The Pharmacology of Sexual Function and Dysfunction
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Sexual Arousal and Performance are Modulated by Adrenergic-Neuropeptide-Steroid Interactions

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Introduction

Sexual function is regulated by a complex interaction between the nervous system, hormones and sexually relevant tissues. In addition to psychogenic causes, organic factors such as aging, hypertension, diabetes, renal failure, malnutrition, and obesity, as well as responses to medications used to treat these disorders, may all contribute to sexual dysfunction. Although the precise identification of the neurochemical messengers (and the appropriate neuroanatomical loci) underlying the expression of male sexual behavior remains to be elucidated, progress has been made. We feel that, with careful attention paid to the aspects of sexuality and the problems associated with continuous (or long-term) pharmacological/hormonal treatment, some degree of relief may be available for those exhibiting sexual dysfunction In our research in male rats, we have frequently observed a repression of sexual function. However, some treatments do facilitate aspects of sexual behavior. We have repeatedly observed two "prosexual" effects in male rats: a facilitation of the ejaculatory response; and a facilitation of sexual arousal. Other prosexual effects have been reported, typically an enhancement of erection.

Assessment of Sexual Function

Animal modeling of human sexual function is viable, and its usage is aimed at elucidating the biological factors affecting male sexual behavior [1-5]. Although it seems reasonable to test drugs for sexual effects in animals first, many clinically useful agents (including antihypertensives) have not been systematically studied. The usefulness of the male rat as a model for human sexual behavior stems from the numerous parallels identified between male rats and men, exemplified by the sexual role of androgens [2,6-8].

Copulatory behavior in male rats consists of a series of stereotyped behaviors. Following a series of mounts and intromissions, with a short refractory period following each intromission, an intromission of longer duration and deeper thrusting occurs - an ejaculation. Following ejaculation the male dismounts slowly and is sexually inactive for a longer period - the postejaculatory refractory period. If allowed to mate ad libitum, a male rat will typically have 5 - 10 ejaculations prior to sexual exhaustion. The latencies to the initial mount (mount latency; ML) and intromission (intromission latency, IL), and the number of mounts (mount frequency, MF) and intromissions (intromission frequency; IF) preceding ejaculation are recorded, as is the time from the initial intromission to ejaculation (ejaculation latency, EL), and the time from the ejaculation to the subsequent intromission (postejaculatory interval;

PEI). From these primary measures, 2 additional measures are derived - copulatory efficiency (CE = IF divided by MF + IF, multiplied by 100), and intercopulatory interval (ICI, the average time between successive intromissions - EL divided by IF)[see 1,4 for further details]. For interpretation of copulatory behavior data we utilize several constructs - the copulatory rate factor with 2 parts - one preceding ejaculation and reflected by the ICI (which we refer to as Maintenance), and the other involving the postejaculatory refractory period (Reinitiation); the copulatory efficiency factor; the initiation factor; and the ejaculatory threshold (or count) factor.

A useful approach to the assessment of sexuality is to stress component analysis of the complex patterns of sexual behavior in rats and humans [1,7,9,10]. There are two essential categories for the components of sexual behavior: libido and potency. Libido is variously identified in animal research as sexual motivation, sexual drive, or sexual arousal. In male rats the latency to initiation of mating, and the frequency of mounts in the absence of intromission and ejaculation, are used as indicators of sexual motivation. Mounting behavior after desensitization of the glans penis (achieved by application of a local anesthetic, and which effectively prevents erection, intromission and ejaculation, as well as suppressing sensory feedback) serves as an accurate indicator of the level of sexual motivation [e.g., 11-13]. There are other aspects of sexual arousal, however. These include the maintenance of a level of arousal sufficient to allow the male rat to continue to pursue the female and gain intromission until ejaculation occurs, and the reinstatement of copulation after ejaculation. Conversely, in rats, reflex erection and ejaculation tests are used to assess ability, and the number of intromissions preceding ejaculation serves as an indicator of the amount of stimulation required to elicit ejaculation during mating (the ejaculatory threshold). It is generally accepted that much of the recent success of sexual therapies stems from distinguishing the separate components (phases) of the sexual response. Research utilizing this component analysis indicates that the categories are indeed separable and are differentially regulated by hormonal [e.g., 8,14-16] and neurochemical [e.g., 2,10,17-19] systems. From this discussion it can be seen that it is almost meaningless to refer to mating as a behavioral unity. Likewise, it is critical that interpretations be based upon clearly identified physiological constructs - initiation, maintenance, efficiency, ejaculatory threshold, and reinitiation of mating following ejaculation. Even there, however, caution must be exercised since one cannot simply state that there is an increase in sexual motivation when there is a shortening of the ML -since IL is also an indication of the propensity to begin copulation, and ICI may be thought of as an indicator of the propensity to continue mating until ejaculation, and PEI is an indicator of the reinstatement of motivation so that the copulatory sequence begins anew. The same is true for IF - a decrease here is most likely indicative of premature ejaculation, which can be viewed simultaneously as a facilitation of the ejaculatory process, an induction of sexual dysfunction, a decrease in likelihood of reproductive success, or simply as facilitatory (in that the completion of the entire copulatory sequence is hastened) and inhibitory (in that a period of sexual refractoriness is induced sooner than "normal"). In order to clarify the nature of effects/changes in arousal and ability several specialized tests are used in conjunction with mating tests, allowing comment on ability separate from mating performance and/or motivation separate from sensory

feedback effects of mating.

Studies with α-adrenoceptor agonists

Adrenergic transmitters have long been implicated in the control of reproductive function, especially hormone secretion, in a steroid-dependent manner [e.g., 20]. Despite this relatively little work has been done to characterize the sexual effects of either adrenergic transmitters or adrenoceptor subtype specific drugs. We examined the effects of an α-2-adrenoceptor agonist, clonidine (an antihypertensive agent with reported antisexual effects in humans). An earlier report indicated that clonidine (3 - 30 μg/kg, administered subcutaneously [SC]) did not alter the percentage of rats that displayed copulatory behavior [21]. In that study castrated males were treated with low doses of testosterone, and the majority of the control rats failed to ejaculate. The 30 μg/kg dose was associated with a decreased mount latency and a decreased number of mounts/minute. This paradigm precluded any evaluation of the effects of clonidine on ejaculatory or postejaculatory behaviors. Using gonadally intact, sexually experienced rats, we observed a dose-related decrement in the number of male rats mating to ejaculation. Most males mounted and achieved intromission with normal latencies, but failed to maintain sexual activity until ejaculation [22]. We have recently completed studies with two other α-2-adrenoceptor agonists, guanabenz and guanfacine, with similar effects observed. Are the effects of clonidine on the maintenance of mating until ejaculation due to an impairment of erectile function? In ex copula penile reflex tests, IP administration of clonidine was followed by a dose-dependent inhibition of erectile function. There was no change in the latency to the initial erection, but the number of erectile responses (erections, cups and flips) were reduced at doses which failed to influence copulatory behavior (i.e., first evident at 5 μg/kg)[23]. Preliminary studies with guanabenz and guanfacine indicate that the effects of clonidine on erectile function are generalizable to other agents. In mounting tests, rats treated with α-2-adrenoceptor agonists exhibit fewer mounts.

In contrast to the clear indications that stimulation of α-2-adrenoceptors inhibits erectile and ejaculatory function, the role of α-1-adrenoceptors is less clear. Methoxamine, a selective α-1-adrenoceptor agonist, when administered IP effected reductions in the ejaculatory threshold and failed to affect mounting after genital anesthetization. In ex copula reflex tests, methoxamine treatment was followed by a reduction in the number of erections, cups and flips, but an increased incidence of seminal emission. Pretreatment with methoxamine failed to influence the suppressive effects of clonidine treatment [24].

Studies with α-adrenoceptor antagonists

Having demonstrated a dramatic antisexual effect for clonidine, we next tested whether this effect was attenuated by α-adrenoceptor antagonists. We assessed the effects of clonidine in rats that had been pretreated with yohimbine, an α-2-adrenoceptor antagonist, or prazosin, an α-1-adrenoceptor antagonist. The sexual inhibition induced by clonidine (0.25 mg/kg IP, five minutes prior to testing) was competitively antagonized by prior treatment with yohimbine (2 mg/kg, 15 minutes

prior to clonidine). Conversely, pretreatment with prazosin (1 mg/kg, 15 minutes prior to clonidine) potentiated the suppressive effects of clonidine, such that there was also a reduction in the number of males achieving intromission. Yohimbine alone resulted in decreases in EL (due primarily to a decreased ICI) and PEI. Treatment with prazosin alone was followed by increases in the latency to initiate copulation, in EL, in ICI and in PEI, as well as a small decrease in the ejaculatory threshold [19]. The inhibitory effects of clonidine are attenuated by pretreatment with α-2-selective antagonists (yohimbine, rauwolscine, idazoxan, imoloxan) , but not by pretreatment with α-1- or non-selective antagonists (prazosin, WB-4101, phenoxybenzamine, phentolamine), nor by pretreatment with naloxone or pimozide.

Subsequently, we proceeded to further evaluate the prosexual effects of yohimbine. Yohimbine has a long folk history as an aphrodisiac, and was used to treat impotence in men during the earlier parts of this century [32]. We observed that yohimbine increased mounting behavior in male rats after genital desensitization, increased intromissive and ejaculatory behavior in sexually naive males, and induced mounting and intromissive behavior in males exhibiting idiopathic sexual inactivity [11]. Yohimbine also induced mounting behavior in non-receptive, but not in receptive, steroid treated ovariectomized female rats, and effectively induced copulatory behavior in castrated, non-testosterone treated, male rats 35, 56, and 91 days after castration [26]. This enhancement of sexual motivation is not simply due to an increase in erectile potential, since yohimbine administration to male rats is associated with decrements in erectile reflexes [19,27]. Note, however, that yohimbine has been observed to induce erection in normal humans. In a parametric study, Smith and Davidson demonstrated that the sexual effects of yohimbine are dose-dependent, with higher doses inhibiting copulation (perhaps related to a catatonic state associated with piloerection)[18,19, and FIGURE 1].

The effects of yohimbine on copulatory behavior are apparently due to interaction with α-2-adrenoceptors since other selective α-2-adrenoceptor antagonists exert qualitatively similar effects [2,18,19,28,29] whereas non-selective antagonists do not [2,27-29]. In this regard, we have recently completed a study comparing the effects of rauwolscine with those of phentolamine [29]. In sexually vigorous males, rauwolscine was associated with increased arousal (indicated by decreased ICI and PEI), whereas phentolamine was associated with premature ejaculation (indicated by decreased IF and EL). In sexually naive males, rauwolscine, but not phentolamine, was associated with an increased incidence of intromissive and ejaculatory behavior. Rauwolscine, but not phentolamine, was associated with an increase in mounting behavior after genital desensitization. Finally, rauwolscine pretreatment attenuated the suppressive effects of clonidine, whereas phentolamine did not. The effects of rauwolscine and yohimbine on mounting behavior following genital desensitization are dose-dependent (FIGURE 1). Smith and Davidson [30] examined the effects of yohimbine (1 or 4 mg/kg IP) on mounting behavior after genital desensitization and parameters of copulatory behavior in middle-aged male rats (15 months of age). 1 mg/kg Yohimbine produced increases in mounting behavior in the middle-aged males, but not to levels observed in young males (3 months of age). Conversely, 4 mg/kg was without significant effect in either age group. Fewer middle-aged males exhibited the complete mating pattern, and this

was reversed by 1, but not 4, mg/kg yohimbine. Parameters of copulatory behavior were modified so that 1 mg/kg (but not 4 mg/kg) yohimbine treated males exhibited values close to those seen in untreated young males. In a different study [2] the effects of 0.5 or 2 mg/kg yohimbine on copulatory behavior and penile reflexes were evaluated. Either dose significantly increased the proportion of middle-aged (18 months of age) copulating to ejaculation, but only the 2 mg/kg dose was associated with reductions in ML and IL, and with increases (towards young values) in IF. In reflex tests, yohimbine suppressed erection in young and middle-aged males, in agreement with earlier reports in young males [19,27].

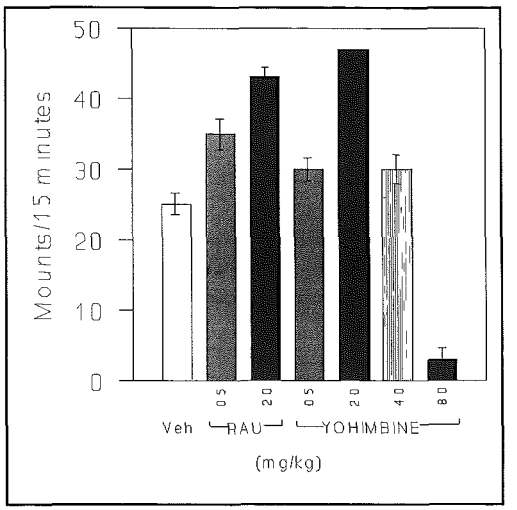

***Figure 1**: Rauwolscine and yohimbine dose-relatedly modify mounting after genital desensitization. High doses of yohimbine are associated with decrements in mounting (N=12-13 per treatment group).*

What are the effects of long-term treatment? Johnson and Diamond [31] reported that treatment with yohimbine (35 days of treatment, 20 mg/kg for 10 days and 10 mg/kg for 25 days) was without significant effect on male rat copulatory behavior, with test duration limited to 10 minutes, during which time few control rats ejaculated. Huhner had earlier cautioned against continuous usage of yohimbine [25]. We evaluated the effects of daily injections of 2 mg/kg yohimbine on mounting behavior and tested different groups of rats 20 minutes after 1, 10 and 21 injections. We observed a decrease in the effectiveness of yohimbine with the increasing number of daily treatments (FIGURE 2).

Where are the relevant α-2-adrenoceptors located? To address this question, we administered clonidine centrally [32], either into the third cerebral ventricle (IIIV) or directly into the medial preoptic area (MPOA). We observed that clonidine effectively suppressed ejaculatory behavior, with MPOA administration effective at lower doses. Further, the effects of IP administration of clonidine were competitively attenuated by unilateral MPOA administration of yohimbine and the effects of MPOA clonidine were prevented by prior IP administration of yohimbine [32]. Intracerebroventricular administration of guanabenz is also followed by an inhibition of ejaculatory behavior. Further support for a CNS site of action comes from the work of Sala et al [33] who demonstrated dose-related prosexual effects of systemic and lateral ventricular administration of yohimbine, and our demonstration that ST-91, a polar analog of clonidine which poorly penetrates the brain fails to modify copulatory behavior following systemic administration [24], but is effective after central administration.

Studies Implicating Epinephrine

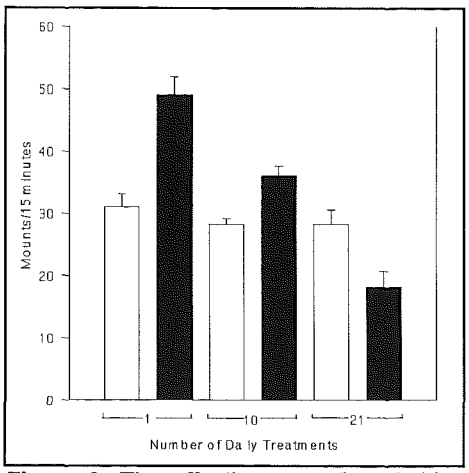

***Figure 2**: The effectiveness of yohimbine decreases with long-term treatment (solid bars represent 2 mg/kg yohimbine 20 minutes prior to testing; N=11-13 per group).*

The data reviewed above implicate *α*-adrenoceptors in sexual behavior in male rats. A state of tonic inhibition via stimulation of *α*-2-adrenoceptors is suggested. What is the endogenous substrate that normally stimulates these receptors? We evaluated the effects of inhibition of dopamine-ß-hydroxylase by diethyldithiocarbamate (DDC, 500 mg/kg IP, 2 hours prior to mating or erectile tests), or of inhibition of phenylethanolamine-N-methyltransferase by 2,3-dichloro-*α*-methylbenzylamine (LY 78335; 50 mg/kg IP, 2 hours prior to mating or erectile tests), on copulatory behavior and penile reflexes in sexually experienced rats [2]. Decreased levels of norepinephrine in the mediobasal hypothalamus [MBH] and preoptic-anterior hypothalamic [PO-AHA] fragments, and increased dopamine levels in the PO-AHA were observed 1 and 2 hours after DDC treatment. DDC treatment also greatly reduced the proportion of males showing any copulatory activity (3/12 DDC versus 12/12 control rats), or displaying erection in ex copula tests (3/12 DDC versus 9/11 controls). Interestingly, seminal plugs were noted (at the time of sheath retraction for observation of erectile reflexes) in half of the DDC treated but none of the control rats. Furthermore, whereas most control males exhibited some facial grooming (9/11) in the ex copula tests, only 1/12 DDC treated rats did so. LY 78335 selectively depleted epinephrine, without altering norepinephrine levels, in the MBH and PO-AHA 2 hours after treatment. Treatment with LY 78335 differentially affected copulatory behavior and penile reflexes. Viz, a slight decrease in the number of rats showing intromissive and ejaculatory behavior (9/12 LY 78335 versus 12/12 controls), but no differences were observed for erectile reflexes ex copula. The rats mating to ejaculation in mating tests begun 2 hours after LY 78335 exhibited prolonged latencies to the initial mount and intromission, and longer intervals between intromissions and following ejaculation. The number of ejaculations in the 30 minute period following the initial intromission was also reduced in the LY 78334 treated rats.

These data provide the first suggestive evidence that epinephrine neural systems may be involved in the CNS regulation of some aspects of male copulation. Administration of epinephrine, either into the IIIV or directly into the MPOA, is followed by a suppression of copulatory behavior similar to that seen with clonidine [2]. A role for epinephrine in the regulation of gonadotropin secretion was initially suggested by Sawyer in 1952 [34]. Later, Hokfelt and colleagues demonstrated the presence of epinephrine-containing pathways in the diencephalon [35]. Later,

additional support for the role of epinephrine in gonadotropin secretion were published [36,37]. The effects of selective depletion of epinephrine, coupled to our observations of the effects of microinjection, provide support for a role for epinephrine, independent of norepinephrine, in the regulation of male sexual behavior.

Studies Implicating Neuropeptide Y

Individual neurons synthesize and secrete multiple neurochemical messengers. Neuropeptide Y (NPY) is a 36 amino acid peptide which is abundant in various regions of the rat brain [e.g., 38]. Brainstem neurons synthesizing adrenergic transmitters demonstrate extensive colocalization with NPY [e.g.,39]. Initial reports on the reproductive effects of NPY indicated that IIIV administration indicated that NPY modified gonadotropin secretion in ovariectomized female rats similar to adrenergic transmitters [20,40,41]. Viz, in steroid treated ovariectomized and in intact male there was an increase in gonadotropin levels, whereas in ovariectomized rats there is a profound decrease in circulating levels of gonadotropins. We reported that doses of NPY which evoked robust feeding produced a dramatic suppression of male rat copulatory behavior following IIIV administration [42]. The majority of rats mounted, fewer intromitted and most failed to maintain copulating until ejaculation. The suppression of ejaculatory behavior was not due to a simple suppression of arousal since those rats that mated initiated copulation with normal latencies. No adverse effects of IIIV administration of NPY on erectile ability were seen in ex copula tests. Thus, the decreased sexual performance of these rats is due to a failure to maintain a sufficient level of sexual arousal to allow for the maintenance of copulation until ejaculation. The suppressive effects of NPY are reminiscent of those seen after clonidine or epinephrine administration (see above), and specificity is inferred since a closely related peptide (rat pancreatic polypeptide) is without effect. It is interesting to note that the effects of NPY on copulatory behavior are evident at lower doses than those required to modify gonadotropin secretion or feeding behavior [20]. The effects of IIIV NPY on feeding are attenuated by prior treatment with yohimbine (as are the effects of epinephrine), but unaffected by prior treatment with either phentolamine or prazosin [43]. The possible effects of prior blockade of adrenergic receptors on NPY-induced changes in copulation have not yet been studied.

Subsequently, we examined the effects of intracerebral microinjections of NPY [2]. Administration of NPY into the MPOA was followed by increased ML and IL, increased EL, decreased CE (increased MF with an unchanged IF), and increased PEI. In contrast, administration into the hypothalamic paraventricular nucleus (PVN) was associated with slightly increased ML and IL, but with a decreased ejaculatory threshold (IF) and a decreased EL. In contrast, microinjection into the lateral preoptic area, or into the hypothalamic dorsomedial or ventromedial nuclei, were without significant effect on parameters of copulatory behavior. Thus, NPY exerts different effects on copulation depending on the site of injection. Global actions on hypothalamic and lower brain regions (as after IIIV administration) leads to profound decrements in the ability to maintain arousal until ejaculation, whereas MPOA actions

are to slow down the behavior and PVN actions are to reduce the amount of stimulation required for ejaculation.

In some preliminary studies, we examined the interactions between the effects of IIIV NPY on feeding and mating. Allowing the male rat simultaneous access to food and a receptive female apparently induced a conflict situation. We observed that the dose-response curve for NPY-induced feeding was shifted to the right when a receptive female was present, irrespective of whether mating actually occurred [2].

What, then are the effects of blocking NPY receptors? Although several NPY receptor antagonists have been proposed, we have only evaluated the effects of benextramine - which is also a nonreversible α-adrenoceptor antagonist. To compensate for this α-adrenoceptor activity we compared the effects of benextramine with those of its parent compound, phenoxybenzamine [2]. Sexually experienced males were treated with benextramine (3 mg/kg, IP, 30 minutes or 24 hours prior to mating tests) or phenoxybenzamine (3 mg/kg IP, 30 minutes or 24 hours prior to mating tests). Benextramine was associated with a selective increase in the copulatory rate (decreased ICI with no major change in IF), whereas phenoxybenzamine was associated with an increased copulatory efficiency. In a subsequent study, we evaluated whether pretreatment with benextramine or phenoxybenzamine would modify the clonidine-induced (250 μg/kg IP, 5 minutes prior to testing) suppression of ejaculatory behavior. As in earlier studies, administration of clonidine was followed by increased ICI and PEI, decreased IF, and a decreased number of males achieving 2 ejaculations. These effects of clonidine were not prevented or attenuated by prior treatment with either benextramine nor phenoxybenzamine. However, clonidine administration reversed the effects of benextramine on the copulatory rate, as well as that of phenoxybenzamine on copulatory efficiency. Thus, blockade of α-adrenoceptors and NPY receptors by benextramine yields qualitatively different copulatory effects than blockade of α-adrenoceptors alone by phenoxybenzamine. Since clonidine reverses the effects of benextramine, some involvement of α-2-adrenoceptors is implied.

We observed an age-related decrease in the number of males copulating to ejaculation, and a moderate systolic hypertension in middle-aged (16-17 month old) rats [44]. NPY content was examined in microdissected brain nuclei in 5 groups of rats: 2 groups of young rats, one heterosexually naive and the other ejaculating in 3 successive mating test; and 3 groups of middle-aged rats, one heterosexually naive, one group that had extensive sexual experience but failed to ejaculate in tests at 16.5 months of age, and the third continuing to ejaculate at 16.5 months of age. NPY levels were found to vary depending on the brain area, the age of the animals, and the maintenance of ejaculatory behavior. In sexually naive middle-aged males, NPY levels were uniformly lower than in younger males. There were no differences in NPY levels of young animals, regardless of sexual experience. In the MPOA, the group that retained ejaculatory behavior through 16.5 months of age, had higher levels of NPY than those observed in young sexually experienced rats. In sexually experienced rats that were no longer ejaculating at 16.5 months of age levels were lower than all other groups except the sexually naive middle-aged group. In the hypothalamic arcuate nucleus, levels were equivalent in the young groups and in the middle-aged rats that retained ejaculatory behavior, being greater than in the middle-

aged rats that were no longer ejaculating or were sexually naive. In the PVN, levels were highest in young rats, lowest in middle-aged rats that were sexually naive or no longer ejaculating and intermediate in the group of rats retaining ejaculatory behavior. In contrast, in the hypothalamic dorsomedial and ventromedial nuclei, there were no significant differences between the 3 middle aged groups. We suggest that as the sexually active rat ages there is a neural site-specific hypersecretion of NPY in an attempt to maintain pituitary-gonadal hormone production and copulatory behavior. Following this there is a decrease in activity of NPY neurons which results in ejaculatory failure. The suggested sexually-relevant source of NPY to the MPOA and the PVN is the NPY-synthesizing cells in the ARC [44].

Studies Implicating Somatostatin

We assessed the effects of MtTW15 (prolactin and growth hormone secreting) tumors, which are associated with copulatory failure in castrated testosterone-treated rats [45], on penile reflexes in gonadally intact males [46,47]. No significant effects were observed in tests 7, 14, or 21 days after inoculation. However, penile reflex activity was essentially absent in tests 35 days after MtTW15 inoculation. In sexually vigorous rats short-term exposure to the tumor (3 to 10 days) was associated with a facilitation of sexual motivation, evidenced by decreases in ICI, EL, and PEI. Conversely, long-term exposure (35 to 49 days) was associated with deficits in copulatory behavior, evidenced by a progressive elongation of ML, IL, EL, ICI, and PEI. Additionally, fewer MtTW15 treated males engaged in any copulatory activity in tests 38 - 49 days after treatment. In ex copula tests, conducted prior to any significant changes in copulatory behavior (28 days after treatment), severe deficits in erectile ability were evident [2]. This last observation leads us to suggest that erectile dysfunction precedes and contributes to subsequent deficits in copulatory performance and finally to decrements in sexual motivation. In rats exhibiting idiopathic sexual inactivity, GH levels were significantly lower than in copulating males. What is the neurochemical basis for the observed antisexual effects of MtTW15-prolactin and GH-secreting tumors? The observation of greatly increased GH in the tumor-bearing rats, coupled to the reduced GH levels in rats exhibiting sexual inactivity - both states are predicted to be associated with increased brain somatostatin - prompted us to measure somatostatin levels in the PO-AHA of these rats. Compared to sexually active males, rats that failed to mate in 20 tests over 10 weeks exhibited increased PO-AHA content of somatostatin. Similarly, rats that were sexually inactive following MtTW15 inoculation exhibited increased PO-AHA content of somatostatin [2].

Somatostatin containing neural elements have been identified in brain areas implicated in the regulation of sexual behavior [48]. Patterns of growth hormone secretion, as well as feedback effects of growth hormone on hypothalamic somatostatin and growth hormone releasing hormone, are sexually dimorphic [e.g., 48-50]. The last observations suggest that somatostatinergic mechanisms may be influenced by gonadal steroids, as is the expression of sexual behavior. Additionally, somatostatin has been reported to co-exist intraneuronally with adrenergic transmitters and NPY [51], which have been implicated in the regulation of sexual

function. NPY has been implicated in the regulation of growth hormone secretion, with a stimulation of somatostatin discharge suggested as the underlying mechanism []. Our observation that somatostatin levels are elevated in rats exhibiting MtTW15-tumor induced and idiopathic sexual inactivity, coupled to these suggestive data prompted us to evaluate the effects of somatostatin on sexual behavior in the male rat. Elevation of brain somatostatin by administration into the lateral cerebral ventricle (LCV) was followed by a minor, dose-related suppression of male sexual behavior [2]. Direct unilateral microinjection of somatostatin into the MPOA (300 or 30 pmol) was followed by a complete suppression of copulation. The effects of MPOA somatostatin are attenuated or prevented by prior systemic administration of yohimbine. In contrast, cysteamine (90 mg/kg, IP) - an agent which effectively depletes hypothalamic somatostatin after stimulating its release - had differential effects, depending upon the time between treatment and testing. Thus, when mating tests were begun 10 minutes after cysteamine, a suppressive effect was observed, evidenced by a decreased number of males achieving intromission and ejaculation. Those rats mating to ejaculation in tests begun 10 minutes after cysteamine exhibited a reduction in ejaculatory threshold (decreased IF). Conversely, in tests initiated 24 hours after cysteamine, a facilitation of some aspects of copulatory behavior was evident (decreased ICI)[2]. These data demonstrate that alterations in sexual behavior are associated with alterations in PO-AHA somatostatin, and that alterations in somatostatin levels are associated with changes in copulatory behavior. Increasing somatostatin is associated with a suppression of copulation, whereas decreasing somatostatin is associated with a facilitatory effect. A major site of action for these sexually relevant effects of somatostatin appears to be the MPOA. The possible utility of somatostatin antagonists to alleviate sexual dysfunction remains to be determined.

Studies Implicating Angiotensin II

Angiotensin II is a biologically active peptide which is of paramount importance in the regulation of fluid balance and blood pressure. Accumulating evidence suggests that this peptide may also be important in the regulation of reproduction [53]. We investigated the effects of IIIV administration of angiotensin II to sexually experienced male rats immediately prior to mating tests, and reported a suppression of copulatory behavior, evidenced by increases in ML, IL, IF, ICI and PEI. The suppression of copulatory behavior was not simply due to a stimulation of drinking [54]. In a subsequent study, we observed that the presence of a receptive female, whether mating occurred or not, served to shift the dose response curve for angiotensin II-induced drinking to the right [2]. Preliminary data from Myers and Steele [55] indicated that blockade of angiotensin II receptors by saralasin has facilitatory effects on copulatory behavior. Angiotensin II effects on luteinizing hormone secretion involves an interaction with α-adrenergic systems since yohimbine pretreatment attenuates the effects of angiotensin II [56]. Whether angiotensin II-adrenergic interactions are involved in the sexual effects of angiotensin II remains to be determined. Long-term treatment with an angiotensin-converting enzyme inhibitor or an angiotensin receptor antagonist is without effect on copulatory

behavior in spontaneously hypertensive rats [57].

Summary and Conclusions

TABLE 1: *Summary of effects on sexual arousal associated with initiation, maintenance or reinitiation in "normal" male rats after acute administration. [+] for initiation is indicated by a reduced ML and/or IL, or in an increased number of mounts in tests after genital desensitization; [+] for maintenance is indicated by a decrease in ICI; [+] for reinitiation is indicated by a decrease in PEI; [-] indicates opposite changes to those indicated by [+]; [0] indicates no change; no entry indicates that the data are not available/applicable.*

	INITIATION	MAINTENANCE	REINITIATION
α-2-Agonists	**0**	**-**	**-**
α-2-Antagonists	**+**	**+**	**+**
α-1-Agonist	**0/-**	**0/-**	**0/-**
α-1-Antagonist	**-**	**-**	**-**
Mixed α-Antagonist	**0**	**0**	**0**
Neuropeptide Y	**-**	**-**	**-**
Somatostatin	**-**	**-**	
Angiotensin$_{II}$	**-**	**-**	
A_{II} Antagonist	**0/+**	**0/+**	**0/+**

We suggest that sexual arousal and performance, and the coordination of these, are differentially modulated by alterations in adrenergic and neuropeptidergic mechanisms. The basal tone of these neurochemical systems is modified by the steroidal hormonal milieu to which they are exposed, to include prior exposure to elevated/reduced levels and the duration/cumulative nature of such hormonal histories. We suggest that α-adrenergic mechanisms play an important role in the regulation of sexual function. We hypothesize that α-2-adrenoceptors located within the CNS, especially the diencephalic medial preoptic area, are "tonically" active in the inhibition of sexuality. This inhibition appears to affect both motivational (or the coordination of motivation with erection) and consummatory (performance or potency) aspects of sexuality. We suggest that changes in adrenergic mechanisms in the medial preoptic area may be involved in sexual dysfunction manifested in conjunction with a variety of disorders [2]. We recognize that other transmitters, especially peptides which colocalize with adrenergic transmitters (Neuropeptide Y, somatostatin, and angiotensin) are also important. Further, the existence of putative transmitters which can stimulate various aspects of sexuality is expected - for a function which is necessary for species survival it would only make sense for the coexistence of excitatory as well as inhibitory mechanisms. Elsewhere in this

symposium, the facilitatory effects of other transmitter systems (dopaminergic and opiatergic, among others) are discussed.

TABLE 2: Summary of effects of adrenergic agents and neuropeptide Y administered to "normal" rats on performance (or ability) aspects of sexual function in male rats. [+] for threshold is indicated by a decreased IF and is, in essence, premature ejaculation. [+] for efficiency is indicated by an increase in CE. [+] for reflexes is an increased incidence of erection ex copula or an increased number of reflexes per test. [-] indicates opposite changes. [0] indicates no observed change in the relevant parameter(s). No entry indicates that the data are not available/applicable.

	THRESHOLD	EFFICIENCY	REFLEXES
α-2-Agonists	+		-
α-2-Antagonists	0/+	0/+	-
α-1-Antagonist	+		-
α-1-Agonist	+	+	-
Mixed α-Antagonists	+	+	-
Neuropeptide Y	0/+	0/+	0

Validated systemic therapy for sexual dysfunction is presently unavailable, but increasing availability of drugs with prosexual effects and knowledge about the neurochemical bases of sexual function gives promise of positive results. At present, with pharmacological intervention it may be possible to restore some aspects of sexual function on an intermittent schedule. The sexual effects of a-adrenergic drugs and selected neuropeptides are summarized in Tables 1 and 2. To date, α-2-adrenoceptor antagonists are the most promising candidates for use as modulators of sexual arousal. Acute administration is associated with attenuation of the sexual dysfunction seen after castration and with aging. However, continuous use is contraindicated. Other treatments are associated with a facilitation of ejaculatory responses [2]. If erectile dysfunction is the primary problem, facilitation of erection in humans can be achieved by intra-penile administration of a variety of agents in man [6], or in rats by chlordiazepoxide [58]. A final caveat is that the sexual effects of pharmacological agents in "normals" may be different those in dysfunctional states.

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Discussion - SEXUAL AROUSAL AND PERFORMANCE ARE MODULATED BY ADRENERGIC-NEUROPEPTIDE-STEROID INTERACTIONS

G. Wagner

I have question about the doses of yohimbine in the studies that you reported. These doses are dramatically larger than those used in the clinic, because you are talking about 2 mg/kg in rats and we are usually talking about 0.1 mg/kg in the human.

J.T. Clark

There is a real problem when one tries to take doses from one species to another. Rats metabolize some drugs more quickly than men, so that the doses are obviously going to be different. One can see effects of clonidine on the erectile function at doses much lower than what one uses in the clinic. One can go down to 5 μg/kg (0.005 mg/kg). The effects on behaviour occur at higher doses. Erectile reflexes seem to be more sensitive. In aging rats, in hypertension, in alcohol use, and in hyperprolactinemia, one first sees a fall off in erectile reflexes, followed later by copulatory changes. One sees changes in erectile potential before one sees changes in blood pressure. An important question that needs to be addressed is what are the effects of clonidine in hypertensive animals as compared with those in normotensive animals?

G. Wagner

Did you say that alpha-blockade shortens ejaculation time in rats?

J.T. Clark

It reduces the number of intromissions that are needed, and associated with that is usually a slight elongation of the time in between intromissions, but ejaculation time is definitely shortened.

G. Wagner

Which is completely opposite to what happens in man because if you have an alpha-blockade you may even completely block the ejaculation. With phentolamine as

well as with phenoxybenzamine you may certainly have an increased latency of ejaculation.

J.T. Clark

Yes, so that is another example of interspecies difference.

S.M. Pomerantz

It seems that all the different alpha adrenergic agents that facilitated male sexual function did so by reducing ejaculation latency. Is that right?

J.T. Clark

They all seem to shorten it, but the mechanism is different. In our lab, yohimbine typically does not alter intromission frequency, or there is only a minor change. What yohimbine does is to make the animal go from intromission to intromission more quickly. They take 5 seconds in between intromissions instead of taking 60 seconds. So what they are doing is having the same number of intromissions with much shorter intervals. Conversely, when you administer an alpha-1-agonist the animals ejaculate with fewer intromissions, but not necessarily with shorter intercopulatory intervals.

S.M. Pomerantz

So then basically what you are saying is that we should consider the effect on copulatory rates and not try to unify in terms of lowering the ejaculatory threshold.

J.T. Clark

A point that we need to make in this meeting is that we need to look at things in more than one way. We cannot say: "the animals don't mate, therefore they cannot" or "ejaculation is facilitated by ejaculation because they ejaculate sooner in the second series". We have to look and see how many intromissions they had, what the interval was, what the pacing is. We need to be able to look at things in a more complex way than simply yes/no.

J. Bancroft

A point that should perhaps be discussed, or explored, refers to continuous, as opposed to intermittent dosage and whether there are pharmacological explanations for why if you give a drug like yohimbine continuously, you lose its effects. As a clinician, I use yohimbine intermittently but I have not any very clear evidence for doing that. I tell my patients to use it just no more than on two or three days in a week and to have gaps in between because my impression has been that you get an effect if you use it intermittently and you lose the effect if you take it continuously.

J.G. Pfaus

Is there any evidence of sensitization to yohimbine when it is given intermittently rather than continuously?

A.J. Riley

There is no evidence of that at all. I use a lot of yohimbine in a PRN short courses, but several workers have suggested that maximum effect comes in after three weeks treatment. I do not particulary believe that.

J.G. Pfaus

There is some evidence with low doses of amphetamine in studies with feeding and lever pressing, for example, in which when it is given continuously, instead of getting sensitization one can actually get a tolerance effect. On the other hand, we see evidence of sensitization to its effects when it is given intermittently, the more space between the doses the better. I wonder if similar mechanisms might be maintaining the of effect yohimbine rather than letting it go.

J. Bancroft

What would be the mechanism?

J.G. Pfaus

Many mechanisms have been suggested. Receptors, activation of glucocorticoids and other systems have been mentioned. There are probably numerous mechanisms

that are coming on line, including increasing dopamine synthesis, allowing more of it to be released, in the case of amphetamine. I do not know what the mechanism might be for yohimbine but I am just wondering if there is any evidence of sensitization that could get us into it.

J.T. Clark

The only thing that I have are some unpublished data from a preliminary dose/response study with yohimbine in rats. I started off with one dose and then went to a lower dose and what I saw was that a lower dose was as effective if they had the higher dose two weeks before, whereas if one used yohimbine in naive animals the lower dose was ineffective. This would suggest a time dependence sensitization. I have also seen similar effects with pimozide and some other drugs. If the animals had had it before and a period had passed they were more sensitive, or they responded as if you had given them a higher dose.

M. Mas

We are taking at face value that yohimbine is just inhibiting alpha2 receptors and thus, increasing noradrenaline release, which is true. But yohimbine also interferes with dopamine and serotonin receptors at some doses.

B.D. Sachs

In the case of males, the term "aphrodisiac" is used in two senses, one is to increase desire and the other is to increase potency. I want to ask the clinicians what they are looking for when they are prescribing yohimbine, is it to promote desire or is it to promote erection, or is it a feedback relation between desire and erection so that there is not much concern about which is being promoted?

A.J. Riley

None of the studies on yohimbine have demonstrated an increase in sexual desire. Where a positive result of yohimbine has been reported it has only been on the erectile function. However, it is obvious that a man that is impotent may well lose desire and if you return him to potency then his desire may return. With yohimbine there has

not been any pharmacological demonstration of increase in desire. With more selective alpha-2 adrenoceptor antagonists we have actually seen an increase in desire.

M. Murphy

In a series of unpublished studies with orally administered idazoxan, which is a selective alpha-2 antagonist we also found no effect on erection. What we did find was enhanced pleasurable penile sensation on tactile stimulation, so we found a sensory effect which may possibly have something to do with the aphrodisiac effect which is linked to these drugs. The other thing we found, which was a fairly small effect, was an increased responsiveness to tactile stimulation in that the penis elongated more after treatment with idazoxan but not amounting to an erection.

K.E. Andersson

I do not think we should discuss yohimbine only as an alpha-2- adrenoceptor blocker because there is an active metabolite which has not been characterized pharmacologically and it might have quite another profile of action. One should expect differences in clinical effects between yohimbine and more selective and stable alpha-2-adrenoceptors.

J. Stewart

What are the measures that you are using to show increases in sexual activity. You are getting increases in mounting. How do you interpret that?

J.T. Clark

We count mounts per 15 minutes, a shorter time is not quite as dependable. Those are mounts in animals that have had their penises swabbed with a local anaesthetic so one has effectively eliminated intromissive and ejaculatory behaviour, and actually eliminated erections in ex-copula tests. Gray and Davidson demonstrated that the number of mounts that one exhibited in that situation was dependent upon the amount of testosterone that they had, in a dose related manner. Our interpretation, through the years, of mounting test data has been that it is an indication of the propensity of the male rat to continue mounting in the absence of any general feedback

and in the absence of any intromission. In fact, even if one does this very carefully, one has a few animals that do gain intromission, and the data from those animals are always eliminated from analysis.

J. Bancroft

Castration has a very widespread effect on most of the systems subserving sexual behaviour, and yet the only evidence that I am aware of a sustained pharmacological effect of reversing castration is with the alpha-2-antagonists. How does this fit in the scheme of things?

J.T. Clark

In a study in rats, I gave yohimbine 35 days after castration and demonstrated an increase in mounting, in intromission, and a slight increase in ejaculatory behaviour. 56 days after castration there was an increase in mounting behaviour and 91 days after castration there was an increase in mounting behaviour. Most people that have studied the effects of drugs in castrated animals have simply looked at a period from 28 to 35 days or so after castration and in that time period many drugs work. I have done some work with RDS-127, which is a dopamine/serotonin drug and people have done work with apomorphine, lisuride, 8-OH-DPAT, and some others. They all work reasonably well in that month after castration period. In the case of apomorphine or RDS-127 after castration that effect is not there 56 days after castration. Two months after castration dopaminergic drugs apparently do not work, but one month after castration many dopaminergic, serotonergic and other drugs work.

B.J. Everitt

I just want to make a comment on mounting post-castration. We made a surprising observation in a study in which we looked at the effects of castration on instrumental behaviour using the second order schedule of sexual reinforcement. When we castrated males we did not want any interference, in terms of the feedback of their impaired copulatory ability, to affect responding. So we castrated two groups of animals, one of which we tested repeatedly, week on week, just to find out when the mounting and the intromitting had completely stopped and then waited a couple of

weeks longer -about eleven weeks in total- before we put the second untested animals into the experiment. To my surprise, when those males gained access to the females they mounted quite a lot. Thus one of the ways in which you can cause mounting to persist in a long-term castrate is by not letting him experience his failing sexual interaction with a female, when he learns gradually of an impairment in his ability to intromit and therefore gives up mounting. I think this interaction of experience with pharmacological manipulations may need to be looked at rather carefully.

J.T. Clark

The idea of experience came up before and I have seen in some studies with aging, castration, and testosterone replacement that aging without intervening sexual experience actually results in a retention of behaviour resembling younger rats than if you let them have sex every week or so, which corroborates what you have been saying. The issue of how experience and abstinence fit into drug effects and the maintenance of behaviour through various crisis or aging or pathologies is an issue that remains to be clarified.

M. Baum

It seems to me that the noradrenergic system has been ignored in the last 15 years because studies back in the 70's and more recently work with self stimulation electrical systems or drugs of abuse has found that destroying noradrenergic systems in the rat brain really has precious little long term consequences. In contrast, in dopaminergic systems one gets very dramatic and reproducible results and as result the whole field is shifted away from that particular line of research. Which raises again interesting questions to point out. If you do see effects of noradrenergic drugs are these not CNS effects but more peripheral effects?

J.T. Clark

If yohimbine is administered unilaterally into the preoptic area it can attenuate the effects of peripheral administration of clonidine. I think that there is clear evidence suggesting that yohimbine does have central effects as far as sexual function goes. They are not totally peripheral.

B.D. Sachs

A few people this morning have alluded to the testosterone dependence of the neurochemical changes that promote sexual activity in males. The sexual activities of long term castrates can be maintained or restored by oestradiol and so I wonder what is known about the neurochemical changes in the wake of oestradiol treatment as opposed to testosterone treatment. It might be that the oestrogen metabolites of testosterone are in fact maintaining these neurochemical changes.

J. Stewart

In studies measuring tissue levels of dopamine after castration, John Mitchell was able to maintain them with oestradiol. But we do not know the response of the dopamine system to sexual stimuli in the absence of testosterone or when testosterone levels are low.

M. Mas

Perhaps it is worth mentioning that prepuberal castration facilitates dopamine release after an injection of amphetamine in adult animals.