can be seen as fundamental to our theoretical model.

5.7. Chronic stress and affective disorders

It is widely assumed that sexual interest and to some extent capacity for sexual response is adversely affected by situations of chronic stress in human males. Anecdotal evidence is commonplace (e.g. increased sexual interest while on vacation) but no systematic studies have so far been reported [140]). Although there is no clear evidence of the effects of T on the HPA axis, as reported in the rat, T levels may go down in relation to stress or subordination in men (see Kemper [141] for review).

Clinical states of altered mood, both anxiety and depression, are of considerable potential relevance to our theoretical model. Recent studies of chronic anxiety, or general anxiety disorder (GAD), have shown that somatic symptoms, such as increased heart rate, are not simply the result of increased sympathetic activity, but involve reduced vagal control [142]. Thus heart rate may be increased because of loss of vagal tone, but also there is reduced cardiovascular responsiveness to external stimuli for the same reason. This may relate to our concept of 'inhibitory tone'. The study of α-2 antagonist action, discussed earlier [123], found a loss of cardiovascular as well as erectile responsiveness in men with psychogenic erectile dysfunction which was attributed, at least in part, to increased α-2 tone as it was partially normalized by the α-2 antagonist. Loss of vagal control may also have been part of this blunted cardiovascular pattern raising the possibility of an overlap between 'psychogenic erectile dysfunction' and GAD which is open to further testing.

Depressive illness is relevant for additional reasons. Many cases of major depression are accompanied by an overactivity of the hypothalamo–pituitary–adrenocortical axis [143] which is not dissimilar to the 'general adaptation syndrome'. Loss of sexual interest is common in depressive illness. At this stage we should be cautious in suggesting what the mediating mechanism between depression and loss of sexual interest may be. Increased levels of β-endorphin have also been reported in major depression [144] and the sexual inhibitory effects of β-endorphin, discussed earlier, could be relevant. The association between stress and altered 5HT activity, previously discussed, is another possibility, though this does not translate simply into depressive terms. Serotonin re-uptake inhibitors are used to treat depression while at the same time commonly inhibit sexual response. Any serotonergic mechanism would therefore have to be selective. Testosterone is lowered in some depressed men [145–147].

Beck [148] found low sexual interest in 67% of severe depressives compared with 27% of non-depressed controls. More recently an association between depressive symptoms and erectile dysfunction has been demonstrated in a non-clinical population sample [149]. However, the relationship between depressed mood and sexuality is variable. A proportion of men experience an increase in sexual interest when depressed [150] and one study showed this pattern to be more likely in men whose depression was associated with anxiety [151]. This raises two issues of theoretical interest. The variable relationship between mood and sexuality may reflect individual differences in propensity for central inhibition of sexual response, with depression having less adverse effect on sexual interest and response in 'low inhibition' men. Furthermore, the co-existence of anxiety and depression in 'low inhibition' men may result in 'excitation transfer' of the anxiety related arousal to the sexual response, accounting for the increase in sexual interest and responsiveness in such men. In those circumstances, the occurrence of sexual arousal may be used as a 'mood regulator' offering an immediate if transient improvement in the negative mood. This, in turn, is of potential relevance to the otherwise poorly understood category of 'compulsive sexual behavior' which is often accompanied by mood disorder [152]. Interestingly, SSRIs are being used to treat 'compulsive' sexual behavior [153,154], although it is not clear to what extent the beneficial effects result from mood improvement or suppression of sexual arousability or a combination of the two. As yet there are no adequately controlled studies of this clinical use.

5.8. Conclusions from the human evidence

As with the animal literature, we find evidence of inhibitory mechanisms of various kinds, certainly sufficient to justify building a theoretical model of central inhibition. Some evidence points to a more stimulus-bound inhibitory response, other evidence is consistent with the concept of

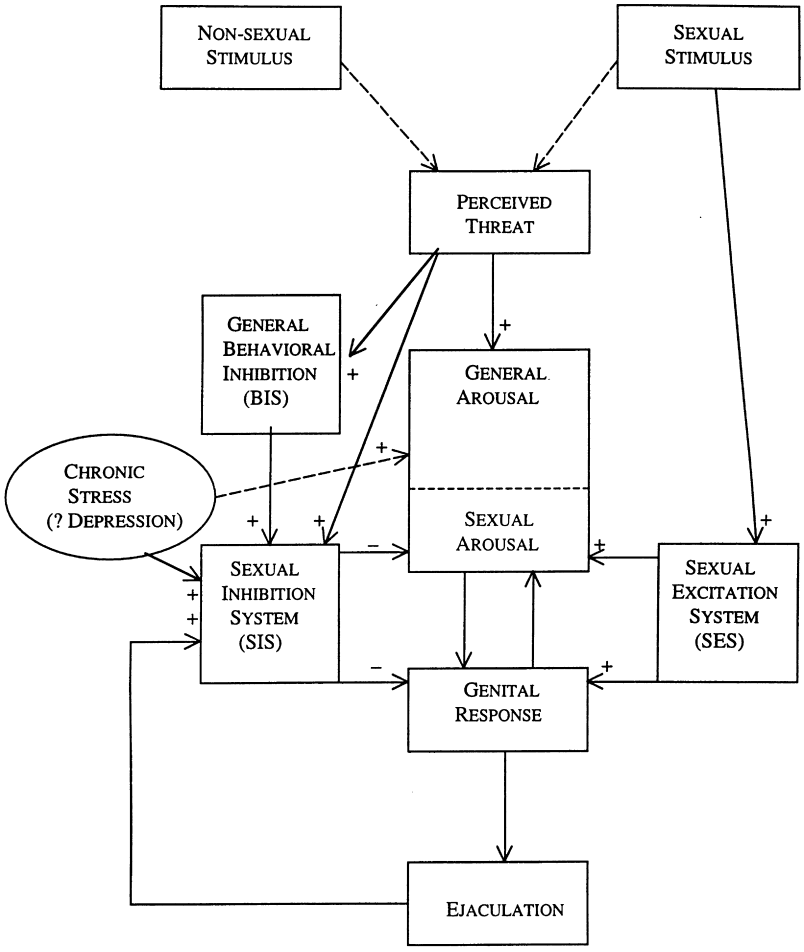

Fig. 1. The conceptual systems of sexual inhibition and excitation.

central inhibitory tone being higher in some individuals than others. The refractory period appears to be similar to that in other species in a number of crucial respects, yet virtually no experimental studies of the refractory period have been done in human males. Whereas we have little or no evidence relating to the effects of chronic stress (particularly that secondary to population density), we have evidence that chronic depression is associated with impaired sexual arousability, at least in a proportion of cases. In general, the evidence is consistent with the theoretically fundamental idea that, with the possible exception of the refractory period, the capacity for inhibition of sexual response varies across individuals.

6. Building a theoretical model

Let us now draw together the theoretical points that have emerged during this paper into a more coherent theoretical model. The model is shown graphically in Fig. 1. It is truly 'conceptual' and no attempt has been made to fit the specific neurophysiological mechanisms, that have been reviewed earlier, into the model (though there is scope for doing so on a speculative basis). The model has been built on a number of basic assumptions:

1. The occurrence of a sexual response will depend on the existence of a sexual stimulus (i.e. a stimulus that has the characteristics necessary to elicit a sexual response), and extent of the response will be determined by the balance between the 'conceptual' sexual inhibitory and excitatory systems (SIS and SES).
2. There is normally a basal level of inhibition that has been called inhibitory tone. This is clearly evident peripherally in the inhibitory tone maintaining flaccidity of the penis, and examples of centrally acting inhibited tone have been suggested (e.g. the activating effect of DA on the MPOA by disinhibiting 'inhibitory tone'). It is postulated that there will be individual variability in this inhibitory tone (determined by genetic factors, early learning or both), constituting an inhibitory trait. There is less reason to postulate the existence of 'excitatory tone'. The point in favor of it is the occurrence of NPT during the 'switching off' of the l.c. during REM. If 'excitatory tone' proves to be a useful concept, we would also predict individual variability in this respect also.

3. The intensity of the activation of SIS (or SES) when responding to external stimuli will depend on the basal 'tone': i.e. a higher tone system will react with a greater increase in inhibition (or excitation).
4. There can be alteration of the basal 'tone' in certain circumstances, such as chronic stress or depression, though vulnerability to such effects will also show individual variability.
5. There is a central arousal system which, in certain conditions (e.g. the appropriate context), can be recruited to sexual response patterns. (Hence 'sexual arousal' is not shown as clearly distinct from 'general arousal' in Fig. 1).
6. Four types of inhibitory response patterns can occur:
    1. In response to a perceived non-sexual threat. This will activate the BIS and increase general arousal and at the same time activate the SIS to inhibit sexual arousal and genital response (as well activating inhibition of other unwanted response patterns such as feeding).
    2. In response to a perceived sexual threat. The principal difference from (i) is that the sexual threat will be derived from or be associated with a sexual stimulus which will also activate the SES. Whether a sexual response then occurs will depend on the balance between SIS and SES. In the presence of a weak SIS, sexual response may not only occur but also be augmented by the effects of the threat-induced general arousal increase (i.e. excitation transfer). A further possible difference from (i) is that there may be direct activation of SIS rather than activation via BIS.
    3. Chronic stress (and possibly depression) will enhance SIS (in vulnerable individuals) and possibly impair SES. General arousal may or may not be increased.
    4. Ejaculation will enhance SIS resulting in the post-ejaculatory refractory period (or in the case of repeated ejaculations in a short time period, sexual 'satiation').

A number of logical but less crucial relationships have been omitted from Fig. 1 to avoid over-complication; e.g., a Behavioral Activation System (BAS) could lead from a non-threatening, non-sexual stimulus to an increase in general arousal of a positive but non-sexual nature; the SES could disinhibit the SIS; genital response could 'feedback' to function as a sexual stimulus.

7. Conclusions

Central to the theoretical model is the concept of individual variability, with individuals distributed on continuums of propensity for inhibition and excitation of sexual response. To test the model in animals we need a species where such individual variability has not been eliminated or reduced by selective breeding. We then need behavioral paradigms, of adaptive relevance, suitable for experimental manipulation, which would provide the opportunity to explore how the various neurophysiological inhibitory mechanisms, already identified, fit into this conceptual inhibitory system. To test the model in humans we need a method to measure such traits. We might postulate that high inhibition is related to sexual dysfunction, and low inhibition with propensity for sexual risk taking. But it should be kept in mind that sexual dysfunction and sexual risk taking may involve different pathways in our model. We might also postulate that inhibition of sexual arousal is relevant to low sexual desire, whereas inhibition of genital response is relevant to erectile dysfunction. And we should keep in mind that the 'arousal' and 'genital response' components may be differentially affected.

The combination, in the human male, of appropriate 'situation–response' patterns for experimental use, and inhibition and excitation trait measures would open up a new research agenda with far reaching implications. Not only would it present opportunities for exploring how pharmacological effects fit the model, it would also lend itself to new technologies, such as functional brain imaging to grapple with the 'conceptual inhibitory system', or genetic marking of transporter genes such as those relevant to serotonin transport to grapple with individual differences.

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