PERGAMON

Neuroscience and Biobehavioral Reviews 24 (2000) 571–579

NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS

www.elsevier.com/locate/neubiorev

The dual control model of male sexual response: a theoretical approach to centrally mediated erectile dysfunction

John Bancroft*, Erick Janssen

The Kinsey Institute for Research in Sex, Gender and Reproduction, Morrison Hall 313, Indiana University, 1165 East Third Street, Bloomington, IN 47405-3700, USA

Abstract

A theoretical model of dual control of male sexual response is considered, based on the balancing of central excitation and inhibition, with individuals varying in their propensity for both sexual excitation and inhibition of sexual response. A questionnaire method for measuring propensities for sexual excitation and inhibition has been developed (SIS/SES questionnaire), resulting in one excitation factor (SES) and two inhibition factors (SIS1 and SIS2). Evidence for the existence of both inhibitory and excitatory tone is discussed. The first inhibition factor (SIS1) may be related to level of inhibitory tone and is associated with fear of performance failure. The second inhibition factor (SIS2) may be related to external threats (e.g. from within the sexual relationship). The implications for the treatment of centrally mediated erectile dysfunction are discussed, with predictions that high SIS2 individuals will respond to psychological treatment, whereas high SIS1 individuals will respond better to pharmacological methods of treatment.

Keywords: Sexual response; Erectile dysfunction; Inhibition; Theoretical model; Treatment implications; Prognosis

1. Introduction

This paper considers a new theoretical model of dual control of male sexual response, involving both excitatory and inhibitory mechanisms in the brain and explores how the model might help to throw light on the etiology of psychogenic erectile dysfunction. The basic theoretical model, together with a detailed review of the evidence pertaining to central inhibitory mechanisms relevant to sexual response, has been published elsewhere [4]. This model postulates that central inhibitory mechanisms are adaptive and that individuals vary in their propensity for inhibition of sexual response as well as propensity for sexual excitation. For the majority, the presence of a fairly typical level of inhibition proneness is adaptive, helping to keep the individual out of trouble. Those whose propensity for central inhibition of sexual response is too high have increased vulnerability to sexual (e.g. erectile) dysfunction. For those whose inhibitory propensity is too low, an increased likelihood of engaging in high risk sexual behavior may result.

It is also assumed that the adaptiveness of central inhibition of sexual response would be of general significance across species, and in the earlier paper consideration was given to the various functions which inhibition of sexual response might serve [4]. Four principal functions were proposed:

1. Where a sexual situation is perceived as threatening and inhibition of sexual response facilitates avoidance of that threat;
2. Where the perceived threat is not sexual but requires an avoidance response for which inhibition of other inappropriate distracting behavioral patterns such as eating or sexual activity is a necessary part;
3. Where sexual response, (e.g., ejaculation in the male) inhibits further sexual arousability to ensure that the pursuit of sexual pleasure does not become excessive (resulting in either reduced fertility or maladaptive preoccupation with sexual rewards);
4. Where sexual and reproductive behavior is inhibited by chronic stress (which, in many social species, has the effect of reducing population overcrowding by selectively inhibiting reproductive behavior in those animals which, as a consequence of being low in the social hierarchy, are more susceptible to chronic stress).

It was concluded that whereas a variety of specific neurophysiological mechanisms have been identified, it is difficult

* Corresponding author. Tel.: + 1-812-855-7686; fax: + 1-812-855-8277.

E-mail address: jbancrof@indiana.edu (J. Bancroft).

0149-7634/00/$ - see front matter
PII: S0149-7634(00)00024-5

to link specific mechanisms to specific behavioral patterns of inhibited sexual response/behavior. The evidence suggests a more complex interactive system. However, this complex system can be considered at two levels: (i) the central arousal system and how it is recruited to produce arousal of a specifically sexual kind (or inhibition of it), and (ii) the inhibitory pathways from the brain stem (e.g. from the nucleus paragigantocellularis and the locus coeruleus) and peripheral genital manifestations of these 'downstream' inhibitory mechanisms.

Whereas the central arousal system is fundamentally based on norepinephric mediation, its recruitment for sexual purposes probably depends on disinhibition of dopaminergic mechanisms and, in some as yet unidentified way, on testosterone-dependent mechanisms. Inhibition of central sexual arousal, on the other hand, probably involves neuropeptidergic as well as serotonergic mechanisms. The peripheral inhibitory pathways clearly involve serotonin and norepinephrine, and quite possibly other mechanisms in addition (see Ref. [4] for review).

When we consider the four postulated functions and consider their relevance to humans, a distinction can be made between the first two, both of which can be regarded as 'context' or 'stimulus' specific, and the fourth which would appear to involve a chronic inhibitory 'state' relatively independent of specific context or stimulus at the time. In this paper, we consider some of our early evidence from measuring inhibition proneness in humans which is consistent with this distinction. The third function, the concept of post-ejaculatory refractoriness, is clearly relevant to humans as well as other species, although as yet we have very little evidence of the mechanisms underlying this phenomenon in humans. But studies of 'sexual exhaustion' in the rat, a state which appears to be an experimental extension of the refractory period, suggest that a wide range of inhibitory mechanisms, including inhibition of central sexual arousal, are involved (see Ref. [4] for review).

Measuring propensities for excitation and inhibition. In order to explore our theoretical model, a questionnaire has been developed which has good psychometric properties [23]. An important feature of this questionnaire is that all questions are aimed at establishing typical response patterns, in terms of sexual arousal or genital response, to two types of situation—one involving non-threatening sexual situations and the other sexual situations which involve some form of threat. This questionnaire was first completed by 408 male students, together with a number of other questionnaires used for establishing discriminant and convergent validity. Factor analysis resulted in three higher order factors, one related to excitation (SES), and two to inhibition (SIS1 and 2). This factor structure was further established in a confirmatory factor analysis of the questionnaire responses from a second sample of 459 male students. Based on the questions loading on the two inhibition factors, we called SIS1 "inhibition due to threat of performance failure" (e.g. losing one's arousal easily, concerns about pleasing one's partner and the effects of external sources of distraction), and SIS2, "inhibition due to threat of performance consequences" (e.g., threat of unwanted pregnancy or sexually transmitted infection, risk of 'being caught' or concerns about causing or experiencing physical pain). As both of these first two samples involved predominantly young men (mean ages 22.8 and 20.9 years, respectively) a third sample of 313 men with a mean age of 46.2 years also completed the 45-item questionnaire.

Table 1
Correlations between sexual excitation (SES) and sexual inhibition. SIS1 and 2 scales (Sample 1). ($n = 408$; mean age = 22.8 years, range = 20–38 years)

	SIS1	SIS2
SES	−0.07	−0.11
SIS1		+0.26 ($p<0.001$)

The correlations among the three scales were similar in each sample (see Table 1) with no correlation observed between either inhibition scale and the excitation scale, and a modest correlation between the two inhibition scales. In the two younger samples there were no significant correlations between scale scores and age. In the older sample age did relate significantly to SES ($r = -0.24$) and SIS1 ($r = +0.34$) scores but not SIS2 ($r = +0.13$).

A psychophysiological experiment was subsequently used to validate the scales [23]. Grouping subjects into high or low SES (with the groups being similar on the two SIS scales), high and low SIS1 and high and low SIS2, genital and affective responses to two types of erotic stimuli ('threatening', i.e. coercive, and 'non-threatening', i.e. consensual) were recorded. We found that the high SES group showed generally higher response levels, both genital and affective. The two SIS2 groups did not differ from each other in response to non-threatening erotic stimuli, but the high SIS2 group showed significantly less genital response to the threatening erotic stimuli, although the two groups did not differ in degree of negative affect associated with the threatening stimuli (i.e. the stimuli were no less threatening in the group which showed the greater genital response). Using distraction and performance demand conditions, we failed to discriminate between our high and low SIS1 groups. Thus we found convincing psychophysiological validation of our SES and SIS2 scales, but we had not found the right experimental manipulation to adequately validate our SIS1 scale.

We can also look at our preliminary data relating SIS/SES scores to frequency of sexual activity and also erectile dysfunction [23]. In the first sample we found a weak negative relationship between SIS2 and frequency of sexual intercourse ($\beta = -.18$; $p<0.002$) and between SIS1 and frequency of any form of sexual interaction with the partner ($\beta = -.12$; $p<0.05$) and a much more marked positive relationship between SES and frequency of masturbation

($\beta = +.43$; $p<0.0001$). A similar pattern was found in the older sample, and in this group there was also sufficient reporting of erectile dysfunction to allow us to examine this variable. Subjects were asked first whether they had ever had difficulties in obtaining or keeping an erection in sexual activities with their partner. Nearly half said they had never ever had difficulty, with 43% saying 'occasionally', 4% 'less than half the time' and 4% 'most of the time'. They were also asked whether they had had such difficulties in the past 3 months; 75% reported 'never', 18% 'occasionally' 2% 'less than half the time' and 5% 'most of the time'. Thus, it was the difference between 'never' and 'occasionally' which distinguished these two assessments most markedly. Taking these frequency assessments as dependent variables, multiple regression analysis was carried out using our excitation score, two inhibition scores and age as independent variables. In the analysis of the 'ever had difficulty' variable, SIS1($\beta = +0.38$; $p < 0.0001$) SIS2 ($\beta = +0.13$; $p<0.02$) and age ($\beta = +0.15$; $p < 0.006$) were all significantly related. SES did not figure in the equation. In the analysis of 'past 3 months', SIS1 again featured strongly and positively, as did age ($\beta = +0.36$ and $+0.25$, respectively; $p < 0.0001$). This time SES was involved, though negatively and weakly ($\beta = -0.12$; $p<0.02$), whereas SIS2 did not feature. Thus SIS1 was clearly related to both dysfunction frequency measures; this is consistent with SIS1 reflecting a trait inhibition characteristic which, for each subject, is and has been for some time, relevant to vulnerability to erectile failure. The association with age is consistent with the well-established fact that erectile function is less efficient as men get older. Given that age is accounted for in the equation, the association between SES and the latest time period score is presumably not simply an age-related loss of sexual arousability and requires further explanation. The relevance of SIS2 to the first variable but not the second is interesting. This is consistent with erectile failure, on occasions (hence, contributing mainly to the 'occasional' category) being a response to a threatening situation which may have occurred from time to time through the individuals life, but not on a regular basis and not necessarily within the last 3 months.

Thus we have established a valid measure of excitation/inhibition to explore our theoretical model with some interesting preliminary results.

2. Are there two types of inhibition?

The main unexpected finding so far is the identification of two inhibition scales rather than one. This had not been anticipated in our original theoretical model, and requires explanation. The principal purpose of this paper is to extend the theoretical model to take this finding into account, and to specifically consider the relevance of the three scales to erectile dysfunction.

We can compare and contrast the threats typically associated with 'fear of performance failure' (SIS1) and 'fear of performance consequences' (SIS2). The second appears related to the perception of an external threat in the specific situation, with variations in the SIS2 score reflecting varying degrees of inhibitory responsiveness to such threats. Clearly, such threats (e.g. fear of hostile response from the partner) are relevant in a fair proportion of cases of psychogenic ED, and may end up as important foci for psychological interventions. The first scale (SIS1) presents a more complex challenge. Here the threat is more intrinsic, based on the learnt awareness that failure of response, for that individual rather than that situation, is to be expected. This can therefore tentatively be conceptualized as the cognitive structuring of a trait reflecting 'high propensity for erectile failure'. In other words, the high SIS1 individual has learnt that he responds unreliably in sexual situations and the anticipation of further failure augments that trait characteristic. It is noteworthy how little attention has been paid to 'performance anxiety', the hallmark of any putative 'fear of performance failure'. Clinical experience suggests that often such individuals are aware of an unpleasant emotional state; they may not spontaneously describe it as 'fear of failure' though they may readily agree to that description if it is suggested to them.

We should remain open to the possibility that these two scales are measuring two different types of inhibitory mechanism. We would also like to propose an alternative explanation; that whereas the SIS2 scale measures inhibitory responsiveness to external threats, SIS1 is reflecting the level of 'inhibitory tone' and that high SIS1 individuals have high 'inhibitory tone'. 'Tone' in this sense refers to the level of inhibition that the system is set at when not actively responding to a sexual stimulus or an external sexual threat.

The heuristic value of this 'inhibitory tone' concept needs to be considered carefully. There are various reasons for believing that inhibition of sexual response is a "tonic" state which requires to be reduced, or at least exceeded by excitation, to allow sexual response to occur. This is clearly evident in the tonic contraction of the smooth muscle of the flaccid penis; the dependence of this state on 'tonic' inhibitory signals from the brain is apparent from the effect of spinal transection which, in both animals [19,29] and man (see Ref. [21] for review) results in a lowering of the threshold for 'reflexive' erections. More centrally, the sexual activation role of the medial preoptic area of the hypothalamus may well depend on reduction of inhibitory tone [22]. For any given level of baseline inhibitory 'tone' we would expect that level to be increased in the presence of a perceived external threat. Whether we would expect this baseline level of inhibition to be lowered, in circumstances where active appraisal of the situation concludes that there is no threat, is less certain. It is possible that in such circumstances the inhibitory 'tone' remains unchanged and the occurrence of a sexual response will depend on the activating effects of a sexual stimulus, with the propensity for

sexual excitation being sufficient to overcome the inhibitory 'tone'. But it is also possible that, typically, the level of inhibitory tone is set to make sexual response unlikely until active appraisal of low threat has been carried out, when the lowering of the inhibitory tone may contribute to the sexual response. Thus, in the typical case (i.e. the individual with a typical level of inhibitory tone) appraisal of the situation as non-threatening, with consequent reduction of inhibitory tone, at least to the level necessary for sexual interaction, would be a prerequisite for sexual response to occur. In the individual with low inhibitory tone, there would be proportionally less need for reduction of inhibition, and consequently a lower threshold for sexual response. If such an individual's propensity for sexual excitation was also high, then we might expect occurrence of a sexual response *even in the presence of a threat*. In the converse situation, with the individual with a relatively high inhibitory tone, particularly if his propensity for sexual excitation is relatively low, we can predict that a proportionally stronger sexual stimulus, and a lesser amount of threat will be required before a sexual response will occur. We are therefore conceptualizing inhibition in two ways, the level of basal inhibitory tone characteristic of an individual, and the degree of responsiveness to the perception of sexually relevant threat (or its absence) with an increase (or decrease) in the level of inhibition. With our two scales SIS1 and 2, we are also conceptualizing two types of threat, one external (SIS2), the other more intrinsic (i.e. the threat of performance failure related to the tendency to fail due to the high inhibitory tone).

Does 'excitatory tone' have similar heuristic value, or is excitation 'stimulus bound', dependent on the existence of a sexual stimulus and the prevailing potential for an excitatory response? The capacity for sexual excitation, or arousability, clearly has intrinsic determinants. The best illustration of this in the human context is the role of testosterone. In hypogonadal men, arousability is impaired. Although we should not overlook the possibility that testosterone has a role in maintaining genital response mechanisms at the spinal level, it is clear that testosterone has a crucial role centrally in relation to sexual arousal. The most robust, predictable testosterone-related impairment of arousability is manifested in the reduced spontaneous erections during REM sleep (nocturnal penile tumescence or NPT). In hypogonadal men, NPT occurs with much the same frequency as in eugonadal men, but with a markedly reduced degree and duration of response [12,13,15,25,33]. In comparison, erectile response to visual erotic stimuli (VES) discriminates much less between hypogonadal and eugonadal states [8,12,26]. At one stage, we had interpreted this finding as indicating that there were at least two response systems in the CNS, one of them testosterone dependent, the other testosterone independent. But in view of the most recent evidence [13] indicating that whereas erectile responses to VES do not differ between hypogonadal and eugonadal states in terms of maximum erectile response, they do differ in terms of duration (and probably rigidity), we should consider other explanations for this discrepancy (e.g. that the capacity for a sexual response to continue even beyond the duration of the erotic stimulus may depend on the testosterone dependent level of arousability, whereas the response to the initial maximum impact of the stimulus may not).

The hypogonadal impairment of NPT is unlikely to be caused by increased inhibitory tone alone since during REM sleep, the NE neurons in the locus coeruleus, the downstream projection of which are responsible, at least in part, for the peripheral inhibitory tone in the erectile tissues, are effectively switched off [34]; hence the assumption that erections occur during REM sleep because of the reduction of inhibitory tone. But clearly the occurrence of only partial erections during REM in the hypogonadal state indicates that normal NPT cannot be explained solely in terms of REM related disinhibition. On the other hand, there is no clear reason to assume that relevant sexual stimulation is involved in NPT. This leaves us with the possibility that some central state of 'excitatory tone', dependent on testosterone, does exist, and when peripheral inhibition is sufficiently reduced, as during REM, then spontaneous erections will occur. The lesser discrimination between hypogonadal and eugonadal states in response to VES may be caused by the fact that VES is a relatively powerful external stimulus. The comparison of hypogonadal and eugonadal states in terms of erectile response to internal erotic imagery (i.e. fantasy) is less consistent than is the case with VES [9,13], suggesting a more variable dependence on androgen (or a more variable potency of such imagery as sexual stimuli). Auditory erotic stimuli, or non-moving erotic visual stimuli (i.e. relatively weaker sexual stimuli) have not been tested in this paradigm. This nevertheless reminds us of the fundamental role of information processing in the excitatory component—the process by which sexual meanings are associated with external stimuli.

Individual variability in propensities for excitation and inhibition. Given that the capacity for sexual excitation varies with testosterone level, at least below a certain threshold level of the hormone, it is not unreasonable to assume that there will be other sources of individual variability in sexual excitation or arousability. Similarly, we can postulate that the propensity for inhibition as well as the levels of inhibitory tone show individual variability. Whether in either case such variability derives from earlier learning, genetic determinants or a combination of the two must remain unanswered for the time being. However, from a clinical perspective we should consider what pathological or otherwise atypical conditions might alter these states. Using testosterone deficiency as a paradigm, we can consider pharmacological effects (e.g. dopamine antagonists, such as butyrophenones, that impair 'excitatory' dopaminergic activity; e.g. Ref. [38], and certain types of brain lesion as having the potential for lowering the

propensity for excitation [27]. Such states are likely to be experienced principally as a loss of sexual interest (or arousability) rather than as a propensity for erectile dysfunction. It is more difficult to find convincing examples of pathologically induced increase in central inhibition, and the equivalent pharmacological effects of centrally acting drugs (e.g. in increasing inhibitory serotonergic activity) are more clearly manifested as an inhibition of orgasm or ejaculation than as an inhibition of sexual interest or arousability.

Depression, however, requires special consideration. The most usual, but by no means invariable, sexual pattern associated with depression is loss of sexual interest and/or erectile dysfunction [1,9]. NPT is also commonly impaired in depressive illness, suggesting a biochemical impairment of 'excitatory tone' [35,39]. On the other hand, depression is commonly associated with overactivity of the hypothalamo–pituitary–adrenal axis [16], a state sharing some features in common with the 'general adaptation syndrome' response to chronic stress. As mentioned earlier, chronic stress is commonly associated with suppression of reproduction and sexual behavior in non-human species, an effect which may involve alteration of serotonergic activity (e.g. Refs. [10,28]), and/or an increase in neuropeptidergic activity, especially with β-endorphin [20]. The increase in corticotrophin releasing factor (CRF) which accompanies many depressive states, probably accounts for increased levels of β-endorphin, which have been shown to be raised in depressive illness [17]. The β-endorphin could be contributing to an increase in inhibitory tone. On the other hand, loss of sexual interest or responsiveness is not an invariable feature of depressed states and some individuals even experience an increase in sexual interest when they are in a negative mood state. This may be more likely when the negative mood is associated with increased arousal, as with anxiety (e.g. Ref. [32]). In such cases a low propensity for inhibition of sexual response may in some way allow 'excitation transfer' of the arousal because of the negative mood state to augment arousal responses to sexual stimuli. This pattern, which we have recently started to study, is of considerable potential interest in explaining patterns of compulsive sexual behavior and deserves closer attention in a separate paper.

3. Other clinical evidence relevant to the concept of 'inhibitory tone'

Three experimental paradigms are considered. The first exploits the smooth muscle relaxant effects of intracavernosal injections (ICI) of compounds such as prostaglandin E1 or papaverine. Whereas response to such injections was initially regarded as a peripheral target organ effect independent of higher influences, it soon became apparent that a substantial proportion of men with psychogenic erectile dysfunction, whose peripheral erectile mechanisms should be relatively intact, responded poorly to such injections [6,11], suggesting that there was some central inhibitory signal counteracting the effect of the injection. Kim and Oh [24] found that in men with psychogenic ED who showed that type of poor response to ICI, there was an increased level of NE in the penile blood, consistent with a high inhibitory NE tone in the erectile tissues. Granata et al. [18] showed that NE levels in the general circulation were significantly lower in such 'high inhibition' men; they also showed higher trait and state anxiety scores than the 'low inhibition' group, although state anxiety was not increased by the ICI. Combining the results from these two studies, we have evidence that in men with psychogenic ED who respond poorly to intracavernosal smooth muscle relaxants, there is increased NE tone in the erectile tissues and low circulating NE combined with high state anxiety scores consistent with central inhibition of sexual arousal and peripheral inhibition of erection.

In the second experimental paradigm, the effects of acute dosage with delequamine, a selective alpha-2 adrenoceptor antagonist, were evaluated [30,31]. An alpha-2 antagonist principally acts on presynaptic norepinephric (NE) autoreceptors, blocking their re-uptake function. Hence this type of drug can be seen to increase available NE at the synapse in the central nervous system, and possibly in the periphery also. Centrally, this NE effect is probably associated with arousal in general; the locus coeruleus, which is involved in central arousal states, has many alpha-2 receptors. Peripherally, the effects of alpha-2 antagonists are not yet clear (see Ref. [5] for fuller discussion), but may involve both pre-synaptic inhibitory effects and post-synaptic excitatory effects which cancel each other out. The central effects may be linked to sexual arousal by a testosterone-dependent mechanism as yet not understood; alpha-2 antagonists partially restore the loss of sexual arousability that follows castration in male animals [14]. It should be emphasised that there is much about the central NE mechanisms and their association with arousal that we do not understand. But it does appear that, with delequamine, we have a drug where the central effects could contribute to sexual arousal.

The effects of the delequamine were evaluated in comparison with a placebo in men with psychogenic erectile dysfunction. Younger dysfunctional men in this study showed both impairment of erectile response and blunting of cardiovascular response to visual erotic stimuli during the placebo condition; differences from the functional controls which were substantially reduced by the drug. Thus, by antagonizing the central alpha-2 activity and increasing available NE centrally, delequamine increased peripheral non-genital (i.e. cardiovascular) manifestations of sexual arousal as well as increasing erectile response. These results are to some extent consistent with those from the ICI study described above.

The third experimental paradigm involved acute dosage with delequamine during sleep [8]. Here we find some interesting effects which are clearly suggestive of increased

inhibitory tone based on alpha-2 receptor activity. In the normal controls, the high dose of the drug only increased erections in the waking state, in fact just before the onset of sleep. In the younger psychogenic dysfunctional cases, the high dose of the drug increased erections after the onset of sleep, in fact mainly between onset of stage 2 and the first REM episode. One interpretation was that with the onset of sleep there was a reduction of inhibition in the dysfunctional men that allowed the high dose of the drug to have an effect. But even during sleep, the dysfunctional men showed a different dose–response relationship to the normal controls consistent with their having higher inhibitory levels of alpha-2 activity [3,5].

To what extent do the results of these three experimental paradigms support the concept of 'increased inhibitory tone' rather than an inhibitory response to an external-threatening stimulus? In the first case, the ICI could be regarded as an external threat, and the impairment of the response to ICI as an inhibitory response to that external threat. However, psychological as well as neuroendocrine indicators of a 'response to threat' were not clearly present and the evidence was more consistent with a 'high inhibitory tone' model. In the second paradigm, external sexual stimuli were clearly involved, and these may have been associated with some threatening meaning, most probably related to 'fear of failure to respond', although once again the pattern of psychophysiological responses was also consistent with a 'high inhibitory tone' model. In the third paradigm, involving genital responses during sleep, the relevance of an external inhibition-provoking threat can be ruled out, and the results are most convincingly supportive of the 'high inhibitory tone' model.

The age factor. A striking finding in the two delequamine studies [7,30,31] was a virtual absence of effects of the drug in the older dysfunctional men, both in the waking study and the sleep study. Their erections, which were impaired in response to the visual erotic stimuli, were unaffected by the drug. There appeared to be a loss of responsiveness to the alpha-2 blockade. Interestingly, cardiovascular responses to the erotic stimuli, which were blunted in the younger dysfunctional men, were no different in the older dysfunctional men to those in the young functional controls; there was some form of dissociation between cardiovascular and erectile response to erotic stimuli in this older dysfunctional group. How can we account for this age effect?

Lerner et al. [26] have reported evidence of increased inhibitory tone in penile smooth muscle in older men. If, as seems likely, peripheral alpha-2 receptors modulate NE inhibitory tone in the penile smooth muscle, then one explanation for this increase of muscle tone could be an age-related loss of alpha-2 receptor responsiveness (i.e. loss of response to both agonist and antagonist), which in the periphery could result in increased inhibition of erectile response.

Obviously, a variety of mechanisms could be involved in the general age-related decline in sexual interest and arousability (see Ref. [36] for review). However, the decreases in both free testosterone and NPT (frequency, degree and duration) that typically accompany aging in men [37], are of potential relevance to our model, consistent with the idea of an age-related decline in the central excitatory mechanisms. The evidence already discussed suggests that there is an age-related loss of alpha-2 receptor responsiveness which is general, i.e. affecting both central and peripheral alpha-2 receptors. The loss of responsiveness in the central alpha-2 receptors may conceivably be associated with an age-related loss of central arousability.

On the basis of the alpha-2 receptor system we can therefore postulate three age-related mechanisms (or 'trait' characteristics). In younger men, increased alpha-2 tone centrally would result in inhibition of central arousal mechanisms. Whether this active mechanism would also apply in the periphery in those circumstances is not clear, but because it is an active mechanism one can postulate that it is selectively confined to central processes. In older men, central loss of alpha-2 responsiveness could be associated with loss of central arousability or excitation, whereas peripheral loss of alpha-2 responsiveness could result in increased inhibitory tone in the penile smooth muscles, i.e. inhibited erection. Both of these effects in older men could help to explain the age-related decline in NPT.

4. The relationship between SIS1 and SIS2

We have argued the case for the usefulness of the 'inhibitory tone' concept. We can now reconsider the relationship between our two inhibition scales, keeping in mind the fact that there is a modest correlation between these two scales, and hence presumably some overlap in what is being measured. We are postulating that the essential feature of SIS1 is the level of inhibitory tone, and of SIS2 the degree of responsiveness of the inhibitory system to external threats. Thus, a high SIS1 individual will have a high level of inhibitory tone and a high SIS2 individual will have a propensity to respond to external threats with marked increases in inhibitory level. The common ground between the two scales we can see as the particular threat incurred by recognition of the consequences of 'high inhibitory tone; i.e. the individual with high tone will learn that he has a tendency to respond poorly in sexual situations. The anticipation of failure thus becomes a threat, his response to which will increase further his already high inhibitory tone. This illustrates how our theoretical model involves both neurophysiological mechanisms and the role of learning.

5. Implications of the model for treatment of erectile dysfunction

The theoretical interpretation that we have presented sees 'threat of performance failure', the hallmark of SIS1, as

more intrinsic, and less context specific than the 'threat of performance consequences'. This could have considerable implications for treatment. If, in a particular case, erectile failure is largely dependent on the SIS2 mechanism (i.e. inhibitory response to the perception of a threat in the sexual situation), then it is conceivable that psychological treatment might alter or reduce that threat. If, on the other hand, erectile failure is a manifestation of a chronic 'high inhibitory tone' state, whatever the cognitive expression of that state may be, changing the inhibitory tone by psychological treatment may be much more difficult, or at least require a different approach. In those circumstances, a pharmacological agent that counteracts the high inhibitory tone may be more appropriate than psychological treatment.

6. Putting the model to the test

So far we have speculated vigorously on the basis of very limited evidence. The model, however, does lend itself to further testing, particularly now that we have apparently valid measures of individual variability.

6.1. Potential experimental studies

1. Explore the relationship between SIS1 scores and evidence of 'inhibitory tone' (e.g. by replication of the sleep study with an alpha-2 antagonist given to men with high and low SIS1 scores; by relating SIS1 scores to circumference of the flaccid penis, and controlling for size of erect penis—the higher the inhibitory tone the smaller the flaccid penis).
2. Explore different types of threatening sexual stimuli that discriminate between high and low SIS2 individuals, looking in particular for threatening sexual stimuli that may be of relevance to psychogenic ED (e.g. certain types of partner response patterns).
3. Look for tests which would enable us to discriminate between our putative age related patterns, with high central inhibition associated with younger age and high peripheral inhibition with older age, using parameters other than age.
4. Explore the extent to which our putative 'high inhibitory tone' is specific for sexual response or more generalized. Investigate the emotional state as well as psychophysiological characteristics of younger individuals with high SIS1 scores. Compare them with subjects with other inhibited response patterns such as Generalized Anxiety Disorder (GAD), while responding to both sexual and non-sexual stimuli. In this way we plan to establish whether the lack of responsiveness in the sexual situation occurs in other non-sexual contexts as well (i.e. to what extent is this type of erectile dysfunction a form of GAD).

6.2. Potential treatment studies

We can at this stage make crude but testable treatment-based predictions:

1. In treatment studies using psychological methods of treatment, high SIS2 individuals are more likely to respond than high SIS1 individuals.
2. Younger age, high SIS1 patients will respond favorably to inhibition reducing drugs. Because of the uncertain effects of simple alpha-2 blockade on peripheral mechanisms, a combined alpha-1 and alpha-2 antagonist, such as phentolamine, might do better than a pure alpha-2 antagonist.
3. In older, high SIS1 patients, treatment may be based on the ratio of SES and SIS1 scores. Relatively high SES and high SIS1 individuals might respond better with a disinhibiting drug such as phentolamine, or a more specific alpha-1 antagonist. The lower the SES score in relation to the SIS1 score, the greater the likelihood of an excitation facilitator such as sildenafil or apomorphine being effective. Where there is a combination of low SES and high SIS1, then a combination of sildenafil (or apomorphine) and phentolamine might have the best chance of success.

7. Conclusions

The decade between the mid-1970s and mid-1980s saw a number of controlled treatment outcome studies aimed at evaluating the effectiveness of different types of psychological treatment for sexual dysfunctions (see Ref. [2], pp. 498–502). A recurring theme was the failure to demonstrate superiority of one psychological approach over another. In an earlier paper [40], it was suggested that the principal explanation for this apparent failure was the considerable degree of prognostic variability, sufficient to overwhelm the variance attributable to the treatment method. The answer, it was proposed, was to establish relevant prognostic indicators and control for them appropriately in future treatment outcome studies. In this paper, we have presented some relatively novel theoretical ideas about the central control mechanisms of erectile response and the interface between such mechanisms and cognitive mechanisms, as well as the relationship between central and peripheral mechanisms. We see this as highly relevant to 'prognostic variability', and with the questionnaire measure now available [23], believe that we have the ability to control for an important component of prognostic variability in future treatment outcome studies. At the same time, we believe that this theoretical approach offers the possibility of a new research agenda for understanding psychogenic erectile dysfunction. It has the added virtue of generating predictions relevant to both psychological and pharmacological methods of treatment. Its relevance to more organic forms of erectile

dysfunction should also not be underestimated. Men with greater degrees of peripheral organic impairment of erectile function are still likely to vary in the relevance of these central mechanisms to their erectile dysfunction, and such factors may well account for a considerable amount of the variance in treatment outcome. We look forward to reporting more evidence based on this model in the near future.

References

[1] Araujo AB, Durante R, Feldman HA, Goldstein I, McKinlay JB. The relationship between depressive symptoms and male erectile dysfunction: cross-sectional results from Massachusetts male aging study. Psychosom Med 1998;60:458–65.

[2] Bancroft J. Human sexuality and its problems. 2nd edn. Edinburgh: Churchill Livingstone, 1989.

[3] Bancroft J. Are the effects of androgens on male sexuality noradrenergically mediated? Some consideration of the human. Neurosci Biobehav Rev 1995;19(2):325–30.

[4] Bancroft J. Central inhibition of sexual response in the male: a theoretical perspective. Neurosci Biobehav Rev 1999;23:763–84.

[5] Bancroft J. Effects of alpha-2 blockade on sexual response: experimental studies with Delequamine (RS15385). Int J Impotence Res 1999 (in press).

[6] Bancroft J, Malone N. The clinical assessment of erectile dysfunction: a comparison of nocturnal penile tumescence monitoring and intracavernosal injections. Int J Impotence Res 1995;7:123–30.

[7] Bancroft J, Munoz M, Beard M, Shapiro C. The effects of a new alpha-2 adrenoceptor antagonist on sleep and nocturnal penile tumescence in normal male volunteers and men with erectile dysfunction. Psychosom Med 1995;57:345–56.

[8] Bancroft J, Wu FCW. Changes in erectile responsiveness during androgen therapy. Arch Sex Behav 1983;12:59–66.

[9] Beck AT. Depression. Clinical, experimental and theoretical aspects. London: Staples Press, 1967.

[10] Brotto LA, Gorzalka BB, Hanson LA. Effects of housing conditions and 5-HT 21 activation on male rat sexual behavior. Physiol Behav 1998;63(4):475–9.

[11] Buvat J, Buvat-Herbaut M, Lemaire A, Marcolin G, Quittelier E. Recent developments in the clinical assessment and diagnosis of erectile dysfunction. Ann Rev Sex Res 1990;1:265–308.

[12] Carani C, Bancroft J, Granata A, Del Rio G, Marrama P. Testosterone and erectile function, nocturnal penile tumescence and rigidity, and erectile response to visual erotic stimuli in hypogonadal and eugonadal men. Psychoneuroendocrinology 1992;17(6):647–54.

[13] Carani C, Granata ARM, Bancroft J, Marrama P. The effects of testosterone replacement on nocturnal penile tumescence and rigidity and erectile response to visual erotic stimuli in hypogonadal men. Psychoneuroendocrinology 1995;20(7):743–53.

[14] Clark JT, Smith ER, Davidson JM. Testosterone is not required for the enhancement of sexual motivation by yohimbine. Physiol Behav 1985;33:517–21.

[15] Cunningham GR, Karacan I, Ware JC, Lantz CD, Thornley II. The relationship between serum testosterone and prolactin levels on nocturnal penile tumescence in impotent men. J Androl 1982;3:241–7.

[16] Goodwin G. Mood disorder. In: Johnstone EC, Freeman CPL, Zealley AK, editors. Companion to psychiatric studies, Vol. 6. Edinburgh: Churchill Livingstone, 1998. p. 399–430.

[17] Goodwin GM, Austin MP, Curran SM. The elevation of plasma beta-endorphin levels in major depression. J Affect Disord 1993;29:281–9.

[18] Granata A, Bancroft J, Del Rio G, Carani C. Stress and the erectile response to intracavernosal prostaglandin E1 in men with erectile dysfunction. Psychosom Med 1995;57:336–44.

[19] Hart BL. Sexual reflexes and mating behavior in the male rat. J Comparative Physiol Psychol 1968;65:453–60.

[20] Herbert J. Sexuality, stress, and the chemical architecture of the brain. Ann Rev Sex Res 1996;7:1–43.

[21] Higgins GE. Sexual response in spinal cord injured adults: a review. Arch Sex Behav 1979;8:173–96.

[22] Hull EM, Lorrain DS, Du J, Matuszewich L, Bitran D, Nishita JK, Scaletta LL. Organizational and activational effects of dopamine on male sexual behavior. In: Ellis L, Eberty L, editors. Male/female differences in behavior: toward biological understanding, Westport, Con: Greenwood Press, 1998.

[23] Janssen E, Vorst H, Finn P, Bancroft J. The sexual inhibition (SIS) and sexual excitation (SES) scales: measuring individual differences in the propensity for sexual inhibition and excitation in men. Submitted for publication.

[24] Kim SC, Oh MM. Norepinephrine involvement in response to intracorporeal injection of papaverine in psychogenic impotence. J Urol 1992;147:1530–2.

[25] Kwan M, Greenleaf WJ, Mann J, Crapo L, Davidson JM. The nature of androgen action on male sexuality; a combined laboratory and self-report study in hypogonadal men. J Clin Endocrinol Metab 1983;57:557–62.

[26] Lerner SE, Melman A, Christ GJ. A review of erectile dysfunction: new insights and more questions. J Urol 1993;149:1246–55.

[27] Lundberg PO. Sexual dysfunction in patients with neurological disorders. Ann Rev Sex Res 1992;3:121–50.

[28] McKittrick CR, Blanchard DC, Blanchard RJ, McEwen BS, Sakai RR. Serotonin receptor binding in a colony model of chronic social stress. Biol Psychiatry 1995;37:383–93.

[29] Meisel RL, Sachs BD. Spinal transection accelerates the developmental expression of penile reflexes in male rats. Physiol Behav 1980;24:289–92.

[30] Munoz M, Bancroft J, Beard M. Evaluating the effects of an alpha-2 adrenoceptor antagonist on erectile function in the human male. II. The erectile response to erotic stimuli in men with erectile dysfunction, in relation to age and in comparison with normal volunteers. Psychopharmacology 1994;115:471–7.

[31] Munoz M, Bancroft J, Turner M. Evaluating the effects of an alpha-2 adrenoceptor antagonist on erectile function in the human male. I. The erectile response to erotic stimuli in volunteers. Psychopharmacology 1994;115:463–70.

[32] Nofzinger EA, Thase ME, Reynolds III CF, Frank E, Jennings R, Garamoni GL, Fasiczka AL, Kupfer DJ. Sexual function in depressed men: assessment by self-report, behavioral and nocturnal penile tumescence measures before and after treatment with cognitive behavioral treatment. Arch Gen Psych 1993;50:24–30.

[33] O'Carroll RE, Shapiro C, Bancroft J. Androgens, behaviour and nocturnal erections in hypogonadal men: the effect of varying the replacement dose. Clin Endocrinol 1985;23:527–38.

[34] Parmeggiana PL, Morrison AR. Alterations in autonomic functions during sleep. In: Loewy AD, Spyer KM, editors. Central regulation of autonomic functions, New York: Oxford University Press, 1990. pp. 367–86.

[35] Roose SP, Glassman AH, Walsh BT, Cullen K. Reversible loss of nocturnal penile tumescence during depression: A preliminary report. Neuropsychobiology 1982;8:284–8.

[36] Schiavi RC. Aging and male sexuality. Cambridge: Cambridge University Press, 1999.

[37] Schiavi RC, White D, Mandeli J, Schreiner-Engel P. Hormones and nocturnal penile tumescence in healthy aging men. Arch Sex Behav 1993;22:207–15.

[38] Tennent G, Bancroft J, Cass J. The control of deviant sexual behavior by drugs: a double-blind controlled study of benperidol, chlorpromazine, and placebo. Arch Sex Behav 1974;3:261–70.

[39] Thase ME, Reynolds CF, Glanz LM, Jennings JR, Sewitch DE, Kupta DJ, Frank E. Nocturnal penile tumescence in depressed men. Am J Psychiatry 1987;144:89–92.

[40] Warner P, Bancroft J. Sex therapy outcome research: A reappraisal of methodology. II. Methodological considerations. Psychol Med 1986;16:855–63.