Reversal of Fluoxetine-Induced Sexual Dysfunction in Male Rats

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Abstract

The effects of the selective serotonin reuptake inhibitor (SSRI), fluoxetine, were examined on appetitive and consummatory sexual behaviors in the male rats. In a long-term dose response and time course study, male, Long-Evans rats received 0, 1.0, 5.0, or 10.0 mg/kg fluoxetine hydrochloride for 41 days and were tested for copulatory behavior every fourth day in bilevel chambers. Animals demonstrated a rapid inhibition of appetitive behavior, no changes in copulatory efficiency, and a progressive inhibition of ejaculation. The greatest effects occurred at 10.0 mg/kg ip. This pattern of sexual inhibition was similar to the fluoxetine-induced sexual dysfunctions reported to occur in humans. Males then received an injection of the neuropeptide oxytocin (200 ηg ip) or saline vehicle 60 minutes before additional sexual behavior testing occurred in a A-B-B-A design. Animals receiving oxytocin demonstrated an increased number of ejaculations, equal to the frequency displayed at baseline. No increases were observed in appetitive behavior frequencies. In Studies 2 through 4, ritanserin (a 5-$HT_{2A/2C}$ antagonist), yohimbine (an α_2 adrenoceptor antagonist), and mianserin (a mixed 5-$HT_{2A/2C}$ and α_2 adrenoceptor antagonist) were tested for their ability to reverse fluoxetine-induced sexual dysfunctions in male rats. In each of studies 2 through 4, decreases in appetitive sexual behavior and in ejaculations were reliably identified after 10 mg/kg chronic fluoxetine treatment. Animals receiving ritanserin co-treatment (3.2 and 5.4 mg/kg ip) demonstrated significant increases in the frequency of ejaculations and copulatory efficiency, but not appetitive behaviors. Animals receiving yohimbine co-treatment demonstrated increased ejaculation frequency

at the higher dose tested (4.0 mg/kg ip), but not the lower dose (2.0 mg/kg ip). Animals receiving mianserin co-treatment demonstrated increased appetitive behavior at the lower dose tested (1.0 mg/kg ip), but not the higher (10.0 mg/kg ip). Post-hoc analyses revealed a suppression of ejaculation frequency by the high dose of mianserin to a level below that induced by fluoxetine alone. Taken together, these results validate the use of male rats to model fluoxetine-induced sexual dysfunction in humans and suggest that SSRIs may inhibit ejaculation by inhibition of the release of oxytocin. It is suggested that facilitation of oxytocin release may underlie the efficacy of 5-$HT_{2A/2C}$ and α_2 antagonists in reversing SSRI-induced sexual dysfunction. The implications of these findings for treating sexual dysfunction in humans are discussed.

Résumé

Cette recherche est consacrée aux effets de la fluoxétine, inhibiteur sélectif de la recapture de la sérotonine (ISRS), sur l'appétit et le comportement sexuels de rats mâles. Dans le cadre d'une étude à long terme portant sur la dose-réponse et le temps d'absorption, on a administré à des rats mâles Long-Evans 0, 1, 5 ou 10 mg par kilo de fluoxétine chlorhydrate pendant 41 jours et l'on a examiné leur comportement copulatoire tous les quatre jours dans des chambres à deux niveaux. Aucun changement dans l'efficacité copulatoire n'a été observé, mais une inhibition rapide de l'appétit sexuel et une inhibition progressive de l'éjaculation ont été notées. Les effets les plus marqués ont été observés avec la dose de 10 mg/kg. L'inhibition sexuelle est comparable aux dysfonctions sexuelles induites par la fluoxétine signalées chez l'être humain. Les mâles ont ensuite reçu une injection d'oxytocine (200 ng ip) ou une solution saline, 60 minutes avant le déroulement d'autres tests sur le comportement sexuel, selon la méthodologie A-B-B-A. Les animaux à qui l'on avait injecté de l'oxytocine ont éjaculé plus fréquemment, selon une fréquence équivalente à celle enregistrée au départ. Aucune augmentation n'a été observée dans la fréquence des signes d'appétit sexuel. Dans les études 2 à 4, on a évalué l'aptitude de la ritansérine (antagoniste 5-$HT_{2A/2C}$), de la yohimbine (antagoniste alpha 2 adrénergique) et de la miansérine (mélange d'antagonistes alpha 2 adrénergique et de 5-$HT_{2A/2C}$) à inverser les dysfonctions sexuelles induites par la fluoxétine chez les rats mâles. Dans chacune des études 2 à 4, une baisse de l'appétit sexuel et une diminution des éjaculations ont été observées après l'administration de 10 mg/kg de fluoxétine. Chez les animaux à qui l'on avait administré de la ritansérine (3,2 et 5,4 mg/kg ip), on a observé une augmentation

sensible de la fréquence des éjaculations et de l'efficacité copulatoire mais aucune augmentation de l'appétit sexuel. Chez les animaux à qui l'on avait administré de la yohimbine, la fréquence des éjaculations a augmenté à la dose la plus élevée (4 mg/kg ip) mais pas à la dose inférieure (2 mg/kg ip). Chez les animaux co-traités à la miansérine, la dose la plus basse a provoqué une augmentation de l'appétit sexuel (1 mg/kg ip) mais pas la dose la plus élevée (10 mg/kg ip). Les analyses postérieures ont révélé une suppression de la fréquence des éjaculations avec la dose la plus élevée de miansérine à un niveau inférieur à la baisse induite par la fluoxétine seule. Considérés dans leur ensemble, ces résultats valident l'utilité des rats mâles pour modéliser les dysfonctions sexuelles induites par le fluoxétine chez les êtres humains et donnent à penser que les inhibiteurs sélectifs de la recapture de la sérotonine peuvent inhiber l'éjaculation en inhibant l'émission d'oxytocine. L'efficacité des antagonistes 5-$HT_{2A/2C}$ et alpha 2 adrénergiques à inverser les dysfonctions sexuelles induites par les ISRS s'expliquent peut-être par le fait qu'ils favorisent l'émission d'oxytocine. Une analyse de l'importance de ces résultats pour le traitement des dysfonctions sexuelles chez l'être humain fait suite.

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Manuscript-Based Thesis

Faculty of Graduate Studies and Research guidelines for thesis preparation require that the following five paragraphs be reproduced in full in the preface of the thesis.

Candidates have the option of including, as part of the thesis, the text of paper(s) submitted or to be submitted for publication, or the clearly-duplicated text of a published paper(s). These texts must be bound as an integral part of the thesis.

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The thesis must still conform to all other requirements of the "Guidelines for Thesis Preparation." The thesis must include: A Table of Contents, an abstract in English and French, an introduction which clearly states the rationale and objectives of the study, a comprehensive review of the literature, a final conclusion and summary, and a thorough bibliography or reference list.

Additional material must be provided where appropriate (e.g., in appendices) and in sufficient detail to allow a clear and precise judgment to be made of the importance and originality of the research reported in the thesis.

In the case of manuscripts co-authored by the candidate and others, the candidate is required to make an explicit statement in the thesis as to who contributed to such work and to what extent. Supervisors must attest to the accuracy of such statements at the doctoral defense.

Since the task of the examiners is made more difficult in these cases, it is in the candidate's interest to make perfectly clear the responsibilities of all the authors of the co-authored papers. Under no circumstances can a co-author of any component of such a thesis serve as an examiner for that thesis.

Contributions of Authors

The four manuscripts contained in this thesis were co-authored by Dr. Irv Binik, Dr. James Pfaus, and myself. Drs. Binik and Pfaus contributed to these studies in an advisory capacity, helping me to develop, operationalize, and express the ideas presented in these papers. Teofilo Reyes and Susan Theberge assisted in the care and treatment of the animals used in Study 1. Jan Matthews assisted by running the animals for Study 2. Sean Wright provided assistance with the drug preparations and data collection for Studies 3 and 4. Through our joint efforts in the communal maintenance of equipment, animals, and other materials, indirect assistance was provided throughout the project by Soraya Centeno, Anik Jacques, Tod Kippin, Myriam Lavoie, Colleen Manitt, and Mark Wilkins.

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Statement of Original Contribution

Portions of Study 1 were presented at the Twenty-Eighth Annual Conference on Reproductive Behavior, Montréal, Canada in June, 1996 and at the Twenty-Sixth Annual Conference of the Society for Neurosciences, Washington, DC in November, 1996, before its final publication in *Psychopharmacology*. The former presentations represent the first report of an animal model of fluoxetine-induced sexual dysfunction. Study 1 is also the first evidence of the role of oxytocin in SSRI-induced sexual dysfunction and the first attempt to use oxytocin to reverse that dysfunction. Study 2 represents the first attempt to reverse SSRI-induced sexual dysfunction with ritanserin in any species. Studies 3 and 4 represent the first attempts to model in animals the reversal of SSRI-induced sexual dysfunction with yohimbine and mianserin.

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Introduction

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Fluoxetine-Induced Sexual Dysfunction in Humans

The original product literature for fluoxetine (Prozac) claimed that the anti-depressant drug caused sexual dysfunction in fewer than 2% of the patients using it (Physicians' Desk Reference, 1989). In fact, the favorable side-effect profile presented by the selective serotonin reuptake inhibitors (SSRIs) as a class, relative to previous anti-depressants (Cooper, 1988; Stark & Hardison, 1985; Wernicke, 1985) led them to become the most widely prescribed psychoactive substances in history. However, soon after their general release to market, case studies and brief reports began to appear in the literature describing incidences of sexual dysfunction in patients taking fluoxetine (Kline, 1989; Solyom, Solyom, & Ledwidge, 1990). Clinicians that reviewed patient records retrospectively produced estimates of the occurrence of fluoxetine-induced sexual dysfunction of 5% to 16% (Ashton, Hamer, & Rosen, 1997; Herman, Brotman, Pollack, Falk, Biederman, & Rosenbaum, 1990; Musher, 1990; Zajecka, Fawcett, Schaff, Jeffries, & Guy, 1991). However, subsequent reports employing prospective recording of direct interviews regarding sexual side-effects found 34% to 75% of such patients to be experiencing sexual dysfunction (Hsu & Shen, 1995; Jacobsen, 1992; Montejo-González et al., 1997; Patterson, 1993). Similar rates of iatrogenic difficulties were also observed with other SSRIs, such as paroxetine, sertraline, and fluvoxamine (Clayton, Owens, & McGarvey, 1995; Hsu & Shen, 1995; Labbate, Grimes, Hines, Oleshansky, & Arana, 1998; Modell, Katholi, Modell, & DePalma, 1997; Piazza et al., 1997; Reynolds, 1997; Robbe & O'Hanlon, 1995; Zajecka, Mitchell, & Fawcett, 1997).

Most authors attributed this extreme range of estimates to physicians' hesitation to query for sexual concerns and patients' reticence to volunteer them spontaneously. The initial research relied on patients' spontaneous reports of adverse effects, as is common in clinical trials (e.g., Physicians' Desk Reference, 1989; Stark & Hardinson, 1985). In later studies, patients were questioned directly regarding their sexual functioning. In an interesting test of the effect of this methodological difference, Montejo-González et al. (1997) treated 344 patients with SSRIs and recorded any spontaneously reported side-effects. They then questioned patients with an independent survey. Although 14% spontaneously reported them to their physicians, 58.1% of the patients reported sexual side-effects on the survey.

Paradoxically, a handful of case studies have described the opposite effect, a facilitating action of SSRIs on sexual behavior. In the first of these, Modell (1989) reported the case of a 30-year-old female patient who experienced persistent yawning and spontaneous orgasms associated with clitoral engorgement. Balon (1994) reported the onset of sexual obsessions in a 46-year-old woman, and Ellison (1996) described the case of a 50-year-old woman who experienced orgasms induced by exercise, yet the delay of orgasm during purposeful sexual activity. Pro-sexual effects of fluoxetine have also been reported in men. Morris (1991) reported the case of a 69-year-old, diabetic patient in treatment with fluoxetine after suffering two strokes. The patient indicated that he spontaneously experienced, two to four times per day, a tingling of the genital skin, independent of penile erection and ejaculation. Garcia-Campayo, Sanz-Carrillo, and Lobo (1995) reported a similar case, wherein a 69-year-old man experienced pleasant, genital,

tingling sensations, but not penile erection. Smith and Levitte (1993) described three men, each with long-standing erectile dysfunction, for whom fluoxetine appeared to facilitate erections, either during sexual stimulation or nocturnal penile tumescence. These effects may also be associated with other SSRIs, as spontaneous orgasm was reported in a man taking venlafaxine (Ravsten, Smith, & Thatcher, 1997).

No controlled, prospective reports with larger samples have been published to substantiate these observations. In addition, given the very large number of people who are prescribed SSRIs, unexpected or sporadic somatic changes cannot be easily attributed to their medication. It therefore remains unclear whether such effects are very rare or an artifact of some other factor.

Although sexual dysfunction can be mistakenly labeled a single side-effect, pharmacological agents frequently alter only particular aspects of sexual response (Crenshaw & Goldberg, 1996). SSRIs appear to interfere most potently with ejaculation/orgasm, less so with sexual desire, and still less with sexual arousal (erection/lubrication). Of the cases reported by Herman et al. (1990) and by Zajecka et al. (1991), all spontaneously presented delayed orgasm as the primary side-effect. The patients did not present with other sexual dysfunctions. Seventy-five percent of the sample described by Patterson (1993) also reported anorgasmia. However, that author did not indicate whether patients were also queried regarding other types of sexual dysfunction. Of the 59 fluoxetine patients in the case review by Ashton et al. (1997), 59.3% experienced orgasmic dysfunctions, 30.5% experienced desire dysfunctions, and 10.2% experienced arousal dysfunctions. The other SSRIs tested, paroxetine ($n = 60$),

sertraline ($n = 23$), and venlafaxine ($n = 15$), produced the same proportions of sexual dysfunction as did fluoxetine.

Several recent reports that used fixed batteries of prospective questions specifically regarding sexual functioning confirmed that ejaculation/orgasm was most affected, followed by sexual desire, followed by arousal dysfunction. Zajeka et al. (1997) developed and administered the Rush Sexual Inventory, asking patients to disclose any changes occurring in each phase of their sexual responses. Male patients on SSRI medication most frequently endorsed "loss of ability to reach orgasm," "delay in achieving orgasm," "decreased intensity of orgasm," and "required more stimuli than usual to maintain an erection." However, significant effects were not detected with regard to other items investigating sexual desire or physiological arousal. Modell et al. (1997) similarly administered a set of five visual analogue scales on which subjects indicated changes, if any, in "libido," "arousal," "time to orgasm," "duration of orgasm," and "intensity of orgasm." In each of the SSRI groups tested—fluoxetine, paroxetine, and sertraline—the greatest changes occurred in the "time to orgasm" category. Administering the Arizona Sexual Experience Scale to a sample of 11 men using sertraline or paroxetine, Piazza et al. (1997) also identified significant reductions in the items, "ease of orgasm" and "orgasm satisfaction," but not the items "psychological arousal" or "physical arousal." However, a trend toward significance was detected in the "sex drive" item.

Montejo-González et al. (1997) conducted the largest and most methodologically advanced study of the pattern of SSRI-induced sexual dysfunctions. A diverse group of patients prospectively received a sexual functioning questionnaire before, during, and after

SSRI treatment. Subjects who experienced sexual dysfunction prior to beginning treatment were excluded. Of the 160 patients using fluoxetine: 48.1% reported a decrease in libido; 51.1%, a delay in orgasm or ejaculation; and 34.4%, anorgasmia. Fewer patients, 16.2%, reported erectile dysfunction or female arousal dysfunction. The effects of the other SSRIs, paroxetine, fluvoxamine, and sertraline were similar. The single significant difference between drugs was increased anorgasmia and erectile dysfunction/arousal dysfunction associated with paroxetine, relative to the other SSRIs.

Jacobsen (1992) also attempted to catalog the types of dysfunction that male patients experienced. Unfortunately, that report provided changes only in patients' "libido" and "sexual response." It is not clear from the report whether 'sexual response' referred to penile erection, ejaculation, or both.

In some situations, the delay of ejaculation caused by fluoxetine and the other SSRIs would be better given the more neutral term *feature*, rather than side-effect. Men presenting to clinics with premature ejaculation experience the delay of orgasm as a substantial benefit. Exploration of the use fluoxetine to treat premature ejaculation has led to clinical trials specifically for its use in that purpose. In the first double-blind trial, 17 men with premature ejaculation were prescribed 20 mg daily fluoxetine for one week followed by 40 mg daily afterward (Kara, Aydin, Agargun, Odabas, & Yilmaz, 1996). The subjects and their wives recorded the latency to ejaculation after vaginal penetration. Mean latency increased from a baseline of 25 seconds before treatment to 180 seconds after one week of treatment. The placebo group did not change significantly from its baseline of 30 seconds. In a second double-blind study with fluoxetine in a cross-over

design (Haensel, Klem, Hop, & Slob, 1998), a combined group of 18 men with premature ejaculation either with or without co-morbid erectile dysfunction experienced a significant increase in ejaculatory delay. Kim and Seo (1998) also attempted a double-blind trial, comparing four weeks of treatment with fluoxetine, sertraline, clomipramine, and placebo in a cross-over design with 53 subjects. Although each of the three active drugs were associated with substantial increases in ejaculation latency, a delay was also associated with the placebo. Although a washout period of one week was used between each treatment, the cellular or neurological effects of chronic SSRI treatment may be substantially longer. Haensel's successful design employed a four-week washout period between drugs rather than one week. Success in treating premature ejaculation has also been reported in double-blind trials of paroxetine (Waldinger, Hengeveld, & Zwinderman, 1994, 1997) and sertraline (Mendels, Camera, & Sikes, 1995), utilizing independent groups designs.

Although studies of SSRIs for premature ejaculation provide important information regarding the role of 5-HT in male sexual function, caution must be applied in their clinical use. Direct comparisons between pharmacological and behavioral or psychotherapeutic interventions have not yet been reported. Nor has the long-term efficacy of the SSRI approach to treating premature ejaculation been established. In fact, the current data indicate that the treatment benefits are lost after discontinuation of the drug. Although this substantiates the chemical role of SSRIs in ejaculation, it also indicates that the drug might require life-long use to control the symptoms.

The reduction of sexual motivation induced by fluoxetine may also be of therapeutic use in some circumstances. The literature contains a number of single case and small group studies describing fluoxetine treatment of several paraphilias, including pedophilia, exhibitionism, voyeurism, frotteurism, and compulsive masturbation (Biachi, 1990; Bourgeois & Klein, 1996; Emmanuel, Lydiard, & Ballenger; Kafka, 1991a, 1991b, 1992; Kornriech, Den Dulk, Verbank, & Pelc, 1995; Lorefice, 1991; Perilstein, Lipper, & Friedman, 1991). Similar claims of efficacy have been made regarding clomipramine, fluvoxamine, sertraline, and paroxetine (Abouesh & Clayton, 1999; Greenberg, Bradford, Curry, & O'Rourke, 1996; Rubenstein & Engel, 1996; Zohar, Kaplan, & Benjamin, 1994).

The simplest explanation for the reduction of paraphilic symptoms during SSRI treatment is that the reuptake inhibitors decrease sexual desire globally, thus reducing paraphilic desires along with all other sexual interest. In contrast with this hypothesis, some case studies claimed that patients' attractions to typical (non-paraphilic) sexual stimuli actually increased during treatment (reviewed in Fedoroff, 1993). However, because of the social unacceptability, even illegality, of enacting many paraphilic desires, those patients may be responding to their own desire for a complete cure or demand characteristics, rather than a genuine increase of non-paraphilic sexual desire. That is, many paraphilic patients, such as voyeurs and exhibitionists, receive treatment under pressure from legal authorities or family members. This may lead them to exaggerate the self-reported benefits from any treatments attempted. Although Stein et al. (1992) failed to find any effect of even high doses of fluoxetine in a group of five paraphilics, authors reviewing this literature unanimously declare the need to proceed to conduct double-blind

studies (Abel, Osborn, Anthony, & Gardos, 1992; Balon, 1998; Bradford & Greenberg, 1996; Fedoroff, 1993; Gijs & Gooren, 1996). Given the severe social sanctions associated with many paraphilic behaviors, only highly rigorous methods would disambiguate actual change from feigned or exaggerated treatment responses.

Serotonin-based treatments of paraphilic behavior would represent a substantial contribution to the management of pedophilic and other paraphilic patients. As reviewed by Greenberg and Bradford (1997), surgical castration is ethically untenable by most standards. Hormonal and anti-androgen treatments produce substantial side-effects which limit compliance, especially among adolescent sex offenders. However, SSRI use is reversible, offers fewer side-effects, and is safer for prolonged use. Because sex offenders are more likely to select SSRI treatments over the endocrinological treatments currently available (Fedoroff, 1995), increased compliance of paraphilic sexual offenders may result.

Despite the multiplicity of clinical phenomena impacted by fluoxetine-induced sexual inhibition—iatrogenic sexual dysfunction, premature ejaculation treatment, and paraphilic symptom reduction—little is known regarding the mechanism through which fluoxetine exerts its anti-sexual effects. Authors reviewing the SSRI-induced sexual dysfunction literature speculate that the effect is related to increased brain serotonin levels (e.g., Gitlin, 1994), reflecting both fluoxetine's neurochemical action to increase extracellular 5-HT and the animal data suggesting an inhibitory role of 5-HT in sexual behaviors. Reviews of SSRIs for premature ejaculation also attribute the cause to a relationship between 5-HT transmission and ejaculation (Balon, 1998; Metz, Pryor, Nesvacil, Abuzzahab, & Koznar, 1997). However, although they note that different

anti-depressants demonstrate different 5-HT receptor specificity profiles, neither Balon nor Metz et al. suggest any specific mechanism for the effect. Discussions of the use of SSRIs to treat paraphilias also lack a theoretical underpinning of the mechanism. Although some writers speculate that paraphilia results from monoaminergic dysregulation (Kafka, 1997), or, more specifically, a serotonergic dysregulation (see Gijs & Gooren, 1996 for a review), most instead discuss whether the data support the re-classification of paraphilias as OCD- or affective-spectrum disorders (Abouesh & Clayton, 1999; Greenberg, Bradford, & O'Rourke, 1996; Stein et al., 1992). In fact, the very application of SSRIs for the treatment of paraphilia has been described as altogether serendipitous (Fedoroff, 1993, 1995).

Serotonin and Sexual Behavior

Speculations about the function of SSRIs and serotonin receptors in human sexuality are derived largely from pharmacological studies in animals.

Waldinger and colleagues (Waldinger, Berendsen, Blok, Olivier, & Holstege, 1998) proposed a theory of the roles of 5-HT receptor subtypes in premature ejaculation. They noted that stimulation of 5-HT_{1A} receptors causes an acceleration of ejaculation while stimulation of 5-HT_{2C} receptors causes a delay. They speculate that premature ejaculation is therefore caused by hypersensitive 5-HT_{1A} and hyposensitive 5-HT_{2C} receptors. However, this conclusion is a logical error of affirming the antecedent. That is, that 5-HT_{1A} stimulation accelerates ejaculation in animals (including humans) does not necessarily imply that already prematurely ejaculating animals must have had over-stimulated 5-HT_{1A} receptors.

Greenberg and Bradford (1997) also implied a dysregulation of the serotonin system as the basis of paraphilia. Unfortunately, their review mischaracterized the role of 5-HT receptors in sexual behavior, writing that "In the male rat 5-HT_{1A} and 5-HT_{1C} receptors inhibit sexual behavior, while 5-HT_2 probably facilitates it (Mendelson & Gorzalka, 1990)" (p. 352). Mendelson and Gorzalka (1990) and a large body of additional research show that 5-HT_{1A} receptors facilitate ejaculation and while 5-HT_{1C} (renamed 5-HT_{2C}) and 5-HT_2 (renamed 5-HT_{2A}) receptors inhibit copulatory behavior in males rats. However, no direct tests of these possibilities have been tested either in animals or humans.

Drawing both from the animal literature and human psychopharmacological literature, Segraves (1989, 1995, 1998) highlighted the complexity of the 5-HT system, but identified the most plausible hypotheses regarding 5-HT interactions with other neurotransmitter systems to produce SSRI-induced anorgasmia. He noted the effect of 5-HT_2 (renamed 5-HT_{2A}) receptor stimulation to inhibit ejaculation, and hypothesized that this occurs through their inhibition of the peripheral noradrenergic fibers of the reproductive nerve tracts. SSRIs cause anorgasmia, he concluded, by stimulating the central 5-HT_2 receptors. However, these specific interactions await direct verification.

Existing Reversal Strategies

The reversal of fluoxetine-induced sexual inhibition can shed light on the relevant mechanisms as well as provide both immediate and potential future clinical implications. Successful reversals using neurochemically specific substances evidence the involvement of specific receptor classes, providing clues regarding the mechanism through which SSRIs

exert their effects. Clinically, for patients who experience the inhibition of sexual behavior as iatrogenic, reversal represents an improvement in quality of life. Given that SSRIs are prescribed, not only for depression, but also for obsessive-compulsive disorder, panic disorder, bulimia nervosa, personality disorders, and other problems (Coccaro, 1998; Goldbloom et al., 1997; Gorman, 1997; Gunasekara, Noble, & Benfield, 1998; Pigott & Seay, 1999), large numbers of patients would benefit from the development of such treatments. In patients for whom sexual inhibition is beneficial, clarification of the mechanism of action may lead to improved interventions. For example, current treatment protocols for premature ejaculation generally recommend medication either daily or several hours in advance of sexual activity. The development of a pill which could be taken only as needed would increase compliance and therefore efficacy. An increased potency of the pharmacological management of sexual offenders would provide substantial social benefit, obviating the more controversial interventions, noted above.

Several strategies have been tested in humans for their ability to reverse the sexual dysfunction induced by SSRIs, yielding mixed success. These have included reduction of dosage, drug holidays (Rothschild, 1995), awaiting tolerance (Ashton & Rosen, 1998), and discontinuation of SSRI treatment in lieu of treatment with a different anti-depressant (for a review of clinical management recommendations, see Assalian & Margolese, 1996; Gitlin, 1995; Segraves, 1995). However, the most widely examined alternative has been an antidote strategy. The two most frequently studied potential antidotes are cyproheptadine, a 5-$HT_{2A/2C}$ antagonist with anti-histaminergic properties, and yohimbine, an α_2 antagonist. Although these drugs appear to reduce the sexual

side-effects for many patients, some reports indicate that the original symptoms return or that altogether new, more severe side-effects begin.

A number of case studies have been reported using cyproheptadine to reverse SSRI-induced anorgasmia. McCormick et al. (1990) reported the remission of anorgasmia in two men suffering from fluoxetine-induced sexual dysfunction. The same observation was made of an additional three male patients by Feder (1991), and of one by Cohen (1992). McCormick noted the possibility that cyproheptadine might reverse the anti-depressant effect of fluoxetine, and Feder reported that, indeed, depression did return in each of his three patients. Goldbloom and Kennedy (1991) prescribed cyproheptadine to reduce the anorgasmia in two bulimic patients using fluoxetine. Those authors noted that, although sexual functioning normalized in one patient, both patients suffered the return of the bulimic symptoms. Aizenberg, Zemishlany, and Weisman (1995) reported mixed success in seven male patients taking either fluoxetine, fluvoxamine, or clomipramine (a tricyclic antidepressant with relative specificity for serotonin). Three of the patients experienced improvement in sexual functioning; the remaining patients reported either no improvement or transient improvement. Additionally, all patients complained of experiencing sedative effects after cyproheptadine treatment. Arnott and Nutt (1994) successfully applied cyproheptadine to reverse the fluvoxamine-induced anorgasmia in a 63-year-old male patient without deterioration of affective state.

In the only sizable study seeking to alleviate SSRI-induced sexual dysfunction, Ashton, Hamer, and Rosen (1997) reviewed 596 case files, identifying those patients who were treated with SSRIs, subsequently presented with sexual dysfunction, and then began

co-treatment to combat the side-effect. A total of 16.4% of SSRI-treated patients reported experiencing sexual dysfunction. As the authors themselves noted, this relatively low frequency likely underestimates the actual prevalence of dysfunction because their patients were asked to report sexual side-effects together with other side-effects. Asking patients specifically about sexual side-effects, as in the other studies noted above, would likely have identified more such subjects. Of the affected individuals, 25 attempted cyproheptadine co-treatment. "Much improvement" was reported by 40% of them, while "some improvement" was claimed by 8%, and "no change or worse," by 52%. Adverse affects of cyproheptadine co-treatment included sedation and weight gain. However, no relapses of depression or other psychopathology were observed.

Jacobsen (1992) treated nine patients experiencing fluoxetine-induced sexual dysfunction with yohimbine on an open-trial basis. Formal data analyses were not conducted, but four patients reported a "good" response, four reported a "fair" response, and one, a "poor" response. However, patients also commonly indicated experiencing anxiety and nausea, as adverse effects. At least two patients discontinued yohimbine co-treatment. Unfortunately, the low *n* of this study obviated any analyses of which dysfunction responded best to yohimbine. In the Ashton et al. (1997) study, 21 patients attempted co-treatment with yohimbine. A majority of those, 71.4%, indicated experiencing "much improvement" on the drug, while 9.5% indicated "some improvement," and 19.1% reported "no change or worse." No data were reported differentiating the effects of yohimbine in the different dysfunctions. Adverse effects included agitation, leading three of the 21 patients to discontinue yohimbine co-treatment.

Although these results are suggestive, few firm conclusions can be drawn. Large-scale, placebo-controlled studies with cyproheptadine or yohimbine have yet to be conducted. Although the Ashton et al. (1997) study provided a sufficiently sized sample, only a low proportion of its patients reported experiencing SSRI-induced sexual dysfunction. Therefore, the results of yohimbine and cyproheptadine co-treatment may reflect an atypical subgroup within it. Prospectively selected samples of patients, interviewed with standardized measures of sexual functioning and psychopathology, are still required to assess both the efficacy and any additional side-effects of cyproheptadine and yohimbine.

In general, even the well-validated treatments have been attempted only haphazardly, without substantial consideration or exploration of the neural mechanisms underlying their effects. The selection of other potential pharmacological treatments or co-treatments has been limited to compilations of clinical anecdotes and single case studies. A more concerted effort, based on advancing the known neurochemical basis of sexual behavior, may produce more effective treatments and the identification of the affected components of the male sexual response system.

Modeling Human Male Sexual Behavior in the Rat

The elucidation of the mechanism through which fluoxetine alters sexual behavior and the development methods to either prevent or augment it can be facilitated by the use of appropriate animal models. Testing in animals would serve as a screen for potential pharmacological and behavioral treatments for the dysfunction. Clues regarding the biological basis of sexual function and dysfunction can be explored with neurochemically

specific substances which cannot be administered safely to humans. Additionally, the screening of new pharmacological agents may assist in the prediction of iatrogenic sexual dysfunction. Indeed, had such dysfunction been explored in animals as a matter of course, fluoxetine's side-effects would have been detected before its own clinical trials began.

Understanding rat models of SSRI-induced male sexual dysfunction requires understanding the species-typical copulatory pattern of male rats. In the experiments which follow, except where otherwise noted, the male rats' sexual behaviors have been operationalized with the criteria originally set forth by Sachs and Barfield (1976), summarized below.

The male rat copulatory pattern, both in nature and in the laboratory, consists mainly of a series of discrete behaviors: mounts, which may occur either with or without the intromission of the penis into the vagina, and ejaculation. The male is said to mount the female when he approaches her from behind, palpates her flanks with his forepaws, and rapidly thrusts his hindquarters. A receptive female will typically respond to the flank palpation by demonstrating lordosis, the dorsiflexion of her spine, which exposes her genitalia to the male. When the male successfully intromits during a mount, he demonstrates a characteristic deep pelvic thrust and a springing dismount. For brevity, *intromission* refers to a mount which includes an intromission, while *mount* refers to a mount without vaginal intromission. The ratio of intromissions to mounts plus intromissions (ie., I / M + I) is frequently labeled the *hit rate*; a term which may be better understood should a mount be considered to be 'a failed attempt at intromission'. However, to avoid unnecessary anthropomorphizing, the present discussions employ the

more simply descriptive term, *intromission ratio*. When the male accumulates sufficient penile stimulation through repeated intromissions, he ejaculates, completing a single ejaculatory series. During a post-ejaculatory interval of approximately five minutes, the male grooms himself, rests, and is unresponsive to further solicitation from female rats. Additional ejaculatory series follow the first, each consisting of the same pattern of behavior until sexual satiety occurs, typically after 4-6 ejaculations.

In the laboratory, animals are tested in transparent cages permitting the direct observation of both the male's and female's behaviors. Because rats copulate in bouts of behavior, the rate of which is paced by the female's solicitations and rejections of the male, specialized test chambers have been developed. These have included bi-level cages which provide the female a continuous path or platform by which to evade the male (Mendelson & Gorzalka, 1987; Pfaus, Mendelson, & Phillips, 1990) and multi-chamber cages throughout which only the female is permitted to travel freely (e.g. Emery, & Moss, 1984; Gilman, Mercer, & Hitt, 1979). These environments permitted the female to escape the male which she could not do in smaller, uni-chamber cages.

Soon after its development, the bi-level arrangement was recognized to have an additional attribute. When introduced to the testing cages and permitted to copulate with receptive females, male rats come to demonstrate heightened motor activity when placed in the cages on subsequent test sessions (Mendelson & Pfaus, 1989). The level of motor activity, operationalized by the frequency of his level changes, is generally interpreted as a measure of pre-copulatory excitement (see also van Furth & van Ree, 1996a, 1996b).

These behaviors—mounts, intromissions, ejaculations, and the motor excitement reflected by conditioned level changes—comprise the standard sexual parameters of male rats in the laboratory. The frequency of their occurrences and the latency to the first display of each behavior can be quantified and analyzed after various pharmacological, surgical, or environmental manipulations are employed.

Animal models of some behaviors, such as aggression or feeding, are relatively transparent, exhibiting direct association with human behavioral equivalents. However, the species-specific behaviors of other domains, such as depression and reproduction, permit only indirect mapping between the human and non-human activities. For example, the rat's recurrent series of discrete mounts and intromissions have no obvious equivalent among human heterosexual behaviors; human penile-vaginal copulation provides continuous, rather than discrete, genital stimulation. Yet, a concise organization of the sexual behaviors of both species along parallel lines is provided by the Incentive Sequence Model of sexual behavior (Pfaus, 1996, in press), which highlights the behavioral homologies between them.

The Incentive Sequence Model adopts the division of motivated behavior into appetitive and consummatory phases, as proposed by comparative psychologists (Beach, 1956). The *appetitive behaviors* are those which occur before the subject comes into contact with its objective: quantities of food or water, a sexual partner, etc. After contact is made with the incentive object, the subject demonstrates *consummatory behaviors*, the utilization of the goal to satisfy its appetite. A third set of behaviors is comprised of the subset of appetitive behaviors which are displayed after the subject has already come in

contact with its sexual objective. These areas of male sexual behavior can be visualized with partially overlapping areas in a Venn diagram (Figure 2).

Appetitive behaviors include both the preparatory and anticipatory activities in which the subject engages before coming into contact with the incentive object, in this context, a sexual partner. *Preparatory activities* are those which bring the subject closer to its objective; these either permit or facilitate direct sexual contact. For humans, preparatory sexual behaviors vary widely with culture and circumstance and may include attendance at social functions, courtship, payment, marriage, or, in some cases, stalking and coercion. For other animals, several paradigms have been developed in which pressing bars, crossing electrified grids, and other actions result in access to receptive partners. In both species, situations and interventions which decrease sexual appetite decrease the frequency of these appetitive behaviors. For example, hypogonadal men and surgically castrated laboratory animals both demonstrate less appetitive behavior (Bancroft, 1989; Stone, 1939). *Anticipatory activities* are those which are associated with sexual arousal and desire, but do not necessarily affect the subject's access to its sexual goal. For humans, sexual fantasy and psychomotor excitement are examples. For other animals, increased motor activation, such as a heightened frequency of conditioned level changes, is detected.

The consummatory phase of sexual behavior is characterized by the subject being in physical contact with its sexual objective, permitting direct physical stimulation. In human males, the behaviors of this phase include sexual intercourse, masturbation,

orgasm, and ejaculation. In male rats, these include their own species-specific copulatory behaviors: mounts, intromissions, and ejaculations.

To summarize, for the purposes of interpreting the results of the experiments presented herein, the following homologies are applied (refer also to Appendix B). The frequency of conditioned level changes shown by male rats represents human male sexual interest or anticipatory excitement. Dysfunction of the penile erectile response in the male rat results in his inability to intromit while mounting, and is therefore detectable as a decreased intromission ratio. Ejaculations and the latency to ejaculation demonstrated by male rats are more directly homologous to those in the human male.

Animal models possess many methodological advantages to offer the empirical study of human sexuality. Conventional moral standards typically obviate direct observation of human sexual behavior. This limits the sources of data to self-reported activities, cognitions, and emotions together with the attendant biases associated with retrospective reporting (e.g., see Catania, 1999). Error would be substantially reduced in variables, such as ejaculatory latency, were they objectively measured rather than subjectively recalled.

The testing of behavior in randomly-assigned groups of animals also eliminates the confounds presented by pre-morbid psychological and psychiatric conditions, generally associated with clinical research in humans. As noted above, the first men and women suffering fluoxetine-induced sexual dysfunction were taking the SSRI to treat depression, and depression itself is associated with sexual dysfunction. The effects of the drug were therefore indistinguishable from those of the initial illness. However, the induction of the

homologous effect in otherwise healthy animals would support the direct, pharmacological hypothesis of low sex drive over the co-morbid depression hypothesis.

The comparison of randomized groups of animals also eliminates the effects of self-selected sampling. The sexual behavior of men can only be tested *in vivo* when they have sexual partners. It is seldom known how the severity of the initial disease (depression, obsessive-compulsive disorder, borderline personality disorder, etc.) confounds relationship status, drug dose, and other variables.

Studies of iatrogenic sexual dysfunction and the proposed treatments in humans typically lack appropriate control groups. Since the medications in question are administered to populations requiring an already established, effective, pharmacological treatment, withholding the treatment to form a control group would be unethical. Animal testing is not so constrained.

Although animal models of human behavior and psychopathology escape these methodological problems, they posses their own short-comings. The greatest disadvantage remains the limitation of generalization across species. As is true with other psychological tools for predicting behavior (such as cognitive tests, observation of behavior in the laboratory situations), all predictions must ultimately be borne out by application in actual, human, clinical samples.

It is worth emphasizing that the goal of an animal model is to predict human behavior. Although it is the predictive validity which drives the animal modeling of any behavior, many researchers frequently rely only on face validity. However, as noted by Willner (1991), "Animal models are tools for our use: They are not developed as part of a

beauty contest, with a prize for the most [a priori] convincing" (p. 1). That is, if manipulations of an animal model correlate with and predict clinical efficacy, then its intuitiveness holds little import of its own.

Successful animal testing may, however, suggest solutions. As one such example, Nelson, Keck, and McElroy (1997) successfully treated sexual dysfunction in a woman by prescribing granisetron, a drug normally used to treat radiation-therapy-induced nausea. Those authors embarked on their single-case experiment based on the data from female animals suggesting a pro-sexual effect of 5-HT_3 antagonists, the class to which granisetron belongs.

Rationale and Objectives

The involvement of 5-HT in human sexual behavior is consistent with the data from the animal literature. However, such explanations beg the question. They fail to elucidate any particular mechanism through which 5-HT might exert its inhibitory effect and do not account for the lack of similar, widely-observed side-effects of the tricyclic anti-depressants, which also block 5-HT reuptake. Nor, given the complexity of the 5-HT system, does the hypothesis predict the relative involvement of any particular 5-HT receptor subtypes. Nor does the hypothesis differentiate the effects of acute versus chronic fluoxetine treatment, each of which is associated with distinct neurochemical effects on the brain.

The goal of the present body of work has been to develop an animal model of fluoxetine-induced inhibition of male sexual behavior and to test specific hypotheses regarding the mechanism through which that inhibition occurs. In Study 1, an animal

model was developed, demonstrating that the sexual behavior of male rats responds to chronic fluoxetine treatment in a manner analogous to human males. Study 1 also explored the hypotheses that the inhibition of sexual behavior is related to the inhibition of oxytocin release, and that exogenously administered oxytocin is sufficient to reverse the anti-sexual effects of fluoxetine. Study 2 replicated the findings regarding chronic fluoxetine use and examined the involvement of 5-$HT_{2A/2C}$ receptors by attempting a reversal of the fluoxetine-induced effects with ritanserin, an antagonist with selective affinity for those receptors. Study 3 investigated the ability of yohimbine, an α_2 adrenoceptor antagonist, to reverse the anti-sexual effects of chronic fluoxetine in rats. Some preliminary attempts have been made with human patients to treat fluoxetine-induced sexual dysfunction. Study 4 explored the use of mianserin to reverse the dysfunctions. Mianserin is an antidepressant which antagonizes both 5-$HT_{2A/2C}$ receptors and α_2 receptors.

Chronic Fluoxetine Inhibits Sexual Behavior in the Male Rat: Reversal by Oxytocin

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ORIGINAL INVESTIGATION

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Chronic fluoxetine inhibits sexual behavior in the male rat: reversal with oxytocin

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Abstract *Rationale:* Selective serotonin reuptake inhibitors, used widely in the treatment of depression, progressively inhibit sexual orgasm in many patients and induce a transient inhibition of sexual desire. *Objectives:* We attempted to model the effects of these drugs in sexually experienced male rats during tests of copulation in bilevel chambers. These chambers allow the study of both appetitive and consummatory sexual responses of male rats. *Methods:* Males were treated daily with fluoxetine hydrochloride (0, 1, 5, or 10 mg/kg) and tested for sexual behavior with receptive females at 4-day intervals. Rats were treated with oxytocin (200 ng/kg) or saline after ejaculations had decreased. *Results:* Fluoxetine decreased ejaculatory responses of male rats in a dose- and time-dependent fashion, but left the copulatory efficiency of the males intact. In contrast, conditioned level changing, a measure of appetitive sexual excitement, was inhibited following acute and chronic treatment with 10 mg/kg, although tolerance may have developed to the effect of 5 mg/kg. Subsequent administration of oxytocin restored the ejaculatory response but not the measure of sexual excitement to baseline levels. *Conclusions:* The reversal by oxytocin of the fluoxetine-induced deficit in ejaculations is consistent with the hypothesis that serotonin suppresses ejaculatory mechanisms by interrupting the action of oxytocin, which normally accompanies sexual behavior. Co-administration of oxytocin may help to alleviate the predominant sexual side effect of serotonin reuptake blockers.

Key words Sexual behavior · Ejaculation · Male rat · Drug · Serotonin · Neuropeptide

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Introduction

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) in widespread clinical use, induces anorgasmia and loss of sexual desire in humans (Crenshaw and Goldberg 1996). Clinical reports indicate orgasm dysfunction in up to 75% of patients (Herman et al. 1990; Zajecka et al. 1991; Patterson 1993) and hypoactive sexual desire in 20–40% (Solyom et al. 1990; Jacobsen 1992; Modell et al. 1997). In fact, fluoxetine has been shown to be an effective means of increasing ejaculation latency in premature ejaculation (Kara et al. 1996; Lee et al. 1996) and of decreasing sexual desire in certain parahilias (Kafka 1991; Kafka and Prentky 1992; Greenberg et al. 1996). Similar observations have been made regarding other SSRIs, including paroxetine, sertraline, and fluvoxamine (Waldinger et al. 1994, 1997; Zohar et al. 1994; Hsu and Shen 1995; Mendels et al. 1995; Ludovico et al. 1996; Model et al. 1997). Despite the reports of fluoxetine-induced loss of sexual desire and delay of ejaculation or orgasm, erectile dysfunction is not as frequently observed with SSRIs as it is with tricyclic antidepressants (Balon et al. 1993; Shiavi and Segraves 1995; Crenshaw and Goldberg 1996). Better understanding of the role of serotonin in this specific pattern of sexual dysfunction would help to refine our understanding of the neurochemical basis of normal sexual behavior and serve as a basis for research to reduce the sexual side effects of SSRI treatment.

Both acute and chronic effects of fluoxetine on the sexual behavior of male rats have been examined. High doses of fluoxetine (10 mg/kg and 20 mg/kg, i.p.) have been reported to increase the post-ejaculatory intervals of male rats during their first ejaculatory series, increase the intromission frequency and ejaculation latencies of males during their last ejaculatory series prior to sexual exhaustion, and decrease the copulatory efficiency during the last series (Yells et al. 1994). A lower dose of 5 mg/kg produced similar effects only during the final ejaculatory series. In contrast, 4 weeks of daily fluoxetine treatment to sexually naive males (0.75 mg/kg/day,

i.p.) produced a progressive decrease in the acquisition of normal sexual performance, as indicated from a composite of measures, including increased intromission latencies, decreased numbers of intromissions, and a reduced frequency of ejaculation (Taylor et al. 1996). Chronic fluoxetine treatment did not alter the relative time that the males spent near sexually receptive versus nonreceptive females, suggesting that sexual motivation was not affected by this treatment. Although Taylor et al. used a dose of fluoxetine within the lower range of therapeutic value for humans, both fluoxetine and its active metabolite, norfluoxetine, clear blood plasma many times more quickly in rats than in humans (Stark and Wong 1985; Caccia et al. 1990). This necessitates the use of higher doses in the rat. In addition, the use of sexually naive males in that study precluded an analysis of the effect of fluoxetine on normal baseline rates of sexual behavior.

The mechanism by which chronically elevated levels of serotonin exert an inhibitory effect on sexual desire, ejaculation, or orgasm remains unclear. In humans, some success has been reported in treating SSRI-induced sexual dysfunction with indirect dopamine agonists such as amantadine or D-amphetamine (Balogh et al. 1992; Gitlin 1995), the α_2 adrenergic antagonist yohimbine (Hollander and McCarley 1992), or the mixed 5-$HT_{2A/2C}/\alpha_2$ adrenergic antagonist mianserin (Aizenberg et al. 1997). Chronically elevated serotonin levels also change certain neuroendocrine systems, some of which may be involved directly in sexual desire and orgasm. In particular, chronic fluoxetine treatment alters the sensitivity of oxytocin neurons to different serotonin receptor agonists (Li et al. 1993a, 1993b, 1996). With regard to human sexual behavior, plasma levels of oxytocin rise during sexual stimulation in both men and women (Carmichael et al. 1987, 1994; Murphy et al. 1987, 1990). Systemic administration of oxytocin to male and female rats facilitates copulatory behaviors (Fjellstrom et al. 1968; Argiolas et al. 1985, 1986; Arletti et al. 1985, 1990, 1992; Stoneham et al. 1985; Moody et al. 1994), whereas oxytocin antagonists disrupt it (Argiolas et al. 1987, 1989). Given the direct influence of oxytocin in sexual behavior, these observations suggest that SSRIs could induce sexual dysfunction by interfering with the endogenous release of oxytocin. Administration of oxytocin exogenously may therefore compensate for its loss and serve to maintain the normal expression of sexual behavior during ongoing fluoxetine treatment. We tested this hypothesis in the present experiments.

Materials and methods

Animals

Male Long-Evans rats (300–500 g) were obtained from Charles River Canada, Inc., St. Constant, Québec. They were housed in pairs in plastic cages (36×26×19 cm) in a colony room maintained on a reversed 12 h:12 h light/dark cycle (lights off at 0800 hours) at approximately 21°C. Food and water were continuously available. Sexually experienced female Long-Evans rats, obtained from the same breeder, were used as stimulus partners in the experiment. The females had been ovariectomized bilaterally under ketamine/xylazine anesthesia and subsequently rendered sexually receptive by subcutaneous injections of estradiol benzoate (10 µg in sesame oil) 48 h and progesterone (500 µg in sesame oil) 4 h before all tests of sexual behavior were performed. All animal housing, handling, injections, and testing procedures conformed to the guidelines of the Canadian Council on Animal Care.

Drugs

Fluoxetine hydrochloride was purchased from Sigma (St. Louis, Mo.) and dissolved in distilled water to obtain four concentrations: 10.0 mg/ml, 5.0 mg/ml, 1.0 mg/ml, and 0.0 mg/ml (vehicle control). All drug concentrations were prepared once a week and stored at 4°C. Daily injections were delivered i.p. at 1.0 ml/kg body weight to obtain final doses of 10.0 mg/kg, 5.0 mg/kg, 1.0 mg/kg, and control. Fluoxetine was injected daily between 1500 hours and 1700 hours, except on testing days, when the males received injections 60 min before behavioral observations began. Oxytocin (Bachem, Sacramento, Calif.) was dissolved in physiological saline at a concentration of 0.001 mg/ml and stored at –20°C. The solution was warmed to room temperature immediately before use. Oxytocin (200 ng/kg) was injected i.p. 60 min before each test at a concentration of 0.2 ml/kg, as in Arletti et al. (1985, 1992).

Behavioral screening

All tests of sexual behavior took place in bilevel chambers, as described previously (Pfaus et al. 1990). Male rats placed into bilevel chambers for a 5-min adaptation period prior to the presentation of a sexually receptive female develop conditioned level changing, a behavior that has been used as a measure of anticipatory sexual excitement in previous studies of opioid and dopaminergic regulation of sexual behavior (Pfaus and Phillips 1991; van Furth et al. 1994; van Furth and van Ree 1996). The 24 females used as copulatory partners in these experiments were given at least ten preliminary trials with sexually experienced males in the bilevel chambers to acquire the full range of sexual behaviors, including high rates of solicitation, pacing, other proceptive behaviors, and lordosis. The males were allowed 1 week to adapt to the animal care facility before preliminary testing began. Prior to sexual contact, males were acclimated to the bilevel chambers for five 30-min sessions over 10 days. After this, each male was placed into the bilevel chamber for 5 min prior to the introduction of a sexually receptive female. Both rats were allowed to copulate for 30 min before the test was terminated. Screening tests continued for a total of eight 30-min sessions at 4-day intervals to provide the males with requisite sexual experience. The final three tests served as injection baselines during which the vehicle was administered to each male 60 min before each test. All noncopulators were discarded.

Procedure

Males were assigned randomly to one of the four groups (n=8–10 per group) and were tested for sexual behavior at 4-day intervals for a total of 11 trials, with the first fluoxetine test commencing 4 days after the last baseline test. Males continued to receive daily fluoxetine treatment on each of the three days between trials. Each test session consisted of the introduction of the male into the bilevel test chamber followed 5 min later by the introduction of the female. The pair was permitted to copulate freely for 30 min. A video camera recorded each session for later scoring. Following the final fluoxetine-alone test, the males in the four groups continued to receive daily injections of fluoxetine (or vehicle). The next four trials consisted of oxytocin or the saline vehicle being admin-

istered to each male using an A–B–B–A design; thus, the fluoxetine groups received oxytocin treatment on trials 1 and 4, and saline on trials 2 and 3, whereas the control group received only the saline vehicle. Daily fluoxetine or vehicle treatment was maintained throughout all four trials.

Data analyses

A scorer, blind to the animals' group membership, coded the videotapes using a real-time, computerized event recorder (Cabilio 1996). Appetitive level changes were scored when the male moved completely from one level to another, as defined by Mendelson and Pfaus (1989). This resulted in two appetitive measures, the total number of level changes (LCs) and the latency to the first level change (LCL). Copulatory behaviors consisted of mounts, intromissions, and ejaculations, and were scored for each male during successive ejaculatory series, as defined by Sachs and Barfield (1976). Latencies were calculated to the first mount (ML), intromission (IL_1) and ejaculation (EL) of the first ejaculatory series. Numbers of mounts without intromission (NM) and mounts with intromission (NI) were calculated for each ejaculatory series, and the total number of ejaculations (NE) were calculated for the entire test. Three secondary measures were calculated from these primary measures: the post-ejaculatory interval (PEI) was calculated as the time from the first ejaculation to the next intromission. The intromission ratio (IR) was calculated as the number of intromissions divided by the total frequency of both mounts and intromissions (IR=NI/NM+NI). The interintromission interval (III) was calculated as the ejaculation latency divided by the number of mounts with intromission (EL/NI). All latency and frequency data from the first ejaculatory series were used in the present analysis.

To study the acute effects of fluoxetine, the mean of the three baseline trials was subtracted from the results of first trial. The resulting difference scores were analyzed using a one-way multivariate analysis of variance (MANOVA) with Wilks' lambda criterion and using dosage (control, 1 mg/kg, 5 mg/kg, and 10 mg/kg of fluoxetine) as the single between-subjects factor. Univariate ANOVAs and stepdown analysis permitted assessment of the individual dependent variables. The dependent variables were the four behavioral frequencies (LC, NM, NI, and NE), the four latency measures (LCL, ML, IL_1, EL), and the three secondary variables (PEI, IR, and III).

With chronic fluoxetine treatment, increasing numbers of animals failed to exhibit all behaviors, obviating the latency and interval measures. Therefore, the five dependent variables which reflect frequency measures were selected for analysis of chronic fluoxetine treatment. For the omnibus tests of dose, time, and their interaction, each of the dependent variables formed a 4(dosage) times 14(trial) ANOVA design, with trial as a repeated measure. Significance tests on the repeated measure (time and the dosage × time interaction) were subjected to Greenhouse–Geisser correction for violations of sphericity. All the significance tests on repeated factors which appear below reflect the reduced degrees of freedom. To examine the time course of changes within each dependent variable, the first three fluoxetine trials, the middle three trials, and the final three trials were each averaged to produce a single mean score for that period. As before, analyses were then conducted on the differences from baseline. For each significant omnibus ANOVA, post-hoc comparisons of the experimental groups to the control group were made using protected one-tailed *t*-tests; differences were considered significant at $P<0.05$ (Keppel and Zedek 1989). One-tailed tests were used to gain statistical power in circumstances where only one direction of effect, e.g., a decrease in ejaculation frequency, is tested.

Finally, the two oxytocin and the two non-oxytocin sessions were each collapsed into single means for each dependent variable. The mean of the final fluoxetine trials was then subtracted from that score to produce the gain scores caused by oxytocin co-treatment. The gain scores were then analyzed by one-way ANOVA to detect differences from the fluoxetine-only trials. For each significant ANOVA, post-hoc comparisons of the experimental groups to the control group were made using protected *t*-tests, one- or two-tailed, depending on the hypothesized direction of effect; differences were significant at $P<0.05$.

Results

Of the original 37 copulating males in the study, 4 did not survive long-term fluoxetine treatment and an additional 2 males died during co-treatment with oxytocin. Data from those animals were removed retroactively from the chronic fluoxetine data set.

Acute effects of fluoxetine

The types of male rat sexual behavior observed after acute administration of fluoxetine are shown in Table 1. The MANOVA on the difference from baseline scores indicated a significant main effect of dose, $F(33, 62.57)=1.62$, $P<0.05$. Univariate analyses on the difference scores showed that the multivariate effect was significantly related to changes in three of the dependent variables: LCL, NE, and PEI – Fs(3,31)=3.38, 3.41, and 3.78; Ps<0.04, 0.04, and 0.03, respectively. A trend toward significance was also found for LC, $F(3,31)=2.52$, $P<0.08$. Due to the known correlations between the various sexual behaviors in male rats (Pfaus et al. 1990), the effect of overlapping variance was eliminated by entering each of the dependent variables into a stepdown analysis. Variables were ordered a priori by the sequence in which they occur during copulatory bouts (e.g., level changes precede mounting, intromissions precede ejaculation, etc.). Stepdown analysis indicated that significant and independent contributions were made by two variables: LCL, $F(3,31)=3.40$, $P<0.04$, and PEI, $F(3,21)=6.53$, $P<0.004$. Although the NE remained the next strongest effect, it was no longer statistically significant, $F(3,26)=1.66$, n.s. Relative to the control group, males in the 10-mg/kg dose group exhibited a significant increase in LCL, $t(31)=4.69$, $P<0.02$, and a significant increase in the PEI, $t(31)=5.91$, $P<0.003$. Neither the 5-mg/kg nor the 1-mg/kg dose groups differed significantly from the control group on these measures.

Chronic effects of fluoxetine

Weight loss

The males showed a strong, dose-dependent decrease in body weight throughout fluoxetine treatment which reflected an inability to gain weight relative to the control group (Fig. 1). The weight loss appeared to occur throughout the first month of treatment, after which the males in the two higher dose groups appeared to gain weight at a slow rate. The ANOVA detected significant main effects of dose, $F(3,27)=5.02$, $P<0.008$; time, $F(3.71,100.23)=51.00$, $P<0.0001$; and their interaction, $F(11.14,100.23)=14.15$, $P<0.0001$. Follow-up analyses

Table 1 Male rat sexual behavior following acute administration of fluoxetine (*LCL* level change latency, *LC* number of level changes, *ML* mount latency, *NM* number of mounts, *IL* intromission latency, *NI* number of intromissions, *IR* intromission ratio, *EL* ejaculation latency, *NE* number of ejaculations, *III* interintromission interval, *PEI* postejaculatory interval). *LC*, *NM*, *NI*, and *NE* are expressed as mean frequency counts (±SEM). *LCL*, *ML*, *IL*, *EL*, *III*, and *PEI* are expressed as mean seconds (±SEM). IR is expressed as a mean ratio (±SEM). All behaviors were calculated for the first ejaculatory series. Univariate and stepdown Fs reflect difference scores from baseline performance

Behavior	Dose of fluoxetine				Univariate $F(3,31)$	Stepdown F
	Vehicle (n=9)	(1 mg/kg) (n=8)	(5 mg/kg) (n=10)	(10 mg/kg) (n=8)		
LCL	16.7 (3.43)	17.2 (5.08)	17.0 (3.60)	41.4 (12.9)†	3.38*	$F(3,31)$=3.38*
LC	10.2 (1.24)	8.38 (1.42)	5.60 (0.60)	5.63 (1.32)	2.52	$F(3,30)$=1.47
ML	5.89 (1.70)	7.25 (1.82)	6.50 (2.05)	9.00 (1.87)	0.62	$F(3,29)$=0.87
NM	11.1 (2.50)	5.25 (1.84)	6.70 (2.53)	4.00 (1.00)	0.75	$F(3,28)$=0.76
IL	20.9 (6.25)	16.5 (4.33)	14.1 (2.68)	12.9 (2.07)	1.61	$F(3,27)$=0.84
NI	10.1 (0.93)	9.38 (1.13)	8.20 (1.01)	5.88 (0.67)	1.43	$F(3,26)$=0.98
IR	0.508 (0.057)	0.718 (0.072)	0.669 (0.080)	0.638 (0.067)	1.88	$F(3,25)$=1.15
EL	234 (32.0)	196 (34.4)	180 (32.8)	145 (28.5)	1.67	$F(3,24)$=0.23
NE	2.89 (0.20)	3.38 (0.18)	3.30 (0.21)	2.63 (0.18)	3.41*	$F(3,23)$=1.66
III	24.2 (3.39)	20.0 (2.13)	22.8 (4.80)	23.2 (2.82)	1.06	$F(3,22)$=0.21
PEI	318 (13.2)	313 (16.5)	357 (33.7)	441 (33.1)***	3.78*	$F(3,21)$=6.53**

*P<0.05
**P<0.01
***P<0.05 from vehicle

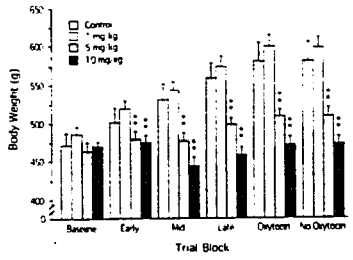

Fig. 1 Body weight of males in each dose group at baseline, as a function of chronic fluoxetine treatment, and following co-administration of oxytocin. Data are means±SEM. **P<0.01 from controls. Each animal's score represents the mean body weight on three consecutive test days during each phase of the experiment, except following oxytocin treatment, during which there are only two test days

indicated significant group differences during the early, mid-way, and late portions of the experiment, $F(3,27)$=15.02, 29.04, and 29.17, respectively; all Ps<0.0001. Relative to the control group, males in the 10-mg/kg and 5-mg/kg dose groups had significantly decreased body weight during each of the three time periods: 10-mg/kg group, $t(27)$=–9.88, –15.65, and –15.31, all Ps<0.0005 (one-tailed); 5-mg/kg group, $t(27)$=–7.23, –10.86, and –10.49, all Ps<0.0005. The weights of males in the 1-mg/kg dose group were not significantly different from those of the control group during any time period, $t(27)$=1.74, –0.68, and 0.18, n.s. (one-tailed).

Appetitive sexual excitement

A dose-dependent decrease in LC was apparent during the early phase of fluoxetine treatment (Fig. 2, top). However, some tolerance appeared to accrue to this effect with chronic treatment, especially at the 5-mg/kg dose. Analysis of LC detected significant main effects of dosage, $F(3,27)$=7.72, P<0.001, and the dose by time interaction, $F(23.17,208.51)$=2.03, P<0.005. Testing the effects of dose within each time phase revealed significant differences between groups during all three periods, Fs(3,27)=7.544, 24.04, and 6.125, Ps<0.0008, 0.0001, and 0.0026. The LCs of the 10-mg/kg group were decreased significantly from control levels during each time period, ts(27)=–9.322, –14.852, and –8.218, all Ps<0.0005 (one-tailed). The 5-mg/kg group showed a decrease relative to controls during the early phase, $t(27)$=–4.362, P<0.02 (one-tailed), but not during the midway or late phases, t s(27)=0.626 and –0.760, respectively, n.s. (one-tailed).

Ejaculation frequency

Despite the fact that all males copulated without any significant disruption of mounts or intromissions, the total number of ejaculations decreased in a dose- and time-dependent fashion. There was a significant dose times time interaction, $F(22.96,206.62)$=1.68, P<0.04, indicating that the different doses caused different changes over time. As shown in Fig. 2 (bottom), the groups differed only marginally during the early time phase, $F(3,27)$=2.53, P<0.08. However, significant differences were detected for the NE during both the mid- and late phases, Fs(3,27)=5.06 and 4.53, Ps<0.007 and 0.02, respectively. Relative to the control group during

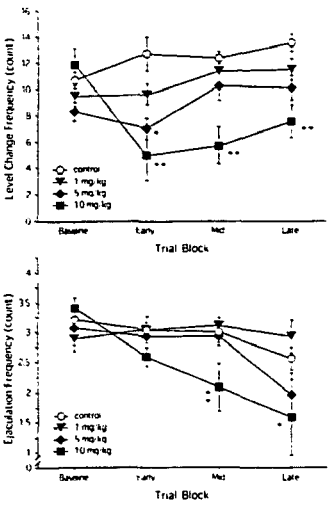

Fig. 2 Conditioned level changes (*top*) and ejaculation frequencies (*bottom*) at baseline and during chronic fluoxetine treatment. Data are means±SEM. Each animal's score represents the mean number of level changes exhibited before the introduction of the stimulus female on three consecutive trials, or the mean number of ejaculations exhibited on three consecutive trials. Analyses were conducted on differences from baseline scores. *$P<0.05$, **$P<0.01$ from controls

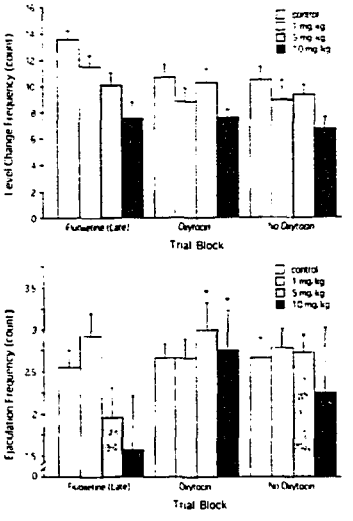

Fig. 3 Effect of oxytocin or vehicle on the number of conditioned level changes (*top*) or ejaculations (*bottom*) shown by male rats treated with chronic fluoxetine. Data are means±SEM. Late phase fluoxetine data from Fig. 2 are included for comparison. *$P<0.05$ from late treatment with fluoxetine

these two testing phases, males in the 10-mg/kg group had significantly decreased NEs, $t(27)=-5.54$ and -4.21, $Ps<0.005$ and 0.03 (one-tailed). Although the 5-mg/kg group decreased from baseline relative to controls during the late phase, this effect was not statistically significant, $t(16)=2.04$, 1.92, $P<0.04$, (one-tailed).

Effects of co-treatment with oxytocin

Weight loss

The analysis of gain scores indicated that the fluoxetine-induced group differences in body weight did not change when oxytocin co-treatment was added to fluoxetine administration, $F(3, 27)=2.33$, n.s., or when oxytocin treatment was discontinued, $F(3, 27)=0.13$, n.s. As indicated in Fig. 1, the groups continued to differ by dose.

Appetitive sexual excitement

There were no significant differences in gain scores with oxytocin co-treatment on measures of LC, $F(3,27)=2.35$, n.s., or with its removal, $F(3,27)=0.29$, n.s. (Fig. 3, top). The overall group differences in LC persisted when oxytocin was added to the treatment, $F(3,27)=3.80$, $P<0.03$, and when it was removed, $F(3,27)=3.41$, $P<0.04$. Specifically, the 10-mg/kg group continued to show fewer level changes than the control group in both cases, $ts(27)=2.25$ and 2.52, $Ps<0.03$ and 0.02, respectively.

Ejaculation frequency

Oxytocin treatment produced a significant increase in the NE relative to controls (Fig. 3, bottom). Analysis of gain scores indicated a differential effect on groups, $F(3,27)=4.29$, $P<0.02$, with both the 10-mg/kg and 5-mg/kg groups significantly increasing relative to the late phase, $t(27)=4.31$ and 3.86, $Ps<0.03$ and 0.02, re-

spectively, (one-tailed). These dose groups no longer differed significantly from controls on NE after oxytocin co-treatment, $F(3,27)=1.14$, n.s. This improvement appeared long lived, as the removal of oxytocin was not associated with the return of any significant group difference in NE, $F(3,27)=1.14$, n.s., or in gain scores from the oxytocin treatments, $F(3, 27)=0.62$, n.s.

Discussion

Chronic administration of fluoxetine produced a dynamic decline in certain appetitive and consummatory aspects of sexual behavior in sexually active male rats. Doses of 5 mg/kg and 10 mg/kg, which are associated with acute antidepressant activity in animal models of depression (Muscat et al. 1992), decreased body weight, decreased appetitive sexual behavior, and decreased ejaculation frequency, but did not alter other copulatory behaviors significantly. The effects on ejaculation appeared to follow relatively linear dose- and time-response relationships, with the greatest effect observed at 10 mg/kg. Although fluoxetine produced a rapid decrease in the measure of appetitive excitement (level changing), tolerance appeared to accrue to the effects of the 5-mg/kg dose. Both of these effects on sexual behavior occurred without a significant decrease in the ability of males to gain intromission.

Oxytocin produced a long-lasting reversal of the decrease in ejaculation frequency produced by chronic fluoxetine treatment. This effect was specific to ejaculation, as no effect of oxytocin was observed on appetitive level changing. Previous studies have shown that chronic fluoxetine treatment decreases the affinity of serotonin receptor subtypes found on oxytocin-synthesizing neurons (Li et al. 1993a, b, 1996), which might alter patterns of oxytocin release. However, it is not known whether the ameliorative effect of oxytocin in the present experiment reflects an action at oxytocin receptors in the brain or in the periphery. Oxytocin receptors exist throughout the dorsal horn of the spinal cord and within the male reproductive tract (Reiter et al. 1994; Ivell et al. 1997; Tribollet et al. 1997). Thus, systemically administered oxytocin could induce ejaculation by stimulating either sympathetic outflow or smooth muscle cells of the reproductive tract directly. Indeed, oxytocin appears to be released in a pulsatile fashion from the posterior pituitary as males reach the threshold for ejaculation (Ivell et al. 1997), and oxytocin injections to the cartoid artery of male rats stimulate ejaculation (Stoneham et al. 1985). However, the ability of the dopamine agonist apomorphine to stimulate ejaculation in rats can be blocked by intracerebroventricular infusions of an oxytocin antagonist (Argiolas et al. 1989), suggesting that central actions of oxytocin may facilitate ejaculation.

Unfortunately, chronic administration of the 10 mg/kg dose into the later phase of testing was lethal for several rats. The LD_{50} (lethal dose for 50% of animals) following oral administration of acute fluoxetine to rats is 452 mg/kg (Stark and Wong 1985). However, we have subsequently found no mortality if daily doses of 10 mg/kg of fluoxetine are administered at the end, rather than the beginning of the dark circadian cycle (Wright and Pfaus, unpublished data). We have also found that 10 mg/kg of fluoxetine produces conditioned taste aversions (unpublished results), suggesting that the increased mortality may have been caused by starvation. Doses as low as 2 mg/kg have been shown to induce a conditioned taste aversion to a novel sucrose solution (Prendergast et al. 1996). Rats tend to eat the largest meal of the day at the beginning of the dark cycle, and prior treatment with fluoxetine may have induced an aversion in some rats to their normal diet. Nevertheless, sickness alone is not sufficient to explain the disruption of sexual behavior. First, this disruption was selective to appetitive sexual excitement and ejaculation; other aspects of copulation were not affected. Second, the ameliorative effect of oxytocin on ejaculation occurred quickly despite these animals continuing the chronic fluoxetine regimen.

The disruption of sexual activity and body weight produced by fluoxetine in rats is generally analogous to that reported in humans (Crenshaw and Goldberg 1996). The dose dependence is also reminiscent of its effects in humans, and lowering the dose or using drug holidays are used by some individuals to combat the sexual effects (Patterson 1993; Rothschild 1995). These results are also consistent with previous reports of the acute effect of fluoxetine on the sexual behavior of male rats (Yells et al. 1994; Taylor et al. 1996). Yells et al. reported a significant increase in the final ejaculation latency prior to sexual exhaustion following a single administration of 5, 10, or 20 mg/kg. This study also reported a significant increase in the PEIs of successive ejaculatory series following the two higher doses. Although the first exposure of our males to fluoxetine produced a dose-dependent increase in successive PEIs, we did not detect significant effects on the ejaculation latencies. It is possible that strain differences or differences in the amount of prior sexual experience could account for these minor discrepancies. Similarly, Taylor et al. (1996) reported increased intromission latencies, interintromission intervals, and decreased frequency of ejaculation following chronic administration of 0.75 mg/kg to sexually naive males. Although we did not observe any effect of 1 mg/kg fluoxetine on sexual behavior, the sexually naive males used in the Taylor study may have been more sensitive to the effects of fluoxetine than the sexually experienced males used in our study. Taylor et al. also reported no effect of chronic fluoxetine on measures of partner preference, which led to the conclusion that chronic fluoxetine affects copulatory behaviors but not sexual motivation.

A recent study of the effects of acute and chronic fluoxetine treatment (10 mg/kg/day for up to 3 weeks) on the sexual behavior of female rats reported significantly reduced lordosis quotients in both intact rats and ovariectomized rats primed with estradiol and progesterone, but no decrease in partner preference and no disruption

of estrous cyclicity in the intact rats (Matuszczyk et al. 1998). It would thus appear that different types of appetitive sexual behavior might be affected by fluoxetine in different ways.

In summary, our results suggest that chronic fluoxetine treatment inhibits ejaculation in male rats in part by altering normal oxytocin transmission. The rapid amelioration of this effect by a low dose of oxytocin may represent a useful approach to managing this side effect of fluoxetine or other SSRIs.

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Preface to Study 2

For the reasons discussed in the following literature review of Study 2, the role 5-$HT_{2A/2C}$ receptors were of interest for their role in the inhibition of sexual behavior. Therefore the 5-$HT_{2A/2C}$ receptor antagonist, ritanserin, was tested for its ability to reverse fluoxetine-induced sexual dysfunction in male rats. Although cyproheptadine, another 5-$HT_{2A/2C}$ antagonist has also been reported to reduce the SSRI-induced sexual dysfunction in humans (Ashton, Hamer, & Rosen, 1997). However, cyproheptadine is not receptor specific, showing affinity for histaminergic receptors. In fact, it is widely used clinically for its properties as an antihistamine (Kaplan & Sadock, 1996). Ritanserin, therefore, could produce similar behavioral effects in SSRI-treated rats, but also implicate more directly the role of 5-$HT_{2A/2C}$ receptors in fluoxetine-induced sexual dysfunction.

Reversal of Fluoxetine-Induced Sexual Dysfunction by Ritanserin

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Abstract

This experiment investigated the role of 5-$HT_{2A/2C}$ receptors in selective serotonin reuptake inhibitor (SSRI)-induced sexual dysfunction. Male, Long-Evans rats received injections of fluoxetine hydrochloride (10 mg/kg ip) each day over a 37-day period plus exposure to sexually receptive, female rats every fourth day. By the end of the first 33 days, males showed significant declines in copulatory efficiency and ejaculation frequency, but not in conditioned level changes, a measure of appetitive sexual excitement. On day 37, males received injections either of the 5-$HT_{2A/2C}$ antagonist, ritanserin (3.2 or 5.6 mg/kg ip), or of vehicle (1.0 ml/kg ip), 20-minutes before a final sexual behavior test. The ritanserin-treated animals demonstrated significantly increased copulatory efficiency and ejaculation frequency relative to the vehicle-treated animals. These results are consistent with the hypotheses that 5-$HT_{2A/2C}$ receptors mediate the SSRI-induced declines in sexual behavior.

Reversal of Fluoxetine-Induced Sexual Dysfunction by Ritanserin

The frequencies of and the latencies to initiating male copulatory behaviors vary in an inverse relationship to manipulated 5-HT neurotransmission. Global increases in 5-HT produced by systemic injection of 5-HT or its precursor, 5-hydroxytryptophan (5-HTP) cause a decreased frequency of ejaculation and an increased ejaculation latency (Fernández-Guasti & Rodriguez-Manzo, 1992; Menéndez-Abraham, Morán-Viesca, Velasco-Plaza, & Marín, 1988). Conversely, reductions in 5-HT levels induced by central administration of the 5-HT-specific neurotoxins 5,6-dihydroxytryptamine (5,6-DHT) and 5,7-dihydroxytryptamine (5,7-DHT) result in increased sexual behavior frequency, decreased delay between intromissions, and a shortening of the post-ejaculatory interval (Da Prada, Carruba, O'Brien, Saner, & Pletscher, 1972; McIntosh & Barfield, 1984). Electrolytic lesions of the median raphe nuclei, where the 5-HT cell bodies are situated, also results in decreased ejaculatory latencies and the post-ejaculatory intervals (Albinsson, Andersson, Andersson, Vega-Matuszcayk, & Larsson, 1996). The provision of a diet free of the essential amino acid, tryptophan (from which all 5-HT is synthesized), results in reduced levels of 5-HT in the brain (Biggio, Fadda, Fanni, Tagliamonte, & Gessa, 1974; Gessa, Biggio, Fadda, Corsini, & Tagliamonte, 1974). When fed such a diet, male rats with low baseline sexual activity demonstrated decreased sexual behavior latencies relative to normal controls (Moja & Benedetti, 1996). The most widely employed method of reducing 5-HT levels in the brain has been the administration of the 5-HT synthesis inhibitor, para-chlorophenylalanine (p-CPA). 5-HT reduction through this drug was widely reported to produce a state of highly energetic mounting behavior in

which males were observed to mount each other (e.g., Salis & Dewsbury, 1971; Tagliamonte, Tagliamonte, Gessa, & Brodie, 1969). McIntosh and Barfield (1984) confirmed that rats also increase show increased frequencies of and decreased latencies to sexual behavior parameters when exposed to sexually receptive females.

As the 5-HT receptor system became better characterized, the complicated role of 5-HT in regulating male sexual behavior became better recognized. 5-HT agonists which target distinct 5-HT receptor subtypes show differential effects on sexual behavior; the stimulation of some receptor subtypes appears to facilitate sexual behavior in male animals, while the stimulation of others appears to inhibit it.

Systemic administration of 5-HT_{1A} receptor agonists potently accelerate ejaculations, as reflected by decreased ejaculation latency and by a reduced number of intromissions required to trigger ejaculation. These changes are induced by the highly selective 5-HT_{1A} agonists, 8-hydroxy-2-(di)-n-propylamino-tetralin) (8-OH-DPAT; Lee, Smith, Mas, & Davidson, 1990; Morali & Larsson, 1984; Schnur, Smith, Lee, Mas, & Davidson, 1989), LY228729 (Foreman et al., 1993), and LY293284 (Foreman et al., 1994) as well as flesinoxan (Ahlenius, Larsson, & Wijkstrom, 1991; Haensel & Slob, 1997) and the clinically available anxiolytic, buspirone (BuSpar; Mathes, Smith, Popa, & Davidson, 1990). The lack of selective 5-HT_{1A} antagonists has hindered the testing of the converse hypothesis that 5-HT_{1A} antagonism would result in reduced sexual behavior.

Based on their observations of the effects of trifluoromethylphenylpiperazine (TFMPP), an agonist with affinity for the 5-HT_{1B} receptor, Fernández-Guasti and colleagues claimed that 5-HT_{1B} receptors inhibit male copulatory behavior (Fernández-

Guasti & Escalante, 1991; Fernández-Guasti, Escalante, Ahlenius, Hillegaart, & Larsson, 1992; Fernández-Guasti & Rodriguez-Manzo, 1992). However, TFMPP shows a 2.5 to 6 times greater affinity for the 5-HT_{2C} subtype and shares most behavioral-pharmacological properties with it (Lucki, 1992; Middlemiss & Tricklebank, 1992; Zifa & Fillion, 1992). Therefore, the results of Fernández-Guasti and colleagues are more appropriately interpreted as evidence for the influence of 5-HT_{2C} receptors (below).

Studying the effects of isamoltane, an antagonist of the 5-HT_{1B} receptor, Ahlenius and Larsson (1998), also posited an inhibitory role of 5-HT_{1B} receptors. They found that isamoltane blocked the otherwise inhibitory effects of 5-HTP, suggesting that the 5-HT_{1B} receptors were contributing to the behavioral inhibitions caused by 5-HTP. However, isamoltane is also a β-adrenergic antagonist, demonstrating greater affinity for the adrenergic receptor than it does for the serotonergic receptor (Waldmeier, Williams, Baumann, Bischoff, Sills, & Neale, 1988).

Agonists with affinity for either of the closely related 5-HT_{2A} and 5-HT_{2C} receptors inhibit copulatory behavior in male animals. Administration of 1-(2,5-dimethoxy-4-iodophenyl)-2-amino propane (DOI; Klint & Larsson, 1995; Watson & Gorzalka, 1990) as well as 1-(3-chlorophenyl)piperazine (m-CPP; Pomerantz, Hepner, & Wertz, 1993a; Pomerantz, Hepner, & Wertz, 1993b), and the less selective TFMPP (Fernández-Guasti et al., 1992; Fernández-Guasti & Rodriguez-Manzo, 1992) have all been reported to retard copulatory behavior in male animals. Unambiguous conclusions cannot be drawn on the basis of those reports, however, due to the complex receptor affinity profiles shown by the 5-$HT_{2A/2C}$ agonists currently available (Middlemiss &

Tricklebank, 1992; Saxena, 1995). Yet, the inhibitory role of 5-HT_{2A} and 5-HT_{2C} receptors is additionally supported by the effects of 5-$HT_{2A/2C}$ antagonists. Systemic injection of ritanserin, a potent drug of this type (Meert, Niemegeers, Gelders, & Janssen, 1989) dose dependently reversed the inhibitory effects of DOI whether DOI was administered systemically (Klint et al., 1992; Watson & Gorzalka, 1991) or directly to the nucleus raphe obscurus/inferior olive (Watson & Gorzalka, 1992). Interestingly, ritanserin did not affect sexual behavior when given alone at the same doses, in the same studies. Similar effects have been noted regarding the other 5-$HT_{2A/2C}$ antagonists, ketanserin and mesulergine (Klint et al., 1992). LY237733, a 5-$HT_{2A/2C}$ antagonist in development by Eli Lilly facilitated sexual behavior in rats which had low baseline rates of copulation (Foreman et al., 1992).

Although the manipulation of 5-HT_3 receptors has not been widely tested for its effects on male copulatory behavior, they do not appear to be strongly involved. Administration of the 5-HT_3 antagonists, ondansetron and granisetron, failed to alter copulatory parameters in male or female rats, at least using the route and doses tested (Tanco, Watson, & Gorzalka, 1993). Intracerebroventricular administration of the 5-HT_3 agonist, 2-methyl-serotonin (2-Me-5-HT), was likewise without effect (Tanco, Watson, & Gorzalka, 1994). However, a second 5-HT_3 agonist in the former study, 1-phenylbiguanide (PBG), was associated with a reduction in the ejaculatory latency of male rats. Interestingly, due to the pattern of effects observed in female rats, those authors concluded that PBG demonstrated its influence through the secondary release of

dopamine and that 5-HT_3 does not actually have an effect on male sexual behavior of its own.

The selective serotonin reuptake inhibitors (SSRIs) have a complex effect on the 5-HT system. Although intercellular 5-HT levels rise quickly after the acute administration of an SSRI, chronic administration induces neuroadaptive changes in individual receptor types. When chronically administered to male rats, SSRIs strongly inhibit copulatory behavior (Cantor, Binik, & Pfaus, 1996, 1999; Taylor et al., 1996; Matuszcyk, Larsson, & Eriksson, 1998). In our previous reports, we observed decreases in appetitive sexual behavior in males rats as well as dramatic declines in ejaculatory frequency. These observations are consistent with the anti-sexual side effects widely reported to occur in men taking SSRI medication (Crenshaw & Goldberg, 1996; Margolese & Assalian, 1996).

The participation of individual 5-HT receptor subtypes has not yet been identified with regard to SSRI-induced sexual dysfunction. Given that 5-$HT_{2A/2C}$ receptors have the most consistent inhibitory effect on sexual behavior, we undertook the following experiment to clarify the role of 5-$HT_{2A/2C}$ receptors SSRI-induced sexual dysfunction in male rats. We administered fluoxetine chronically, to male rats in order to explore the ability of the 5-$HT_{2A/2C}$ antagonist, ritanserin, to restore normal sexual function.

Materials and Methods

Animals

Thirty-one male, Long-Evans rats (400-450 g) were obtained from Charles River Canada, Inc., St. Constant, Québec. They were housed in pairs, in plastic cages (36 x 26 x 19 cm) in a colony room maintained on a reversed 12h:12h light/dark cycle (lights off at 0800 hours) at approximately 21°C. Food and water were continuously available. Sexually experienced, female Long-Evans rats, obtained from the same breeder were used as stimulus partners in the experiment. The females had been ovariectomized bilaterally under ketamine/xylazine anesthesia and subsequently rendered sexually receptive by subcutaneous injections of estradiol benzoate (10 μg in sesame oil) 48 hours and progesterone (500 μg in sesame oil) 4 hours before tests of sexual behavior. All animal handling, housing, injections, and testing procedures conformed to the guidelines of the Canadian Council on Animal Care.

Drugs

Fluoxetine hydrochloride (Atlantic Chemicals, Toronto, Ontario, Canada) was dissolved in 0.9% saline at a concentration of 10.0 mg/ml. The mixture was heated slightly to facilitate solution, and new solutions were prepared daily. Injections were delivered ip at 1.0 ml/kg body weight to produce a dose of 10.0 mg/kg. Fluoxetine was injected daily between 1500 and 1700 hours. After test session 5, fluoxetine was administered after 1700 hours to reduce hypophagic effects during the animals' normal feeding period. Ritanserin (Sigma, St. Louis, MO) was dissolved in glacial acetic acid and

diluted to a buffered pH of 4.8 at concentrations of 3.2 mg/ml (low dose) and 5.6 mg/ml (high dose).

Behavioral Testing

All tests of sexual behavior took place in bilevel chambers, as described previously (Pfaus, Mendelson, & Phillips, 1990). Male rats placed repeatedly in such chambers for five-minute adaptation periods prior to the presentation of sexually receptive females come to demonstrate conditioned level changing, a behavior that is frequently used as a measure of anticipatory sexual excitement (e.g., Mendelson & Pfaus, 1989; Pfaus & Phillips, 1991; van Furth & van Ree, 1996a, 1996b,). The females used as copulatory partners in this experiment were given at least ten preliminary sessions with sexually experienced males in the bilevel chambers to acquire the full range of sexual behaviors, including high rates of solicitation, pacing, and other proceptive behaviors, as well as lordosis. The males were allowed one week to adapt to the animal colony before their behavior training began. Prior to their first sexual contact, males were acclimated to the bilevel chambers for five 30-minute sessions across ten days. After these sessions, each male was placed into a bilevel chamber for five minutes prior to the introduction of a sexually receptive female. Both rats were allowed to copulate for 30 minutes before the test terminated. Eight such sessions were conducted to provide the males with requisite sexual experience.

Procedure

After completing the sexual behavior training sessions, one vehicle baseline session was conducted. All males then began receiving daily injections of fluoxetine hydrochloride

(10 mg/kg ip). Tests of sexual behavior were conducted every fourth day throughout fluoxetine treatment for a total of nine sessions. Each test session consisted of the introduction of the male into the bilevel test chamber followed five minutes later by the introduction of the female and the opportunity to copulate freely for 30 minutes. A videocamera recorded each session for later scoring. For test session 10, the males were stratified into three groups according to the latency to ejaculation they demonstrated at baseline. The two experimental groups received a co-treatment of ritanserin, either at 3.2 mg/kg (low dose) or 5.6 mg/kg (high dose) ip. The control group received vehicle co-treatment in a volume of 1.0 ml/kg ip. All co-treatments were administered 20 minutes before test session 10 began.

Data Analysis

Videotapes of the test sessions were coded using a real-time, computerized event recorder (Cabilio, 1996). An appetitive level change was noted to have occurred when the male moved completely from one level of the bilevel testing chamber to the other. The number of level changes (LC) during the 5-minute adaptation session was recorded. Also recorded were the number of mounts displayed without vaginal intromission (NM), the number of mounts with intromission (NI), and the number of ejaculations (NE) displayed by the male during the 30-minute session, each as defined by Sachs and Barfield (1976). To yield a measure of copulatory efficiency, the intromission ratio (IR) was calculated as the number of mounts with intromissions divided by the total number of mounts both with and without intromission.

Results

Nineteen males survived the chronic fluoxetine treatment. No mortalities occurred after test session 5, at which time the fluoxetine injections began to be administered at the end of the animals' normal feeding period. All data analyses regard these nineteen animals.

Effects of Chronic Fluoxetine Treatment

At this phase of the experiment, the male animals formed a single group, all having received identical treatment thus far. Comparison of the males' baseline behaviors to their behaviors at the end of chronic fluoxetine treatment was conducted by paired samples *t* tests. Consistent with our previous observations (Cantor et al., 1999) and present hypotheses, the male rats were anticipated to demonstrate fewer sexual behaviors. This permitted test statistics to be compared to one-tailed critical values.

Consistent with our previous observations, male rats receiving chronic fluoxetine injections demonstrated reduced sexual activity in a behavior-specific pattern (Table 1). After fluoxetine treatment, the number of appetitive level changes shown by the males was not significantly different from baseline, $t(18) = -1.78$, n.s., corroborating the observation that changes in appetitive sexual behavior tolerate over the long-term, in this case, 37 days. Significant decreases were detected in the animals' intromission ratio, $t(18) = 8.22, p < .001$ (one-tailed) and the number of their ejaculations, $t(18) = 8.15, p < .001$ (one-tailed).

Effects of Ritanserin Co-Treatment

No significant differences were detected between the groups receiving low doses versus high doses of ritanserin, *t*s (11) < 1.96, n.s. (two-tailed), on any of the dependent variables. The two experimental groups were therefore combined into a single ritanserin-treated group and compared to the control group for the subsequent analyses.

Table 2 shows the male sexual behavior frequencies exhibited during the final chronic fluoxetine trial and during the subsequent experimental trial of ritanserin (or vehicle). The behavior frequencies from the final fluoxetine session were subtracted from the frequencies of the ritanserin session to yield the gain scores associated with ritanserin co-treatment. The gain scores of the ritanserin group were then compared to those of the control group with independent groups' *t* tests.

Appetitive sexual behavior did not significantly increase, at least as demonstrated through any increase in LCF, $t(17) = -.28$, n.s. However, it remains possible that potential effects are being masked by a ceiling effect; the frequency of appetitive level changes already returned to baseline levels before the ritanserin test session took place.

The ritanserin-treated males demonstrated a significant increase in IR relative to the males receiving vehicle co-treatment, $t(17) = 1.89$, $p = .038$ (one-tailed). However, no differences were detected in the absolute number of mounts, either with intromission, $t(17) = 1.21$, n.s., or without intromission, $t(17) = -0.63$, n.s. This difference in the sensitivity of the variables is attributable to the derivation of the intromission ratio. IR increases as the number of intromissions increases, and IR decreases as the number of mounts increases. In the present situation, the number of intromissions increased, and the

number of mounts decreased. Yet, neither change was significant individually. However, their individual effects are combined in calculating the IR.

Also detected was a significant increase in the EF of the ritanserin group relative to the control group, $t(14.94) = 1.76, p = .049$ (one-tailed).

Discussion

The high mortality of the fluoxetine-treated animals we reported in Study 1 occurred in the present experiment. Because rats consume most of their daily food intake during the dark portion, and fluoxetine produces a hypophagia, chronic administration may have produced a chronic anorectic effect. No mortalities occurred once the rats began receiving injections at end of the dark portion of their light cycle.

The present results confirm that male rats receiving chronic administration of fluoxetine demonstrate behavior-specific reductions in sexual activity. A clear dissociation was observed between the appetitive variable, the number of appetitive level changes, and the consummatory variables (number of intromissions, the intromission ratio, and the number of ejaculations). The return of the number of appetitive level changes to baseline levels prior to the end of the long-term administration of fluoxetine is consistent with the trend toward such tolerance we previously reported. This demonstration of baseline levels of appetitive level changing demonstrated by fluoxetine-treated males also argues against the supposition that the observed sexual dysfunctions were due to generalized illness or gross motor retardation. Generalized somatic distress would be more likely associated with global rather than specific behavioral suppression. The dramatic decline in the number of ejaculations during chronic

fluoxetine treatment strongly replicates our previous observation of the effect of chronic fluoxetine in male rats.

Also observed was a significant decrease in the number of intromissions, despite that such a difference was not previously observed. This difference may be due to the increased power associated with the current design. Our previous study (Cantor et al., 1999) divided 40 animals into four independent groups. Only one group received the high dose (10 mg/kg) of fluoxetine, and several of the animals in the group died, further decreasing power. In the present design, all animals received the high dose and were examined as a single, larger group in a pre/post design.

The administration of ritanserin to fluoxetine-treated male rats resulted in significant increases in consummatory sexual behaviors, although not in appetitive sexual behavior. The recovery of normal consummatory behavior after ritanserin treatment supports the hypothesis that such behavior is moderated by 5-$HT_{2A/2C}$ neurons. Yet, the failure of appetitive behavior to increase does not necessarily argue that such behavior is free of 5-$HT_{2A/2C}$ influence. As noted above, because the number of appetitive level changes already returned to baseline levels before the ritanserin test, many effects of the co-treatment could be obscured by a ceiling effect. It would be interesting to speculate whether changes in the appetitive behavior variable would have been observed were ritanserin administered after fewer than 41 days of fluoxetine treatment.

Ritanserin has not yet been marketed for clinical use in humans. However, the success of ritanserin to reverse fluoxetine-induced anorgasmia in male rats suggests that ritanserin may be of use in this regard. Because of the unpleasant side-effects reported to

be associated with cyproheptadine, ritanserin may be the preferred adjunctive treatment by patients taking SSRI medication.

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Table 1

Mean (SEM) Sexual Behavior Frequencies After Chronic Fluoxetine Administration

	Frequency of Behavior		
Behavior	Baseline	After Fluoxetine	$t(18) =$
LC	5.8421 (.873)	8.4737 (1.14)	-1.78
NM	7.3684 (2.352)	4.4211 (1.316)	1.00
NI	8.2105 (1.239)	1.6316 (.831)	6.11***
IR	.6317 (.067)	.1021 (.042)	8.22***
NE	2.3158 (.276)	.1053 (.072)	8.15***

Note: Behaviors measured: number of appetitive level changes (LC); number of mounts without intromission (NM); number of mounts with intromission (NI); ratio of intromissions to all mounts (IR), where IR = NI / (NM + NI); and the number of ejaculations (NE).

*** $p < .001$, one-tailed.

Table 2

Mean (SEM) Sexual Behavior Frequencies Before and After Co-Administration of Ritanserin

	Test Day 37 (Comparison Session)	Test Day 41 (Experimental Session)		
Behavior	Chronic Fluoxetine Only (n = 19)	Fluoxetine plus Vehicle (n = 6)	Fluoxetine plus Ritanserin (n = 13)	Comparison of Gain Scores
LC	8.4737	6.1667	6.5385	$t(17) = -0.28$
	(1.14)	(1.721)	(.882)	
NM	4.4211	10.8333	6.9231	$t(17) = -0.63$
	(1.316)	(5.588)	(1.792)	
NI	1.6316	2.6667	4.1538	$t(17) = 1.21$
	(.831)	(1.430)	(1.109)	
IR	0.1021	0.1029	0.3341	$t(17) = 1.89$*
	(.042)	(.050)	(.062)	
NE	.1053	.6667	1.4615	$t(14.94) = 1.49$*
	(.072)	(.494)	(.369)	

Note: Behaviors measured: number of appetitive level changes (LC); number of mounts without intromission (NM); number of mounts with intromission (NI); ratio of intromissions to all mounts (IR), where IR = NI / (NM + NI); and the number of ejaculations (NE). Gain scores reflect the increase in behavior frequency from the pre-experimental session to the experimental session. Degrees of freedom are adjusted in cases of heterogeneous variance.

* $p < .05$, one-tailed.

Preface to Study 3

Studies 3 and 4 continued to replicate the original model of fluoxetine-induced sexual dysfunction developed in Study 1. It employed the improved fluoxetine dosing schedule to confirm that it would solve the mortality problem formerly observed in Study 1. Studies 3 and 4 were run simultaneously with independent experimental groups and a single control group. They are included here as separate manuscripts to increase clarity.

Study 3 tested the ability of yohimbine, an antagonist at type 2 alpha adrenoceptors (α_2), to reverse the SSRI-induced sexual dysfunction. Although several anecdotal reports and small group studies in humans have used yohimbine to reverse anorgasmia, controlled tests have not yet been conducted. Additionally, yohimbine is frequently regarded as a drug which, used on its own, facilitates penile erection without accelerating ejaculation in men (Crenshaw & Goldberg, 1996). Therefore, the specific pattern of copulatory behaviors produced by yohimbine in a controlled environment is of interest to inform the interpretation of these contradictory reports.

Reversal of Fluoxetine-Induced Sexual Dysfunction by Yohimbine

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Abstract

The ability of yohimbine hydrochloride, an α_2 antagonist, to reverse selective serotonin reuptake inhibitor (SSRI)-induced sexual dysfunction was investigated. Thirty male, Long-Evans rats received injections of fluoxetine hydrochloride (10 mg/kg ip) over a 29-day period and received exposure to sexually receptive, female rats every fourth day. By the end of the first 25 days of fluoxetine treatment, males showed significantly fewer ejaculations and appetitive level changes, but no changes in mount or intromission frequency. They also demonstrated significantly increased mount latencies and post-ejaculatory intervals. On day 29, males received injections of either the α_2 adrenoceptor antagonist, yohimbine (2.0 mg/kg or 4.0 mg/kg ip) or distilled water, 30 minutes before the final sexual behavior test. The animals treated with the high dose of yohimbine exhibited a significant and specific increase in ejaculatory frequency. Other sexual behavior frequencies were not affected. The implications of these results for the clinical use of yohimbine in fluoxetine-induced sexual dysfunction are discussed.

Reversal of Fluoxetine-Induced Sexual Dysfunction by Yohimbine

Evidence exists supporting that the ejaculatory responses inhibited by chronic fluoxetine treatment may occur by inhibiting the release of the neuropeptide, oxytocin. Oxytocin potently facilitates ejaculation in animals (Arletti, Bazzani, & Bertolini, 1992; Arletti, Bazzani, Castelli, & Bertolini, 1985; Fjellstrom, Kihlstrom, & Melin, 1968; Moody, Steinman, Komisaru, & Adler, 1992; Stoneham, Everitt, Hansen, Lightman, & Todd, 1985), while antagonists of oxytocin deter it (Argiolas, Collu, Gessa, Melis, Serra, 1988). Chronic fluoxetine treatment, in turn, has been shown to alter oxytocin responses to 5-HT receptor agonists through neuroadaptive changes in 5-HT receptor sensitivity (Li et al., 1993; Li, Levy, Cabrera, Brownfield, Battaglia, & Van de Kar, 1993; Li, Muma, & Van de Kar, 1996). Consistent with these findings, we have demonstrated that both oxytocin and the 5-$HT_{2A/2C}$ receptor antagonist, ritanserin, reverse the fluoxetine-induced inhibition of ejaculation in male rats [Studies 1 and 2]. However, despite the successful reversal of ejaculation dysfunction by these co-treatments, neither drug affected appetitive sexual behavior, as measured by the frequency of pre-copulatory level changes in a bi-level testing chamber. Thus, the 5-$HT_{2A/2C}$-oxytocin conduit may be specific to ejaculation. Appetitive and consummatory sexual behaviors load onto different factors in factor analytic studies of animal sexual behavior (Pfaus, Mendelson, & Phillips, 1990), also supporting the general view that separate neurological systems may underlie them (e.g., Everitt, 1990).

Another possible approach to reversing inhibited sexual behaviors is through administration of α_2 antagonists, such as yohimbine. The application of yohimbine, as

well as the other α_2 antagonists, idazoxan and delequamide, has been shown to increase sexual excitation in male rats (e.g., Clark, Smith, & Davidson, 1984; Tallentire, McRae, Speeding, Clark, & Vickery, 1996), an effect which appears to be specific to excitatory or motivational sexual parameters. This sexual excitation has been observed through several paradigms: mount frequency following penile anesthetization (Clark et al., 1984), recovery from sexual exhaustion (Rodríguez-Manzo & Fernández-Guasti, 1994), and decreases in behavior latencies in normal, freely copulating males with estrous females (Clark, Smith, & Davidson, 1985).

The mount frequency paradigm assesses sexual motivation by first anesthetizing the glans of the penis. This blocks sensory feedback, preventing the male from tactile location of the vagina during copulation. This, in turn, prevents intromission and ejaculation. Relative sexual motivation is then inferred from the frequency of the male's attempts to intromit despite repeated failure. When in this paradigm, anesthetized male rats demonstrated significantly more mounts after receiving yohimbine treatment than did controls after receiving vehicle treatment (Clark et al., 1984).

In the exhaustion paradigm, male rats are permitted to copulate freely until they cease to respond to additional solicitations from estrous females. Researchers apply various experimental manipulations to male rats who are in this state, and any resumption of sexual behavior is quantified and analyzed. Rodríguez-Manzo and Fernández-Guasti (1994) administered yohimbine and 8-OH-DPAT, a potent 5-HT_{1A} agonist, to sexually exhausted rats and noted that animals treated with either drug copulated with significantly greater frequency than did sexually sated control animals. However, the two drugs

produced different patterns of sexual facilitation. 8-OH-DPAT, but not yohimbine, appeared to lower the ejaculatory threshold. That is, the 8-OH-DPAT animals ejaculated after fewer intromissions than did controls, while yohimbine-treated animals required increased penile stimulation to trigger ejaculation. By contrast, only the yohimbine-treated animals showed increased sexual motivation, as reflected by decreased intromission latencies.

In standard testing procedures with freely copulating rats, yohimbine has also been observed to induce sexual excitation (e.g., Clark et al., 1985). The latency to ejaculation, the mean delay between intromissions, and the intervals between copulatory bouts all decreased after yohimbine treatment. The facilitating effects of yohimbine appear specific to sexual excitation in that experiment, no changes were noted in the copulatory efficiency of the animals; the ratio of intromissions to mounts and intromissions remained the same. In extending these findings with a more comprehensive dose-response and time course study, a similar pattern was revealed (Smith, Lee, Schnur, & Davidson, 1987). Behavioral latencies again decreased, while the frequency of mounts and intromissions remained the same. A dose response effect was also noted. Maximum excitation occurred in the dose range from 1.0 to 4.0 mg/kg ip, while significant decreases in excitation were observed at the highest dose of yohimbine, 8.0 mg/kg ip. Unfortunately, the protocols employed in these studies did not include the measurement of the animals' total ejaculatory frequency.

In human males, yohimbine has a long, but mostly anecdotal, history for enhancing male sexual function in human males. In their comprehensive review, Crenshaw and

Goldberg (1996) concluded that yohimbine does outperform placebo in the treatment of psychogenic erectile dysfunction, but that the effects are less pronounced in patients with organic sexual dysfunctions. No changes in ejaculation latency were ever reported. However, despite having no independent facilitating effect on human ejaculation, yohimbine has been used sporadically to attempt to reduce SSRI-induced sexual dysfunctions in uncontrolled studies in humans (Ashton, Hamer, & Rosen, 1997; Jacobsen, 1992). Although both studies indicated improvement in self-reported, general sexual functioning of patients receiving yohimbine co-treatment, neither study explicitly reported whether it was the anorgasmic symptoms which resolved.

The specificity of yohimbine for the sexually excitatory parameters of male rat behavior suggests a potential to reverse the inhibition of appetitive sexual behavior induced by fluoxetine. Where oxytocin and ritanserin demonstrated a specificity for fluoxetine-induced inhibition of ejaculation, yohimbine might represent demonstrate specificity for fluoxetine-induced inhibition of sexual excitation. Yet, where yohimbine has been non-specifically reported to reverse SSRI-induced sexual dysfunction, it might represent a different mechanism to produce the same effect as oxytocin and ritanserin. After chronic fluoxetine treatment, male rats received yohimbine hydrochloride co-treatment. Reversal of sexual dysfunction was anticipated, as with yohimbine's clinical application in humans. In addition, excitatory effects were also hypothesized to occur in appetitive level change frequency, consistent with previous animal data regarding the administration of yohimbine.

Materials and Methods

Given our observation [in Study 2] that animals tolerated chronic fluoxetine more easily when receiving it at the end of the normal feeding period, the daily injections were maintained at 2100h. Our previous data regarding the time course of fluoxetine-induced sexual dysfunction [Study 1] revealed that appetitive level changes drop early during chronic treatment and then recover somewhat, while ejaculatory frequency decreases more slowly over time. Therefore, for the present experiment, the duration of chronic fluoxetine treatment was reduced to seven sessions. This length was judged sufficient to instantiate the long-term effect of ejaculatory inhibition, but be less likely to permit the inhibition of appetitive level changes to recover.

Animals

Thirty male, Long-Evans rats (400-450 g) were obtained from Charles River Canada, St. Constant, Québec. They were quadruply housed in suspended, stainless steel cages (65 × 180 × 26 cm) and maintained on a reversed 12h:12h light/dark cycle (lights off at 0900 hours) at approximately 21°C. Food and water were available *ad libidum*. Sexually experienced, female Long-Evans rats, obtained from the same breeder were used as stimulus partners in the experiment. The females were ovariectomized bilaterally under ketamine/xylazine anesthesia and subsequently rendered sexually receptive by subcutaneous injections of estradiol benzoate (10 μg in sesame oil) and progesterone (500 μg in sesame oil) administered 48 hours and 4 hours before tests of sexual behavior,

respectively. All animal handling, housing, injections, and testing procedures conformed to the guidelines of the Canadian Council on Animal Care.

Drugs

Fluoxetine hydrochloride (Atlantic Chemicals, Toronto, Ontario, Canada) was dissolved in distilled water to a concentration of 10.0 mg/ml and delivered ip at 1.0 ml/kg body weight. Fluoxetine was prepared daily and administered at the end of the dark cycle, to minimize hypophagia during the animals' normal feeding period. Yohimbine (Aldrich, Milwaukee, WI) was dissolved in distilled water at concentrations of 2.0 mg/ml (low dose) and 4.0 mg/ml (high dose). Yohimbine was delivered ip in volumes of 1.0 ml/kg body weight, 30 minutes before beginning sexual behavior testing.

Behavioral Testing

Tests of sexual behavior took place in bilevel chambers, as described previously (Pfaus et al., 1990). Male rats placed repeatedly in such chambers for five-minute adaptation periods prior to the presentation of a sexually receptive female come to demonstrate conditioned level changing, a behavior that serves as a measure of anticipatory sexual excitement (Mendelson & Pfaus, 1989; Pfaus & Phillips, 1991). The female copulatory partners in this experiment were given at least four preliminary sessions with sexually experienced males to acquire the full range of sexual behaviors, including high rates of solicitation, pacing, and other proceptive behaviors, as well as lordosis. Prior to their first sexual contact, the subject males were acclimated to the bilevel chambers for five 30-minute sessions. On subsequent test sessions, each male was placed into a bilevel chamber for five minutes prior to the introduction of a sexually

receptive female. Both rats were then allowed to copulate freely for 30 minutes before the termination of the test. Five such sessions were conducted to provide the males with sexual experience.

Procedure

After the set of sexual behavior training sessions, one baseline session was conducted. All males then began receiving daily injections of fluoxetine hydrochloride (10 mg/kg ip). Tests of sexual behavior occurred every fourth day throughout fluoxetine treatment for a total of eight sessions across 29 days. Each test session consisted of the introduction of the male into the bilevel test chamber followed five minutes later by the introduction of the female and the 30-minute copulation period. A videocamera recorded each session for later scoring. For the final test session (day 29), the males were divided randomly into three groups. Two experimental groups received co-treatment of yohimbine, either at 2.0 mg/kg ip (low dose) or 4.0 mg/kg ip (high dose). The control group received vehicle co-treatment at a volume of 1.0 ml/kg ip. All co-treatments were administered 30 minutes before the final behavioral test session began.

Data Analysis

Scorers, blind to the animals' group assignments, used a real-time, computerized event recorder (Cabilio, 1996) to code level changes and male sexual behaviors as operationalized by Sachs and Barfield (1976) and as summarized below. An appetitive level change was noted to have occurred when the male moved completely from one level of the bilevel testing chamber to the other. The latency to the first level change (LCL) and the total number of level changes (LC) occurring during the 5-minute adaptation session

were recorded. Also recorded were: the number of mounts (NM) and the number of intromissions (NI) displayed before ejaculation occurred; the total number of ejaculations (NE) displayed during the 30-minute test session; the latency to the first mount (either with or without an intromission; ML); the latency to the first intromission (IL); the ejaculation latency (EL) or the time from the first intromission to the ejaculation; and the post-ejaculatory interval (PEI) or duration of the period from the ejaculation to the intromission of the next series. Two other behavioral parameters were calculated from these raw data. To yield a measure of copulatory efficiency, the intromission ratio (IR) was calculated as the number of intromissions divided by the total number of mounts both with and without intromission (ie., IR = NI / NI+NM). To yield a measure of copulatory rate, the inter-intromission interval (III) was calculated as the mean time between intromissions during the first ejaculatory series (ie., III = EL / NI).

Changes in each of the sexual behaviors occurring from the baseline (day 1) to the post-chronic fluoxetine sessions (day 25) were tested for statistical significance with *t*-tests for correlated samples. Because of the highly skewed distributions exhibited by the latency and interval data, the time variables (LCL, ML, IL, EL, III, PEI) were also tested with the Wilcoxon signed rank test for matched pairs. To test the significance of changes in animals' sexual behaviors after co-treatment with yohimbine (day 29), difference scores were calculated relative to the previous fluoxetine-only test session (day 25). These gain scores were then compared with one-way ANOVAs, with the group membership forming a three-level independent variable. Follow-up testing of the ANOVA results was limited to the comparison of the difference scores of the experimental groups to those of the

controls. Because of our specific interest in fluoxetine-induced decreases of behavior and yohimbine-induced increases in behavior, test statistics were compared against one-tailed critical values.

Results

Of the 30 animals beginning the experiment, two died during chronic fluoxetine administration. All results reported below reflect the remaining 28 animals.

The frequencies of and latencies to each sexual behavior at day 1 (baseline) and at day 25 appear in Table 1. Through day 25, all animals had received identical treatment, not yet having been divided into the experimental co-treatment groups. They therefore formed at that point, a single, chronic-fluoxetine group. At the end of chronic fluoxetine treatment, males demonstrated significantly inhibited sexual behavior as reflected by decrease behavior frequencies and increased latencies in behavior. Specifically, the rats showed changes in the number of appetitive level changes, $t\,(27) = 2.63, p = .007$, the mount latency, $t\,(26) = -2.97, p = .0035$, the intromission ratio, $t\,(26) = 2.46, p = .011$, the number of ejaculations, $t\,(27) = 4.79, p < .001$, and the duration of the post-ejaculatory interval, $t\,(18) = -3.45, p = .002$ (all one-tailed). The degrees of freedom of some latency variables are reduced, reflecting the missing latency values of animals which did not exhibit each behavior during the tests. No significant differences were detected in the other copulatory behaviors. The application of the Wilcoxon signed rank test to these data revealed the identical pattern of results.

The mean sexual behavior frequencies of yohimbine and controls groups appear in Table 2. No significant group differences were detected in the number of appetitive level

changes, $F(2, 25) = 0.141$, n.s., after yohimbine treatment. Copulatory parameters also appeared unaffected, as no group differences were detected in mounts, $F(2, 25) = 1.13$, intromissions, $F(2, 25) = 0.25$, or the intromission ratio, $F(2, 22) = 1.19$, each n.s. A significant group difference in gain scores was detected in the number of ejaculations displayed by the rats, $F(2, 25) = 3.66$, $p = .032$. The planned comparisons between the control groups and the experimental groups revealed a significant increase in the high dose yohimbine group $t(25) = 2.78$, $p = .005$ (one-tailed), but not the low dose, $t(25) = 0.93$, n.s. No differences between the low dose and control group were detected.

Discussion

The present design successfully avoided much of the mortality associated with our previous dosing schedule of chronic fluoxetine [Studies 1 and 2]. Ninety-three percent of the present sample survived chronic treatment with 10 mg/kg fluoxetine, while only fifty percent did so in our first fluoxetine study. Administration of fluoxetine at the end of rather than earlier in the dark portion of the circadian cycle effectively reduces hypophagia and loss of body weight in chronically treated animals.

In Study 1, the smaller sample and proportion of animals which did not display each behavior prevented the analysis of behavioral latencies. However, the greater number of animals in the present study receiving and tolerating 10 mg/kg permitted those analyses. The pattern of fluoxetine-induced sexual dysfunction reported here replicate those we previously observed in male rats in Study 1. That is, prolonged treatment with fluoxetine produced decrease appetitive behavior and ejaculation frequencies, while leaving the number of mounts and intromissions intact. The present design shortened the

administration of fluoxetine to 25 days, from the 33 days used in Study 2 in order to test the rats before tolerance to fluoxetine would accrue in level change frequency. The detection of a significant decrease in level changes after chronic fluoxetine treatment supports that methodological change. The greater tolerance of the treatment of the animals in the present study and the strong similarity between the present and original results also argue that the behavioral decreases observed were due to direct chemical action rather than to any general illness or hypophagia of the animals.

Analyses of latency data demonstrated significantly increased delay before the initiation of mounts, consistent with decreased sexual excitation. Interestingly, no such increased delay to appetitive level changes was observed. Because of few animals demonstrating two (or more) ejaculatory series, the post-ejaculatory intervals of only 17 of 28 animals are available. Those animals which did show multiple ejaculations demonstrated increased intervals of time between them, relative to baseline.

Despite previous findings of the animal literature that yohimbine induces increased sexual excitation, it did not augment the frequency of appetitive level changes. Interestingly, the present pattern of results more closely resemble the existing human clinical data regarding the effects of yohimbine in SSRI-treated patients. That is, yohimbine partially reversed the fluoxetine-induced decreases in ejaculatory frequency in the experimental animals, and the clinical use of yohimbine demonstrates some efficacy to treat SSRI-induced anorgasmia in humans.

This reversal pattern from yohimbine on fluoxetine-induced sexual dysfunction — i.e., increased ejaculation frequency but not level changes or intromission ratio—strongly

resembles what we observed from oxytocin (Cantor et al, 1999). This suggests that yohimbine may exert its effects through oxytocin neurons. Norepinephrine infused into the cerebral ventricles produces increased release of oxytocin (Knigge, Willems, Kjaer, Jorgensen, & Warberg, 1999) and systemically administered yohimbine induces oxytocin neurons in the hypothalamus to express FOS, indicating increased protein synthesis activity in those cells (Tsujino et al., 1992).

It remains possible that the failure to observe a facilitation of level changes is caused by a ceiling effect. Although the number of appetitive level changes significantly decreased in this study after chronic fluoxetine treatment, the difference was small in absolute terms. A parallel increase might be detectable only with the statistical power associated with larger samples. Additionally, our fluoxetine time course study [Study 1] revealed that the frequency of level changes decreases during initial chronic treatment, but begins to increase again over time. It would be interesting to apply yohimbine co-treatment after 17 days of fluoxetine treatment rather than 29.

The present results represent the first controlled trial of yohimbine to reverse fluoxetine-induced sexual dysfunction and support its clinical use. Research with other α_2 antagonists may also prove useful in this regard, possibly identifying those which lack the unintended effects associated with yohimbine use in humans.

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Table 1

Mean (SEM) Sexual Behavior Frequencies After Chronic Fluoxetine Administration

	Test Phase			
Behavior	Baseline	post-Fluoxetine	df	*t* (one-tailed)
LCL	17.29 (3.66)	17.11 (3.25)	27	0.04
LC	11.33 (.74)	8.78 (.822)	27	2.63**
ML	8.27 (.82)	18.42 (3.46)	26	2.97**
NM	5.19 (.98)	8.70 (1.89)	27	-1.60
IL	18.04 (3.43)	133.95 (73.14)	22	-1.57
NI	10.07 (1.11)	7.74 (1.19)	27	1.65
III	22.16 (2.09)	26.25 (2.10)	18	-1.25
IR	.682 (.03)	.484 (.062)	26	2.46*
EL	224.9 (43.21)	260.7 (42.27)	18	-0.74
NE	3.19 (.13)	1.78 (.26)	27	4.79***
PEI	295.6 (10.34)	355.28 (17.30)	18	3.45**

Note: Behaviors measured: level change latency (LCL); number of level changes (LC); mount latency (ML); number of mounts (NM); intromission latency (IL); number of intromissions (NI); inter-intromission interval (III); ratio of intromissions to all mounts (IR), where IR = IF / (MF + IF); ejaculation latency (EL); number of ejaculations (NE); and the post-ejaculatory interval (PEI).

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Table 2

Mean (SEM) Frequency of Copulatory Behaviors of Male Rats after Co-treatment with Yohimbine or Vehicle.

	Vehicle	Yohimbine		
	0 mg/kg	2 mg/kg	4 mg/kg	Gain Score
Behavior	(n = 10)	(n = 9)	(n = 9)	F (2, 25) =
LCF	9.6	6.67	8.33	0.14
	(1.00)	(1.37)	(1.19)	
MF	5.50	5.00	6.44	1.13
	(1.99)	(2.46)	(1.25)	
IF	7.60	7.22	5.56	0.25
	(1.63)	(1.91)	(1.02)	
IR†	.592	.653	.492	1.19
	(.103)	(.049)	(.090)	
EF	1.80	1.89	2.11**	3.96*
	(0.42)	(0.42)	(0.31)	

Note: Behaviors measured: frequency of appetitive level changes (LCF); frequency of mounts without intromission (MF); frequency of mounts with intromission (IF); ratio of

intromissions to all mounts (IR), where IR = IF / (MF + IF); and the frequency of ejaculations (EF). Gain scores reflect the increase in behavior frequency from the pre-experimental session to the experimental session.

†Some subjects displayed zero mounts and intromissions during testing, obviating the intromission ratio because of division by zero. The removal of these subjects reduces the degrees of freedom available for the analysis of this variable from 25 to 22.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Preface to Study 4

Because we have found that antagonists at 5-$HT_{2A/2C}$ receptors and antagonists at α_2 receptors were both able to reverse fluoxetine-induced sexual dysfunction, Study 4 tested the ability of mianserin, an antagonist at both 5-$HT_{2A/2C}$ and α_2 receptors, to effect the same result. One uncontrolled report, without formal analyses, supported mianserin to reverse anorgasmia, but no controlled tests have yet been conducted.

Reversal of Fluoxetine-Induced Sexual Dysfunction by Mianserin

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Abstract

The ability of mianserin hydrochloride, an antagonist at both 5-$HT_{2A/2C}$ and α_2 receptor sites, to reverse selective serotonin reuptake inhibitor (SSRI)-induced sexual dysfunction was investigated. Thirty male, Long-Evans rats received injections of fluoxetine hydrochloride (10 mg/kg ip) over a 29-day period and received exposure to sexually receptive females every fourth day. By the end of the first 25 days of fluoxetine treatment, males showed significantly fewer ejaculations and appetitive level changes, but no changes in mount or intromission frequencies or copulatory efficiency. They also demonstrated significantly increased post-ejaculatory intervals. On day 29, males received injections of either mianserin (1.0 mg/kg or 10.0 mg/kg ip) or distilled water, 30 minutes before the final sexual behavior test. The animals treated with 1.0 mg/kg mianserin exhibited a significant and specific increase in appetitive level changes. Other sexual behavior frequencies were not affected. The implications of these results for the clinical use of mianserin in fluoxetine-induced sexual dysfunction are discussed.

Reversal of Fluoxetine-Induced Sexual Dysfunction by Mianserin

Pharmacological and surgical interventions which increase serotonin (5-HT) transmission generally inhibit sexual function, while the interventions which decrease 5-HT transmission serve to increase copulatory behavior (Da Prada, Carruba, O'Brien, Saner, & Pletscher, 1972; Fernández-Guasti & Rodriguez-Manzo, 1992; McIntosh & Barfield, 1984; Menéndez-Abraham, Morán-Viesca, Velasco-Plaza, & Marín, 1988). This relationship has been frequently suggested as the explanation for the inhibition of ejaculation and of sexual desire produced by the clinical use of fluoxetine (Balon, 1998; Gijs & Gooren, 1996; Gitlin, 1994; Metz, Pryor, Nesvacil, Abuzzahab, & Koznar, 1997; Segraves, 1989, 1995, 1998; Waldinger, Berendsen, Blok, Olivier, & Holstege, 1998). Our previous findings with chronic fluoxetine in male rats indicate that the inhibition of ejaculation can be reversed with the 5-$HT_{2A/2C}$ antagonist, ritanserin [Study 2], and with the α_2 antagonist, yohimbine [Study 3]. These results suggest that a similar effect would be produced by the anti-depressant drug, mianserin, which acts as an antagonist both at 5-$HT_{2A/2C}$ sites, similarly to ritanserin, and at α_2 sites, similarly to yohimbine. In contrast with selective serotonin reuptake inhibiting and tricyclic anti-depressants, mianserin does not inhibit the reuptake of 5-HT at synaptic sites.

In an uncontrolled study, a mixed group of 15 men with depression, panic, posttraumatic stress disorder, or obsessive–compulsive disorder received mianserin (15 mg daily) to combat the sexual dysfunctions induced by their anti-depressant medication (Aizenberg, Gur, Zemishlany, Granek, Jeczmien, & Weizman, 1997). The

anti-depressants included fluoxetine (n = 7), fluvoxamine (n = 1), and clomipramine (n = 7). The most pronounced sexual dysfunction reported was anorgasmia, but some levels of inhibited sexual desire and erectile dysfunction were also present. The authors reported that, after two weeks of co-treatment with mianserin, "improvement...was noted mainly in orgasmic function...and satisfaction," and that sexual "desire and erection improved to a lesser degree" (p. 213). Unfortunately, no statistical analyses were conducted on the patients' ratings. Nor were any objective or psychometrically validated rating instruments employed.

For the present experiment, mianserin was tested for its ability to reverse fluoxetine's effects in our animal model of fluoxetine-induced sexual dysfunction. Due to its simultaneous effects to antagonize 5-$HT_{2A/2C}$ receptors as well as α_2 receptors, mianserin was hypothesized to produce a reversal of the decrease in ejaculation frequency, as did the previously tested drugs.

Materials and Methods

Animals

Thirty male, Long-Evans rats (400-450 g) were obtained from Charles River Canada, St. Constant, Québec. They were quadruply housed in suspended, stainless steel cages (65 × 180 × 26 cm) and maintained on a reversed 12:12 light/dark cycle (lights off at 0900 hours) at approximately 21°C. Food and water were available *ad libidum*. Sexually experienced, female Long-Evans rats, obtained from the same breeder, were used as stimulus partners in the experiment. The females were ovariectomized bilaterally under

ketamine/xylazine anesthesia and subsequently rendered sexually receptive by subcutaneous injections of estradiol benzoate (10 μg in sesame oil) and progesterone (500 μg in sesame oil) administered 48 hours and 4 hours before tests of sexual behavior, respectively. All animal handling, housing, injections, and testing procedures conformed to the guidelines of the Canadian Council on Animal Care.

Drugs

Fluoxetine hydrochloride (Atlantic Chemicals, Toronto, Ontario, Canada) was dissolved in distilled water to a concentration of 10.0 mg/ml and delivered ip at 1.0 ml/kg body weight. Fluoxetine was prepared daily and administered at the end of the dark cycle, to minimize hypophagia during the animals' normal feeding period. Mianserin (Sigma, St. Louis, MO) was dissolved in distilled water to a concentration of 1.0 mg/ml (low dose) and 10.0 mg/ml (high dose). Mianserin co-treatments were delivered ip in volumes of 1.0 ml/kg body weight, 30 minutes before beginning sexual behavior testing.

Behavioral Testing

Tests of sexual behavior took place in bilevel chambers, as described previously (Pfaus et al., 1990). Male rats placed repeatedly in such chambers for five-minute adaptation periods prior to the presentation of a sexually receptive female come to demonstrate conditioned level changing, a behavior that serves as a measure of anticipatory sexual excitement (Mendelson & Pfaus, 1989; Pfaus & Phillips, 1991). The female copulatory partners in this experiment were given at least four preliminary sessions with sexually experienced males to acquire the full range of sexual behaviors,

including high rates of solicitation, pacing, and other proceptive behaviors, as well as lordosis. Prior to their first sexual contact, the subject males were acclimated to the bilevel chambers for five 30-minute sessions. On subsequent test sessions, each male was placed into a bilevel chamber for five minutes prior to the introduction of a sexually receptive female. Both rats were then allowed to copulate freely for 30 minutes before the termination of the test. Five such sessions were conducted to provide the males with sexual experience.

Procedure

After the set of sexual behavior training sessions, one baseline session was conducted. All males then began receiving daily injections of fluoxetine hydrochloride (10 mg/kg ip). Tests of sexual behavior occurred every fourth day throughout fluoxetine treatment for a total of eight sessions across 29 days. Each test session consisted of the introduction of the male into the bilevel test chamber followed five minutes later by the introduction of the female and the 30-minute copulation period. A videocamera recorded each session for later scoring. For the final test session (day 29), the males were divided randomly into three groups. The two experimental groups received co-treatment of mianserin, either at 1.0 mg/kg ip (low dose) or 10.0 mg/kg ip (high dose). The control group received vehicle co-treatment at a volume of 1.0 ml/kg ip. All co-treatments were administered 30 minutes before the final behavioral test session began.

Data Analysis

Scorers, blind to the animals' group assignments, used a real-time, computerized event recorder (Cabilio, 1996) to code level changes and male sexual behaviors as

operationalized by Sachs and Barfield (1976) and as summarized below. An appetitive level change was noted to have occurred when the male moved completely from one level of the bilevel testing chamber to the other. The latency to the first level change (LCL) and the total number of level changes (LC) occurring during the 5-minute adaptation session were recorded. Also recorded were: the number of mounts (NM) and the number of intromissions (NI) displayed before ejaculation occurred; the total number of ejaculations (NE) displayed during the 30-minute test session; the latency to the first mount (either with or without an intromission; ML); the latency to the first intromission (IL); the ejaculation latency (EL) or the time from the first intromission to the ejaculation; and the post-ejaculatory interval (PEI) or duration of the period from the ejaculation to the intromission of the next series. Two other behavioral parameters were calculated from these raw data. To yield a measure of copulatory efficiency, the intromission ratio (IR) was calculated as the number of intromissions divided by the total number of mounts both with and without intromission (ie., IR = NI / NI+NM). To yield a measure of copulatory rate, the inter-intromission interval (III) was calculated as the mean time between intromissions during the first ejaculatory series (ie., III = EL / NI).

Changes in each of the sexual behaviors occurring from the baseline to the post-chronic fluoxetine sessions (day 25) were tested for statistical significance with *t*-tests for correlated samples. Because of the highly skewed distributions exhibited by the latency and interval data, the time variables (LCL, ML, IL, EL, III, PEI) were also tested with the Wilcoxon signed rank test for matched pairs. To test the significance of changes in animals' sexual behaviors after co-treatment with mianserin (day 29), difference scores

were calculated relative to the previous fluoxetine-only test session (day 25). These gain scores were then compared with one-way ANOVAs, with the group membership forming a three-level independent variable. Follow-up testing of the ANOVA results was limited to the comparison of the difference scores of the experimental groups to those of the controls. Because of our interest in changes in specific directions—fluoxetine-induced decreases in behavior frequencies, increases in latencies to behavior, and mianserin-induced increases in behavior—test statistics were compared against one-tailed critical values.

Results

Of the 30 animals beginning the experiment, two died during chronic fluoxetine administration. All results reported below reflect the remaining 28 animals.

The frequencies of and latencies to each sexual behavior at baseline and at day 25 appear in Table 1. Through day 25, all animals had received identical treatment, not yet having been divided into the experimental co-treatment groups. They therefore formed at that point, a single, chronic-fluoxetine group. At the end of chronic fluoxetine treatment, males demonstrated significant behavioral decreases relative to baseline in three specific parameters: the number of appetitive level changes, $t\,(27) = 2.74, p = .006$, the number of ejaculations, $t\,(27) = 2.98, p = .003$, and the duration of the post-ejaculatory interval, $t\,(21) = -2.38, p = .014$. The degrees of freedom of some latency variables are reduced, reflecting the missing latency values of animals which did not exhibit each behavior during the tests. No significant differences were detected in the other copulatory behaviors. The application of the Wilcoxon signed rank test to these data revealed the identical pattern of results.

A significant omnibus difference was detected among the three treatment groups in the number of appetitive level changes, $F(2, 25) = 5.93$, $p = .008$. The comparisons between the mianserin groups and the controls revealed that this difference was attributable to a significant increase in appetitive level changes in the low dose group, $t(25) = 3.44$, $p = .001$ (one-tailed), and not the high dose group $t(25) = 1.48$ (one-tailed), n.s.

No overall differences were detected among the numbers of either mounts, intromissions, or ejaculations Fs (2, 25) = 2.45, 2.10, and 2.52 respectively, n.s., or the intromission ratio, $F(2, 25) = 1.16$, n.s. A significant change in ejaculation frequencies was specifically hypothesized, and a planned comparison revealed that the decrease observed in ejaculation frequency in the high dose mianserin group was significant relative to controls, $t(25) = -2.101$ (two-tailed), $p = .037$. However, this difference was no longer significant after adjustment for multiple comparisons.

Discussion

The present experiment did not exhibit the substantial mortality associated with our initial dosing schedule of chronic fluoxetine (Cantor, Binik, & Pfaus, 1999). Administration of fluoxetine at the end of rather than earlier in the dark portion of the circadian cycle effectively reduces hypophagia and loss of body weight in chronically treated animals. Additionally, the pattern of fluoxetine-induced sexual dysfunction reported here broadly replicate those we previously observed in male rats. That is, prolonged treatment with fluoxetine inhibited appetitive behavior and reduced ejaculation frequency, while leaving other copulatory behaviors intact.

The neuropharmacological profile of mianserin—a combined 5-$HT_{2A/2C}$ and α_2 receptor antagonist—suggested that the drug would demonstrate the same effect on fluoxetine-treated rats as did the 5-$HT_{2A/2C}$-selective and α_2-selective drugs previously tested [Studies 2 and 3]. That is, a specific reversal of fluoxetine-induced ejaculation was anticipated. However, mianserin instead demonstrated a novel behavioral effect in the present paradigm. Appetitive level changes were significantly increased, not the frequency of ejaculations.

This result may be partially due to the dose response curves of the α_2 antagonists for sexual behavior. Our previous findings indicated that reversal of fluoxetine-induced inhibition of ejaculation occurs at a dose of 4.0 mg/kg yohimbine ip, but not 2.0 mg/kg [Study 3]. As well, Tallentire, McRae, Spedding, Clark, & Vickery (1996) demonstrated that sexual facilitation in healthy rats occurred after administration of 1.0 to 4.0 mg/kg yohimbine, but that inhibition occurred after 8.0 mg/kg. The doses of mianserin tested in the present study may lie outside the effective range for a positive ejaculatory response.

The detection of a significant increase in level change frequency, although unexpected, is intriguing. All of the drugs as yet tested with the current paradigm demonstrated a specificity for ejaculation, among the sexual behavior parameters recorded and analyzed. This includes drugs with an antagonist affinity at either 5-$HT_{2A/2C}$ or α_2 receptor sites. The observation that mianserin, a drug with antagonist affinity at each of these sites, selectively affected appetitive level changes suggests that the behavior may be moderated with a more complex interaction or balance between the 5-HT and

norepinephrine (NE) neurotransmitter systems. This may lend insight into the relative lack of sexual dysfunction caused by anti-depressants which act at both 5-HT and NE sites.

The lack of an mianserin-induced reversal in ejaculatory inhibition seems to contrast with the results reported to have occurred in the one study of mianserin in humans for that purpose (Aizenberg et al., 1997). Although formal analyses were not conducted in that study, its authors described that an increase in orgasm ability ensued from mianserin co-treatment. Although it may seem relevant that the present study applied an acute dose of mianserin to the male rats while Aizenberg used chronic co-treatment. However, our previous acute administrations of yohimbine and ritanserin exhibited effects quickly—30 minutes after intraperitoneal injection.

Although a species difference is frequently the simplest explanation for such a contradiction, the preponderance of our data [Studies 1-3] support that the human-rat analogy holds strongly in the present paradigm. It may therefore be constructive to consider alternative methodological explanations. For example, the Aizenberg et al. (1997) study was uncontrolled and employed a self-selected population. The only patients available for that study were those who were already experiencing anti-depressant-induced sexual dysfunction.. They were not a prospective sample of SSRI-treated men, as were those described by Ashton, Hamer, and Rosen (1997). Patients experiencing decreased sexual desire might reasonably be expected to be less likely to present the problem to their physician than patients experiencing anorgasmia. This would bias the sample against showing changes in sexual desire/appetite. Additionally, seven of the

fifteen patients in that study were taking clomipramine, which is less selective for serotonin than is fluoxetine. Clomipramine, a tricyclic anti-depressant, may interact differently with mianserin that does fluoxetine.

Two future manipulations are suggested for future research with mianserin in SSRI-induced sexual dysfunction in animals. To better elucidate the dose response curve of mianserin a wider range of doses should be tested with less distance between each dose. Additionally, mianserin can also be applied in a chronic paradigm, as was reported for its clinical use in humans. Because the pattern of behavioral changes detected here suggest that mianserin may effect systems other than the ejaculatory response, a closer monitoring of patients' individual iatrogenic symptoms should be conducted in any future human studies.

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Table 1

Mean (SEM) Sexual Behavior Frequencies After Chronic Fluoxetine Administration

	Test Phase			
Behavior	Baseline	post-Fluoxetine	df	*t* (one-tailed)
LCL	20.74 (4.89)	23.3 (7.03)	27	-0.34
LC	11.14 (.82)	8.78 (.76)	27	2.74**
ML	11.32 (2.17)	20.52 (8.68)	25	-1.00
NM	7.518 (1.82)	6.78 (1.46)	27	0.34
IL	30.58 (8.26)	34.54 (12.31)	24	-0.38
NI	9.67 (1.16)	8.48 (1.06)	27	0.91
III	26.73 (3.71)	27.05 (3.28)	21	-0.06
IR	.616 (.049)	.594 (.047)	25	0.30
EL	263.4 (44.56)	299.3 (62.56)	21	-0.49
NE	3.00 (.18)	2.07 (.25)	27	2.98**
PEI	313.19 (13.35)	372.0 (25.15)	21	-2.38*

Note: Behaviors measured: level change latency (LCL); number of level changes (LC); mount latency (ML); number of mounts (NM); intromission latency (IL); number of intromissions (NI); inter-intromission interval (III); ratio of intromissions to all mounts (IR), where IR = IF / (MF + IF); ejaculation latency (EL); number of ejaculations (NE); and the post-ejaculatory interval (PEI).

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Table 2

Mean (SEM) Frequency of Copulatory Behaviors of Male Rats after Co-treatment with Mianserin or Vehicle.

	Vehicle	Mianserin		
	0 mg/kg	1 mg/kg	10 mg/kg	Gain Score
Behavior	(n = 10)	(n = 9)	(n = 9)	$F(2, 25)$ =
LCF	9.6	15.11***	8.78	5.93**
	(1.00)	(1.95)	(1.75)	
MF	5.50	10.22	2.78	2.45
	(1.99)	(5.09)	(1.41)	
IF	7.60	4.67	3.67	2.10
	(1.63)	(1.27)	(1.65)	
IR†	.592	.465	.424	1.16
	(.103)	(.131)	(.151)	
EF	1.80	1.67	0.78	2.52
	(0.42)	(0.55)	(0.32)	

Note: Behaviors measured: frequency of appetitive level changes (LCF); frequency of mounts without intromission (MF); frequency of mounts with intromission (IF); ratio of intromissions to all mounts (IR), where IR = IF / (MF + IF); and the frequency of

ejaculations (EF). Gain scores reflect the increase in behavior frequency from the pre-experimental session to the experimental session.

†Some subjects displayed zero mounts and intromissions during testing, obviating the intromission ratio because of division by zero. The removal of these subjects reduces the degrees of freedom available for the analysis of this variable from 25 to 20.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Summary and Conclusions

These studies demonstrate that fluoxetine-induced sexual dysfunctions in men can be effectively modeled in male rats. Reviews of the clinical literature indicate that human males experience anorgasmia as the most severe side-effect of fluoxetine, followed by decreases in sexual desire, and then by erectile dysfunction. The experiments presented here show the effects of chronic fluoxetine in male rats to be decreased frequency of ejaculation, followed by decreased appetitive level changes, and only inconsistent decreases in copulatory efficiency [Studies 1-4]. Although ejaculation latency might appear to be the more obvious analogy to fluoxetine-induced inhibition of ejaculation in humans, a proportion of treated rats show no ejaculation, obviating the measurement of any latency to that behavior.

The substantial mortality demonstrated by the first dosing schedule of fluoxetine would seem to require the model of fluoxetine-induced sex dysfunction to be considered tentative. However, the replication of that pattern with an improved dosing schedule, not strongly influenced by mortality, supports the original model. Additionally, the increase in the rats' sexual behavior frequencies after oxytocin co-treatment argue against any illness effects. Although hypophagia would be a reasonable alternative explanation of decreased behavior, it does not easily explain the increased sexual behavior after oxytocin co-treatment.

The validity of the current model is further evidenced by the analogous changes reported to occur in men and laboratory animals receiving chronic SSRI-treatment and then co-treatment of either 5-$HT_{2A/2C}$ or α_2 antagonists. Men prescribed the 5-$HT_{2A/2C}$

antagonist, cyproheptadine, report a mitigation of sexual dysfunction, and rats receiving ritanserin, another 5-$HT_{2A/2C}$ antagonist, demonstrate increased ejaculation frequency in controlled laboratory conditions [Study 2]. Likewise, men prescribed yohimbine report decreased sexual dysfunction secondary to SSRI treatment, while rats receiving yohimbine again demonstrate increased ejaculation frequency [Study 3]. The single potential exception to this analogy detected thus far is the effect induced by mianserin. The data presented in Study 4 indicate a facilitation of appetitive sexual excitement in male rats. The one study of mianserin in human males to reverse anti-depressant-induced sexual dysfunction implied that the greatest reversal occurred with regard to anorgasmia (Aizenberg, Gur, Zemishlany, Granek, Jeczmien, & Weizman, 1997). However, the uncontrolled design, lack of any statistical analyses, and the diverse patient population used in that study prevent any strong or direct comparison.

The application of the current model in rats allows the study of SSRI-induced sexual dysfunction to apply the greater methodological rigor available to animal researchers. Better matched controls, the wider range of neurobiologically active chemicals, and the opportunity for direct behavioral observation all serve to complement and guide clinical research in humans. Although human sexual behavior is best studied in humans, practical and ethical constraints strongly hinder doing so properly.

The present studies suggest that two drugs, already approved for medical use in humans for other clinical purposes, may be effective in treating fluoxetine-induced sexual dysfunction: oxytocin and ritanserin. Of each of the four drugs tested in rats here, oxytocin demonstrated the most potent pro-sexual effect. Oxytocin proved to be the

only drug which resulted in complete reversal. Although the other agents significantly increased ejaculation frequency, they did not return it to baseline levels. Given that the pharmacokinetics of oxytocin are already well established, clinical research for this new application could be appreciably accelerated. Additional research regarding its chronic administration has not yet been conducted, but would be of invaluable aid in this effort. The primary antidotes suggested in the clinical literature to reverse fluoxetine-induced sexual dysfunction are each associated with side-effects of their own, which often result in their discontinuation. The introduction of a new approach may prove more tolerable to patients. Study 2 suggested that ritanserin may also be of use for the reversal of fluoxetine-induced sexual dysfunction. This would not be surprising, given the number of anecdotal and retrospective reports supporting the use of cyproheptadine, which has a similar receptor affinity pattern. On one hand, ritanserin may avoid some of the unpleasant anti-histaminergic side-effects of cyproheptadine. On the other hand, it may also share cyproheptadine's intermittently reported property of causing the re-emergence of depressive and other symptoms which led to the original treatment with the SSRI.

The nearly identical effects demonstrated by oxytocin, yohimbine, and ritanserin on SSRI-treated rats suggest that they may be acting through a similar final common mechanism. Specifically, oxytocinergic stimulation may be functioning as a common final link, multiply regulated by central neurotransmitter systems. The efficacy of the very low doses of oxytocin (200 ηg ip) used in Study 1, the location of oxytocin receptors throughout the male reproductive tract, and the low permeability of the blood-brain barrier to oxytocin (Leckman et al., 1994) all argue that oxytocin was acting through

peripheral receptors to facilitate ejaculation. The norepinephrine (NE) system participates in the regulation of oxytocin in a excitatory manner. Yohimbine, which indirectly enhances NE release, enhances the release of oxytocin (Knigge, Willems, Kjaer, Jorgensen, & Warberg, 1999). Therefore, yohimbine may enhance ejaculation by releasing oxytocin. Administered alone, ritanserin administration does not appear to affect oxytocin (Bagdy & Kalogeras, 1993; Saydoff, Rittenhouse, Van De Kar, & Brownfield, 1991). However, pretreatment with ritanserin attenuates the surges in plasma oxytocin levels caused by the 5-$HT_{2A/2C}$ agonists 1-(2,5-dimethoxy-4-iodophenyl)-2-amino propane (DOI) and 6-chloro-2-[1-piperazinyl]-pyrazine (MK-212), demonstrating the regulatory control of oxytocin of the 5-HT system through 5-$HT_{2A/2C}$ receptors (Bagdy & Kalogeras, 1993; Saydoff et al., 1991).

The finding that 5-$HT_{2A/2C}$ agonists inhibit oxytocin release seems to contradict the findings that oxytocin and 5-$HT_{2A/2C}$ antagonists both produce effects in the same direction, that is, they both facilitate ejaculation. However, the set of results may be understood through the dual role of oxytocin. Oxytocin triggers ejaculation in mammals, as previously noted by the effects of oxytocin in humans, rats and other animals (Carter, 1992), for which oxytocin is generally described as a pro-sexual substance (Crenshaw & Goldberg, 1996). However, administration of higher doses of oxytocin actually inhibit sexual behavior in a pattern which resembles the post-ejaculatory interval in rats (Stoneham, Everitt, Hansen, Lightman, & Todd, 1985). That is, rats which received doses of oxytocin which inhibit copulatory behavior also emitted a 22kHz vocalization, which normally occurs after ejaculation. This finding indicates that higher doses may inhibit

copulatory behavior through a satiety mechanism. Therefore, interventions which facilitate the release of oxytocin in oxytocin-deficient animals and interventions which attenuate oxytocin in over-stimulated animals may both paradoxically act to enhance sexual behavior.

The inverted-U shaped effect of oxytocin and sexual response has been observed for other drugs, notably 1-(3-chlorophenyl)piperazine (m-CPP), a non-selective 5-$HT_{2A/2C}$ agonist (Bagdy, Kalogeras, & Szemeredi, 1992). Those researchers administered a range of doses of m-CPP to male rats, resulting in dose dependent increases in plasma oxytocin levels and the display of penile erections. However, penile responses were noted at the lower dose range. As oxytocin levels continued to rise with higher doses of m-CPP, penile erections ceased. Interestingly, yohimbine also produces a similar inverted-U pattern in sexual responses. Yohimbine facilitates sexual behavior when injected alone at doses between 1.0 and 4.0 mg/kg ip, but it is inhibitory at 8.0 mg/kg (Smith, Lee, Schnur, & Davidson, 1987).

In a healthy male rat or human male, the ejaculatory and refractory systems operate in concert. After sufficient sexual stimulation, oxytocin levels peak, ejaculation is triggered in peripheral anatomy, and subjective orgasm and the refractory period begin in central areas. After chronic SSRI-treatment however, 5-$HT_{2A/2C}$ neurons alter in their sensitivity to 5-HT stimulation, and therefore, in the sensitivity of the oxytocin neurons they regulate. This may occur either directly, through up- and down-regulation, or indirectly, though the up- and down-regulation of the presynaptic or autonomic 5-HT_{1A} receptors which precede them in neuronal circuits. The altered sensitivity of 5-$HT_{2A/2C}$

neurons may be asserting their effects in the central regulation of the refractory periods and the peripheral regulation of ejaculation.

The neuroendocrinological effects of mianserin have not yet been tested. However, the novel behavioral effects of mianserin in the present SSRI paradigm suggests that its endocrinological profile may also be complex. That is, other 5-$HT_{2A/2C}$ antagonists inhibited oxytocin release after the administration of 5-$HT_{2A/2C}$ agonists. However, these other 5-$HT_{2A/2C}$ antagonists demonstrate a behavior profile independent of the one observed from mianserin here. Therefore, an independent effect on oxytocin release for mianserin may also be anticipated in future studies.

It is hoped that the present results will stimulate continued research on the role of oxytocin in SSRI-induced sexual dysfunction. Li et al. (1993) specifically noted the potential of oxytocin to serve as a reliable marker for testing the function of 5-$HT_{2A/2C}$ receptors after exposure to antidepressants. Uvnäs-Moberg and colleagues further suggested that the anti-depressant effect of SSRIs may be causally related to their effects on oxytocin (Uvnäs-Moberg, Björkstrand, Hillegaart, & Ahlenius, 1999). Finally, the approach applied here should encourage clinical researchers to continue to develop and employ animal models of human sexual behavior and dysfunction. Certainly, all efforts to cross-pollinate researchers of human and non-human animal behavior will benefit both.

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Appendix A:

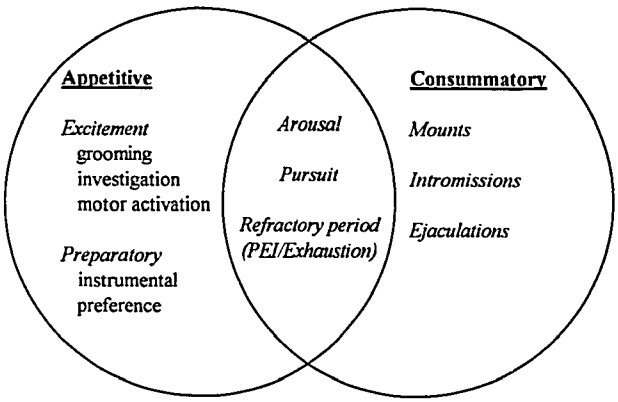
Table of Chemical Abbreviations

Abbreviation	Full Name	Primary Biological Activity
5-HT	5-hydroxytryptamine (serotonin)	neurotransmitter
5-HTP	5-hydroxytryptophan	5-HT precursor
8-OH-DPAT	8-hydroxy-2-(di)-n-propylamino-tetralin)	5-HT_{1A} agonist
DOI	1-(2,5-dimethoxy-4-iodophenyl)-2-amino propane	$5\text{-HT}_{2A/2C}$ agonist
LY228729	(–)-4-(dipropylamino)-1,3,4,5-tetra hydrobenz-[c,d,]indole-6-carboxamide	5-HT_{1A} agonist
LY293284	(–)-4R-6-acetyl-4-(di-n-propylamino) 1,3,4,5-tetrahydrobenz[c,d]indole	5-HT_{1A} agonist
LY237733	8B-N-cyclohexyl-6-methyl-1(1-methyl ethyl)ergoline-8-carboxamide	$5\text{-HT}_{2A/2C}$ antagonist
m-CPP	1-(3-chlorophenyl)piperazine	$5\text{-HT}_{2A/2C}$ agonist
MK-212	6-chloro-2-[1-piperazinyl]-pyrazine	$5\text{-HT}_{2A/2C}$ agonist
p-CPA	para-chlorophenylalanine	serotonin synthesis inhibitor
TFMPP	trifluoromethylphenylpiperazine	5-HT_{2C} and 5-HT_{1B} agonist

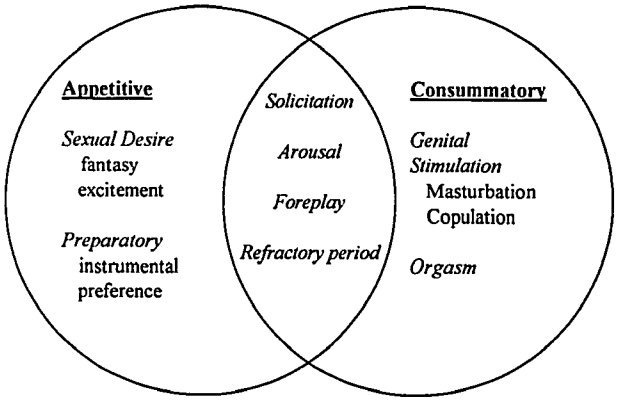
Appendix B:

Venn Diagram of the Incentive Sequence Model

Male Rat



Male Human



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