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ALPHA ADRENOCEPTORS AND HUMAN SEXUAL FUNCTION

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Introduction

Sexual functioning involves complex physiological processes which rely on the interplay of many central and peripheral neurotransmitter systems. Disturbances in any one of these systems might be associated with disturbed sexual function which, when recognised, may be alleviated by appropriate pharmacological manipulation, although at the present time this is more hypothesis than reality. The sympathetic nervous system is involved actively at various levels in the normal control of sexual responses. The effects of sympathetic activation are mediated by the release of noradrenaline from nerve terminals and the increased secretion of adrenaline from the adrenal medulla. These catecholamines selectively activate specific cellular sites in target tissues known as adrenoceptors (previously termed adrenergic receptors) to mediate responses. Almost fifty years ago, Alquist realised that tissue responses to catecholamines were mediated through two distinct types of receptors which he designated α and β [1]. This review focuses on the involvement of α-adrenoceptors in human sexual functioning and dysfunction.

Alpha adrenoceptors are located both pre- and post- synaptically and they were classified as either α_1- or α_2- adrenoceptors according to location; α_1 being postsynaptic and α_2 presynaptic. This classification continues to be used in some texts. However, as highly specific and selective pharmacological tools became available, this locational subclassification is found not always to be appropriate. Nowadays, classification of α-adrenoceptors is more appropriately based on pharmacological activity and additional subtypes of α-adrenoceptors have been identified by radioligand binding and molecular biological techniques [2]. Hence α_1-adrenoceptors include postsynaptic receptors that classically mediate smooth muscle contraction and α_2-adrenoceptors include both the pre-synaptic autoregulatory α-receptor and some less typical post-synaptic α-receptors such as on many blood vessels where they effect smooth muscle contraction [3].

The pharmacological classification of α-adrenoceptors is based on interaction with selective agonists and antagonists. Classically, phenylephrine and methoxamine are considered to be α_1 -selective agonists and clonidine a selective α_2- agonist. Prazosin and phenoxybenzamine are considered to be α_1-selective antagonists whilst yohimbine is a selective α_2-adrenoceptor antagonist. The endogenous agonists adrenaline and noradrenaline are approximately equipotent at α_1- and α_2 -adrenoceptors. A number of other selective α_1- and α_2 -adrenoceptor agonists and antagonists have been developed, both as pharmacological tools in tissue and animal studies and as potential pharmacotherapeutic agents; some of these will be discussed in this paper.

Penile α-adrenoceptors

Noradrenaline induces concentration-dependent contraction of isolated strip preparations of corpus cavernosum or isolated corpus cavernosum muscle cells, the contraction being inhibited by α-adrenoceptor antagonists [4,5,6,7]. Whilst both phenylephrine and clonidine contract trabecular tissue from corpus cavernosum, clonidine was less potent in this respect than phenylephrine [6,8,9]. In addition, prazosin and thymoxamine (moxisylate), α_1-adrenoceptor antagonists, blocked noradrenaline-induced contraction of isolated corpus cavernosum muscle cells whilst tolazoline, an α_2-adrenoceptor antagonist, was ten times less potent than prazosin and thymoxamine in this model [7]. Taken together, these observations provide evidence that postsynaptic α_1-adrenoceptors predominate in isolated corpus cavernosum tissue. Confirmatory evidence is provided by the effects of intracavernous administration of different α-adrenoceptor antagonists. The non-selective α-adrenoceptor antagonist, phentolamine, and the selective α_1-adrenoceptor antagonist, thymoxamine, induce tumescence or erection whereas idazoxan, a selective α_2-adrenoceptor antagonist had no such effect [10]. In the rabbit corpus cavernosum, the density of α_1-adrenoceptors decreases following castration and is increased by testosterone replacement [11], although castration has no effect on corpus cavernosum smooth muscle contraction induced by noradrenaline [12].

Studies have also been undertaken on the adrenergic pharmacology of the cavernosal artery and the circumflex and deep dorsal veins. Cavernosal artery preparations contract in response to noradrenaline and clonidine, the latter having a more potent effect [8]. These contractions were inhibited to the same extent by both prazosin and rauwolscine, a selective blocker of α_2-adrenoceptors, whereas rauwolscine was more potent than prazosin in attenuating contraction of this preparation induced by electrical stimulation [8]. These findings suggest that α_2-adrenoceptors predominate in the cavernosal artery. Both α_1 and α_2 -adrenoceptors have been demonstrated in the deep dorsal [13] and circumflex veins [14].

Effect of α-adrenoceptor agonists on erection

As can be expected from *in vitro* studies, α-adrenoceptor agonists at appropriate doses inhibit erection. In the dog, intracavernous administration of noradrenaline abolished erection induced by cavernous nerve stimulation in a dose-dependent manner [15]. Intravenously administered midodrine (5mg), a non-selective α-adrenoceptor agonists inhibited erection in three out of five male volunteers [16] and metaraminol administered intracavernously induced penile 'shrinkage' [10]. Intracavernous administration of α-adrenoceptor agonists may therefore be an appropriate approach to the management of prolonged erections.

Metaraminol has been used in the management of priapism (17,18]. Clonidine has also been used for the treatment of prolonged erection [19]. Intracavernous administration of phenylephrine has been advocated as a means to reduce erection during urogenital surgical procedures [20].

Effect of α_1 adrenoceptor antagonists on erection

As flaccidity of the penis is maintained by contraction of the trabecular muscle which is mediated through α1- adrenoceptor stimulation, drugs that block these receptor sites will be expected to promote tumescence and/or erection. Priapism has been reported during treatment with drugs that have $_{\alpha}$-adrenoceptor blocking activity, including prazosin [21] which has a high degree of selectivity for α_1-adrenoceptors [22]. In a controlled laboratory based study, orally administered labetalol, an antagonist at both α- and β adrenoceptors delayed detumescence in a dose-related manner [23]; an effect not seen with the β-adrenoceptor antagonist, propranolol (unpublished observations). Isolated tissue studies have shown labetalol to be a highly selective antagonist at α_1-adrenoceptors as opposed to α_2-adrenoceptor [24]. These observations suggest that α_1-adrenoceptor activation is involved in detumescence.

The best demonstration of the effects of α_1- adrenoceptor antagonists on erection is provided by the erectogenic activity of these agents after intracavernous administration. However, drugs exhibiting α_1- adrenoceptor antagonist activity differ in their erectogenic potential. Whereas phenoxybenzamine induces good erections [25], phentolamine, a non-selective α adrenoceptor antagonist does not provide a satisfactory erection [26] but augments the erectogenic activity of papaverine [27]. The poor effect of phentolamine has been attributed to its lack of effect on venous return in the erectile mechanism [28], but may also be related to pharmacokinetic and tissue distribution factors. Although thymoxamine (moxisylate), a relatively selective competitive α_1- adrenoceptor antagonist can induce erection when administered intracavernously [10], in a double-blind cross-over study it was less potent than papaverine and its effect was described more as facilitating (by inducing prolonged tumescence) rather than inducing erection [29]. *In vitro*, thymoxamine is less potent than prazosin and phentolamine in relaxing noradrenaline-induced contractions of human corpus cavernosum [30].

Effects of centrally acting α_2-adrenoceptor antagonists

The most widely researched centrally acting α_2-adrenoceptor antagonists is yohimbine an alkaloid that also has affinity for other receptor systems, including dopamine and 5-hydroxytryptamine, which may be involved in the control of sexual behaviour. However, activity at these additional sites is not considered significant at plasma concentrations normally achieved from dosing in man [31]. Other α_2-adrenoceptors antagonists that have been studied, from the point of view of sexual function, in animals or man are imiloxan [32], idaxozan [33], RS-15385 [34] and fluparoxan [35]. These antagonists have extremely high selectivity for α_2-adrenoceptors. By antagonising the presynaptic α_2-adrenoceptor, α_2-adrenoceptor antagonists increase noradrenaline release and enhance the firing rate of cells located in brain noradrenergic nuclei [36.37] resulting in noradrenergic hyperactivity. Studies have shown yohimbine, idazoxan and imiloxan, to enhance sexual arousal in male animals [38 - 41] and to restore sexual activity in castrated rats [42].

Volunteer studies: Males

Erection associated with yohimbine administration was reported to have occurred in 10 to 29% of healthy volunteers taking part in early cardiovascular and psychological studies of the drug [43,44]. There have been few reported studies of the effects of α_2-adrenoceptor antagonists on sexual functioning in non-sexually dysfunctional subjects. Single oral dose of yohimbine (30 mg) had no effect on sexual drive or penile erection but when given concomitantly with naloxone in the same study resulted in full erection in all of six subjects studied [45]. Only three of the subjects reported partial erection following naloxone alone. Although the assessment of sexual outcome variables in this study was far from satisfactory, relying only on the response to direct questioning by the research nurse, the results suggest a synergism between the noradrenergic and opiate systems. Synergism was also seen in anxiety symptoms and plasma cortisol levels in the same study. No synergism between yohimbine and naloxone was seen in effects on sexual behaviour in male rats [46].

Intravenously administered yohimbine (0.3mg kg^{-1}) did not induce penile tumescence (measured by plethysmography) nor did it modify the physiological response to viewing erotic slides in any of the ten subjects studied [47]. Yohimbine was, however, associated with decreased sexual excitement during the post-stimulation phase. Apomorphine (0.009 mg kg^{-1} subcutaneously) was erectogenic in the same subjects providing a positive control in this study.

The effect of RS-15385 on erectile function has been studied [48,49, 50]. In normal volunteers, infusion of RS-15385 increased spontaneous erections and increased the duration of erectile response to erotic stimulation. It also increased subjective ratings of sexual arousal before presentation of erotic stimuli. A curvilinear dose-response effect of RS-15385 was found on nocturnal penile tumescence in normal volunteers. Whereas a low dose of RS-15385 increased erectile response during REM and non-REM sleep, a higher dose did not.

The effects on sexual functioning of four weeks oral treatment with RS-15385 has been studied by means of a double-blind placebo controlled study [51]. The main outcome variable was scores on the Derogatis Interview of Sexual Function -Male (DISF-M) [52]. This instrument assesses five domains of sexual function. RS-15385 increased scores for sexual fantasy, sexual arousal and sexual experiences but had no significant effect on scores for ejaculation, sexual drive or sexual satisfaction. The most striking finding was enhancement of the scores for sexual fantasy, sexual arousal and sexual experiences two weeks after drug withdrawal. The explanation for this is not clear but may be related to down regulation of adrenoceptors by RS-15385. This agent has been shown to cause β-adrenoceptor down-regulation in the cortex [53].

Volunteer Studies: Women

Single oral dose of yohimbine (30mg) in four women had no apparent effect on sexual desire, or vaginal secretion (in response to direct questioning by research nurse) in the sexually unstimulated condition [45]. Preliminary results of a double-blind placebo controlled evaluation of the effects of single oral dose yohimbine on

sexual responses induced by masturbation and viewing erotic video have been presented [54]. Yohimbine at 2mg and 12mg had no effect on sexual response induced by viewing an erotic video but the lower dose enhanced and the higher dose impaired the sexual response induced by masturbation.

The effect on sexual arousal induced by an erotic video of single oral doses of the α-adrenoceptor antagonist indoramin (25mg) and the β-adrenoceptor antagonist propranolol (120mg) have been compared in female subjects [55]. Propranolol but not indoramin significantly reduced the level of reported sexual arousal. The effect of propranolol (80 mg) has be compared with that of labetalol (100mg) on sexual arousal induced by masturbation (vibration) in healthy women [56]. Although the principle objective of this study was to investigate the effects of these drugs on the pressor response associated with sexual arousal, the subjects reported on the subjective features of their sexual response by means of visual analogue scales. Subjects reported a significant reduction in vaginal lubrication with labetalol compared to both placebo and propranolol. However, this effect of labetalol on vaginal lubrication was not seen in a further study in which genital secretion during sexual arousal was measured gravimetrically [16]. Interestingly, it has been reported that vaginal secretion decreases with prolonged sexual arousal [57] and therefore the subjective reduction in secretion reported in the earlier study [56] may have been caused by labetalol delaying orgasm; an effect seen in the later study [16].

Studies of α_2-adrenoceptor antagonists in male erectile disorder

For more than fifty years yohimbine has been prescribed for the management of erectile disorder. It was not until the last decade that controlled trials of yohimbine in this indication have been undertaken. Unfortunately, all reported trials suffer from methodological weaknesses in terms of trial design and measurement of outcome variables. Nevertheless, on balance yohimbine appears to have modest therapeutic gain over placebo, especially in psychogenic erectile disorder. The published trials have recently been reviewed [58].

Three other orally active α_2-adrenoceptor antagonists, idaxozan, RS-15385 and fluparoxan have been evaluated in patients with erectile disorder. Idaxozan, 40mg tds was assessed in a small (29 patients completed the study) placebo controlled double blind study [59]. Scores on a sexual performance scale showed a trend ($p = 0.06$) in favour of idazoxan compared with placebo at the end of the first week of treatment. Thereafter there was no further improvement. At the end of the trial 14 patients expressed a preference for idazoxan, nine for placebo and the remaining six showed no preference. Nine of the eighteen idazoxan failures improved when the treatment was changed to yohimbine hydrochloride (5 to 10 mg tds).

RS-15385 increased erectile response during non-REM sleep in younger (under 47 years) subjects but had no effect on nocturnal penile tumescence (NPT) in older (over 47 years) subjects with predominantly psychogenic erectile disorder [50]. RS-15385 also enhanced the erectile response induced by viewing erotic video in men with psychogenic erectile disorder but not to the same extent as it did in normal volunteers [48,49]. Results of trials of RS-15385 in the management of erectile disorder are awaited.

The third α_2-adrenoceptor antagonist to be evaluated in the management of erectile disorder is fluparoxan [60]. Thirty-two men diagnosed as having secondary, predominantly psychogenic erectile disorder and who had undergone at least eight weeks behavioural and/or couple therapy, were entered in to a one week placebo run-in phase during which they received a once daily placebo challenge dose on days 3 and 7 under single (patient) blind conditions. Subjects (n = 8) who successfully completed intercourse on both of these two challenges were withdrawn from the study. The remaining subjects were randomised, under double blind conditions, to either fluparoxan 8 mg bd or placebo bd for two weeks (Phase 1). Phase 1 was followed by a two week washout period after which the patients received the alternative treatment for two weeks during phase 2. Efficacy data were obtained from daily diary cards completed by the patients. Of the 24 patients who were randomised to treatment, two patients withdrew before taking any active medication and one patient completed Phase 1 (fluparoxan) but lost the Phase 2 diary card. Therefore due to cross-over design of the study, only 21 patients were included in the intent-to-treat population.

The primary efficacy variable was the proportion of patients who achieved a good erection which enabled completion of intercourse on at least 50% of attempts. An overall trend in favour of fluparoxan compared with placebo was shown for this variable but statistical significance was not achieved ($p = 0.21$). A number of secondary efficacy variables were included in the daily record cards completed by the subjects. Sexual interest and quality of erection were reported on visual analogue scales. Quality of erection was assessed for morning erections, erections during masturbation and lovemaking and erections before and after vaginal penetration if intercourse was attempted. A record of spontaneous erections was also kept.

Among secondary outcome variables analyzed, fluparoxan significantly increased maximum sexual interest ($p = 0.01$), median quality of erection from lovemaking ($p = 0.04$), maximum quality of erection before penetration ($p = 0.04$) and frequency of spontaneous erections ($p = 0.05$). In addition, there was a trend for fluparoxan to be associated with increase frequency of lovemaking ($p = 0.09$). Interestingly all these effects were more pronounced in the group who received placebo followed by fluparoxan.

Alpha-adrenoceptors and ejaculation and orgasm

The male internal genital duct system is richly supplied with adrenergic fibres and animal studies have shown α-adrenoceptor activation to be involved in seminal emission and closure of the bladder sphincter [61]. The relatively high occurrence of ejaculatory disturbances during treatment with drugs that have α-adrenoceptor blocking activity suggests that α_1-adrenoceptors are involved in the ejaculatory process of man.

Two forms of ejaculatory disturbance during treatment with α-adrenoceptor antagonists are seen; delay or failure of emission and retrograde ejaculation. The factors determining which of these two ejaculatory dysfunctions arise from a

particular α-adrenoceptor antagonists in a particular patient have not been determined. Clinical experience suggests that it is not drug or dose related.

In laboratory based studies orally administered phenoxybenzamine (40 mg to 120 mg) caused failure of ejaculation without impairing erection or orgasm in male volunteers [62] and labetalol caused a dose-related prolongation of ejaculatory latency also in male volunteers [23]. The delay of ejaculation with labetalol did not occur with propranolol (unpublished observation) suggesting that the effect was mediated through labetalol's α-adrenoceptor antagonist property. The ejaculation delaying property of phenoxybenzamine has been utilised in the treatment of premature ejaculation [63].

Orgasmic dysfunction has been reported during treatment with drugs possessing α-adrenoceptor antagonist activity. In a double-blind placebo controlled study in healthy female volunteers, labetalol caused a statistically significant dose-related retardation of orgasm induced by masturbation, determined both by blinded stop clock and by subjective assessment, an effect not seen with propranolol [16].

Alpha adrenoceptor agonists in ejaculatory dysfunction

Anecdotal case reports have described the use of α adrenoceptor agonists in ejaculatory dysfunction. Phenylpropanolamine [64] and the more selective α_1 adrenoceptor agonist, midodrine [65,66] have been reported to be effective in reversing retrograde ejaculation in some patients. Midodrine has also restored normal ejaculation in patients with anejaculation resulting from extensive damage to the nerve supply of the internal ducts following abdominal surgery [65]. This drug has also been found to improve ejaculatory function in partial ejaculatory incompetence which may be caused by uncoordinated activity of the internal duct system during the ejaculatory process [67].

Discussion

Increases in circulating noradrenaline levels occur during sexual arousal in both men and women [68] indicating activation of the sympathetic autonomic nervous system. The finding that the combined α- and β-adrenoceptor antagonist labetalol (100 mg) produced a significant reduction in the pressor response to orgasm in women whereas propranolol at a dose (80 mg) which provides four to six times greater β- adrenoceptor blocking activity than the dose of labetalol used did not, provides evidence for marked α-adrenoceptor activation during sexual arousal [56]. At first this may appear a paradoxical response because increasing levels of noradrenaline would be expected to inhibit erection through α_1-adrenoceptor stimulation. Indeed, in the non-sexually aroused state, stimulation of the α-adrenoceptors on the trabecular smooth muscle and on the helical and cavernosal arteries maintain penile flaccidity. Withdrawal of this basal adrenergic tone enables the sinusoids and cavernosal and helicine arteries to dilate resulting in penile tumescence. Basal adrenergic tone in the penis is generated by the noradrenergic

system originating in the locus coeruleus although the paragigantocellular region of the brain stem reticular formation (PGC) has also been shown to generate a tonic suppression of sexual reflexes [69]. Animal studies have shown the noradrenergic neurones of the locus coeruleus to be under tonic α_2-adrenergic inhibition [70] and that stimulation of α_1-adrenoceptors by noradrenaline in these central noradrenergic mechanisms induces sexual arousal [39]. Hence a role for increasing noradrenaline levels during sexual arousal is established.

That the central noradrenergic control mechanisms are under tonic α_2-adrenergic inhibition provides a possible explanation for the sexual effects of α_2-adrenoceptor antagonists. By blocking the tonic inhibition of the locus coeruleus α_2-adrenoceptor antagonists increase arousal and sympathetic tone. Although the reported sexual effects of α_2-adrenoceptor antagonists in man have not been as dramatic as those seen in animals, this may reflect methodological weakness in study design or the influence of inhibition by higher centres not present in animals. Increased tonic inhibition of the central noradrenergic control mechanisms could be an aetiological factor in sexual arousal dysfunction. In the case of men, such inhibition would result in increased noradrenergic tone in the erectile tissue.

The finding of increased concentration of noradrenaline in penile blood from men with psychogenic erectile disorder, relative to normal controls and men with vasculogenic erectile disorder provide some evidence for this [71]. Furthermore, penile blood noradrenaline levels are higher in men with psychogenic erectile disorder in whom intracavernous injection of papaverine fails to induce erection than in men with similar diagnosis who respond to papaverine [71]. However, an increase in intrapenile noradrenaline concentration is not necessary for increased noradrenergic tone as it is known that alterations in adrenoceptor number and responsiveness can contribute to increased sympathetic activity [72]. No difference was found in penile α-adrenoceptor function between potent and erectile dysfunctional (venous leak) men [73] but differences might be expected between potent men and those with predominantly psychogenic erectile disorder. Increased number or responsiveness of adrenoceptors could be a factor increasing risk of erectile disorder in hypertensive men.

Whilst there is activation of the sympathetic division of the autonomic nervous system during sexual arousal, the classic erectile pathway is parasympathetic mediated through an atropine resistant mechanism [62]. Acetylcholine relaxes noradrenaline-induced contraction of corpus cavernosum tissue [8,74]. Acetylcholine - induced relaxation of cavernosal tissue is reduced or abolished by destruction of the endothelium suggesting that the relaxation is brought about by factors released from the endothelium [74]. In addition, stimulation of muscarinic receptors on adrenergic nerve terminals may inhibit noradrenaline release [75]. It is therefore probable that tumescence may be initiated by combined sympathetic and parasympathetic activation although both systems can induce tumescence independently of each other. Evidence of the synergism between noradrenergic and cholinergic mechanisms in the erectile process is provided by the observation made by Taylor Segraves that priapism occurs more frequently with drugs that have α-adrenoceptor blocking activity and negligible concomitant anticholinergic activity than those α-adrenoceptor blockers that also have anticholinergic property [76]. As further evidence for this hypothesis he mentions the reversal of α_1-adrenoceptor

antagonist- induced priapism by drugs possessing anticholinergic activity, such as diphenhydramine reversing priapism induced by fluphenazine hydrochloride [77].

Non-adrenergic, non-cholinergic (NANC) mechanisms are also involved in the erectile process and presynaptic α_2-adrenoceptors appear to be involved in the modulation of these mechanisms in many tissues [78], although cavernous tissue has yet to be studied in this respect. It has been shown that nitric oxide or a related autocoid synthesised from L-arginine is involved in NANC neuromuscular transmission and is probably the most important mediator of neurogenic corpus cavernosum smooth muscle relaxation required for erection [79, 80]. The number of nitric oxide synthase-containing nerve fibres in the corpus cavernosum is androgen dependent [81, 82], establishing a peripheral role for testosterone in the erectile process. In canine iliocolonic junctional tissues, nitric oxide release is inhibited by α_2-adrenoceptor stimulation [83]. If this occurs also in the corpus cavernosum then α_2-adrenoceptor antagonists might be expected to facilitate erection by blocking the inhibition of nitric oxide release. This has not been supported experimentally where intracavernous injections of α_2-adrenoceptor antagonists are not erectogenic [10] although yohimbine ointment applied to the balanopreputial sulcus has improved erections in men with erectile disorder [84]. Yohimbine levels in corpora cavernosal blood reached a peak by 30 minutes and was cleared within an hour. Unfortunately, yohimbine concentrations in peripheral blood were not determined and so a central effect can not be excluded.

There is little information on the involvement of α-adrenoceptors in the early stages of female sexual arousal. There is no reason to suspect that the mechanisms involved in erection of the clitoris are different from those involved in penile erection. This being the case, α_1-adrenoceptor antagonists would be expected to promote clitoral erection. In rather weak support of this, clitoral priapism has been reported during trazodone treatment [85] which may be attributed to the α_1-adrenoceptor antagonist activity of the drug [86]. However, trazodone has other pharmacological properties including dopamine and 5-hydroxytryptamine receptor blocking activity and its metabolite, *m*-chlorophenylpiperazine (mCPP) has $5HT_{1C}$ agonist activity and is a potent erectogogue in laboratory animals [87].

Increasing circulating noradrenaline levels, activating α_1-adrenoceptors during sexual arousal may be involved in triggering ejaculation. Spontaneous ejaculation can occur when noradrenaline levels increase under non-sexual arousal conditions such as acute anxiety [88] and α_1-adrenoceptor antagonists either delay [23, 63] or abolish [62] ejaculation. In women, α-adrenoceptor antagonists delay orgasm [16]. Whilst it may seem reasonable to explain ejaculatory or orgasmic delay induced by α-adrenoceptor antagonists in terms of peripheral mechanisms, a central involvement can not be completely dismissed. Central involvement may be mediately through two mechanisms: an indirect effect through changes in neurohypophyseal hormone release and direct effect on central neurotransmitter activity involved in the central control of ejaculation and/or orgasm. Circulating oxytocin levels increase during sexual arousal in both men and women [89]. Although the exact role of oxytocin in the physiology of ejaculation and orgasm is not known, there is circumstantial evidence for an involvement. For example, women may experience orgasmic-like sensations during breast feeding. Alpha adrenoceptors are stimulatory to the central

control of the milk ejection reflex [90] and therefore α-adrenoceptor antagonists might be expected to inhibit this reflex by reducing oxytocin release.

The involvement of central noradrenergic mechanisms in the ejaculatory and orgasmic processes are not well understood. In the dog, intracerebroventricularly administered clonidine produced a dose-related inhibition of ejaculation without affecting erection induced by manual stimulation of the penis [91]. Furthermore, clonidine inhibition of ejaculation was antagonised by yohimbine but not by prazosin, providing evidence that the effect of clonidine on ejaculation is mediated through α_2 adrenoceptors. Clonidine is also associated with ejaculatory and orgasmic disturbances in the human [92] and yohimbine has been reported to reverse antidepressant-induced orgasmic [93, 94] and ejaculatory [94] dysfunction.

Yohimbine has been shown to reverse age-related deficits in the sexual behaviour of the male rat: for example, the intercopulatory interval increases with age and this effect is reversed by yohimbine [95] although yohimbine had no consistent effect in the aged Rhesus male [96]. It is tempting to suggest that age-associated changes in sexual functioning may be related to changes in number or sensitivity of adrenoceptors. It has been reported that although the reduction of plasma noradrenaline concentration after clonidine administration was not influenced by age, elderly men had a greater reduction of plasma noradrenaline concentration for any given plasma clonidine concentration than did younger men [97]. The effect of yohimbine or other α_2-adrenoceptor antagonists on age-related changes in human sexual function has not been studied specifically although erectile and haemodynamic effects of RS-15385 were markedly attenuated in older relative to younger men [47, 48].

With the exception of fluparoxan, increases of sexual drive have not been reported during treatment with α_2-adrenoceptor antagonist in man whereas in the rat yohimbine, imiloxan and idazoxan [28, 39, 40] increases sexual motivation and mating behaviour. Fluparoxan increased sexual desire in men with erectile disorder [49], but this could be secondary to improvement in erectile function or to alleviation of depression (only patients with major depression were excluded from the study).

In the castrated rat, yohimbine restores sexual behaviour without concomitant androgen replacement [42]. Yohimbine (2mg to 30 mg daily) had no discernible effect on sexual desire and other elements of sexual functioning in any of five hypogonadal men, whereas when yohimbine was replaced by androgen replacement sexual functioning was improved in four of the subjects (Riley, unpublished observations). The remaining subject improved with a combination of testosterone and trazodone.

With a physiological process as complicated as the sexual response it is perhaps unrealistic to discuss one small component in isolation because the activity of any single component can be influenced by changes in other inter-related processes. However, data from studies undertaken in animals confirm a crucial role for both centrally and peripherally located α-adrenoceptors in the control of male and female sexual behaviour [Review 98]. There are now accumulating experimental data, though much of it circumstantial, to support the same conclusion in human sexual functioning.

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Discussion - ALPHA ADRENOCEPTORS AND HUMAN SEXUAL FUNCTION

A.K. Slob

Could you explain this impairment in sexual response with masturbation in subjects receiving a high dose of yohimbine?

A.J. Riley

With 12 mg yohimbine, the total score for the sexual response induced by masturbation was significantly lower than after placebo. A similar type of response has been elicited by other studies with alpha 2 blockers where a higher dose was inhibiting and a lower dose was stimulating. I cannot explain why.

R.C. Rosen

Aside from what you presented here, you have some of the best data to date on positive prosexual effects of yohimbine in males with erectile dysfunction. Could you comment on the relative size of the effects that you achieved in the two studies with the Syntex and Glaxo drugs, compared to the size of effects that you obtained in the earlier yohimbine study with men? A second question is whether you have any data at all on the effects of yohimbine in post menopausal women, or women with sexual dysfunction.

A.J. Riley

The answer to your second question is no. We have not any experimental data, only some clinical observations. In my experience from the clinical observations it does not seem to enhance sexual arousal or sexual desire in women, but that is purely anecdotal and I think it is something that needs to be looked at, perhaps not with yohimbine but rather with one of the more selective alpha 2 antagonists. With respect to the effect of yohimbine in male erectile function in men who are erectile dysfunctional, most of the studies - including our own - have shown almost a doubling of the placebo response rate. The response rate with placebo varies, of course, but is around 15%, and the studies with yohimbine have shown benefits in about 30%. Just how that compares with what we have seen with fluparoxan is difficult to assess

because the study designs were totally different. But, considering all the data available, there does not seem to be a major difference between yohimbine and some other more selective compounds. However, comparative trials would be needed to assess the relative effectiveness of different compounds.

K.E. Andersson

I want to follow up on that because there does not seem to be a very clear relation between the selectivity for the alpha 2 adrenoceptor and the clinical effect. And also a comment: if you look at the antihypertensive effect of clonidine, there is a definite window where you can see a lowering effect on blood pressure and if you increase the dose you have the opposite effect. Have you the same feeling for this kind of blockade of alpha 2 adrenoceptors that there is a window of dosages?

A.J. Riley

I think that is probably true. The right way of using this drug is to titrate against the response of the patient. One of the problems with yohimbine is that its bioavailability is quite unpredictable and as you mentioned yesterday it almost certainly has an active metabolite of which we really do not know its actions at all. What has been surprising about the fluparoxan study, and also with the RS 15385 study, is that although we have seen an effect on sexual function, we have not really seen an increase in blood pressure. In some of the RS 15385 studies there has been a short-lived increase in blood pressure and we have not really been troubled by symptoms of anxiety, which one would expect with this class of drug. Certainly these have been reported in the literature with yohimbine when it is given by intravenous injection and also when is has given orally in some of the non-sexual studies.

A.K. Slob

In the study with yohimbine in women you used 12 mg. At least for men that is not a very high dose.

A.J. Riley

I do not agree, actually. I see effects at 2 mg. My practice in using yohimbine

is to use it on a PRN basis. I start with 5.4 mg and if that does not work, I either decrease or increase it. I find that some people in fact respond to a reduction in dose or an increase in dose. Yohimbine shows a curvilinear dose-response curve in animals and we believe that this class of compounds has a curvilinear dose-response curve in man as well. I suspect that people vary in their position in the sensitivity to this class of compounds and that is why I think these drugs should always be titrated rated against response rather than using a fixed dose.

M. Murphy

I wonder if I could try to answer the last question about the failure to feel satisfied and continued arousal. Although you have commented that your subjects did not report increased anxiety, I think a lot of individuals do experience increased arousal; I mean generalized arousal on alpha-2-antagonists, and perhaps that is what the subjects are reporting. I would like to make a second comment just to draw your attention to the fact that there are data showing that the effect of yohimbine is greatly enhanced by pretreatment with naloxone; in fact it guarantees an erection.

A.J. Riley

It guarantees an erection in volunteers but not necessarily in dysfunctional men. Yes I agree with that.

J.T. Clark

I have one question about a possible complication introduced by the age factor on the first study with fluparoxan. It seems that the median age was 51 and my data in animals suggest that there is a shift in the dose-response curve and John Bancroft also reported that there is an age-related variation.

A.J. Riley

I think that is a good point and it is something I thought about but have not yet analyzed the data.