Mechanisms for the Inhibition of Genital Vascular Responses by Antidepressants in a Female Rabbit Model

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ABSTRACT

Vaginal and clitoral vasodilator responses (genital vascular responses; GVRs) to pelvic nerve electrical stimulation in female rabbits were measured by laser Doppler flow needle probes. The intravenous administration of various treatments was evaluated. GVRs were attenuated by a nitric-oxide synthase inhibitor (48.5 and 51.8% of control at 8 Hz in the vagina and clitoris, respectively) and norepinephrine (NE) (78.5 and 61.5%), whereas serotonin (5-HT) had no inhibitory effect. The selective 5-HT reuptake inhibitor (SSRI) escitalopram did not modify GVRs, whereas the SSRI paroxetine dose-dependently inhibited GVRs in female rabbits (43.3 and 53.1% at 5 mg/kg). GVRs were also significantly inhibited by the 5-HT and NE reuptake inhibitors venlafaxine (53.4 and 52.6% at 5 mg/kg) and duloxetine (40.9 and 37.4% at 1 mg/kg). L-arginine prevented the inhibitory effects of paroxetine (105.5 and 115.3%) and partially prevented duloxetine-induced reduction of GVRs but had no effect on the inhibition of GVRs induced by venlafaxine. Conversely, the α-adrenergic receptor blocker phentolamine had no effect on paroxetine-induced reduction of GVRs, partially prevented the inhibitory effects of duloxetine, and fully prevented the effects of venlafaxine (93.0 and 96.7%). Duloxetine-induced inhibition of GVRs was completely prevented by combined administration of L-arginine and phentolamine (123.5 and 103.6%). Although 5-HT or the highly selective SRI escitalopram did not inhibit GVRs, NE or inhibition of nitric oxide (NO) synthesis did. Inhibition of the NO pathway by paroxetine and duloxetine or activation of α-adrenergic mechanisms by venlafaxine and duloxetine lead to antidepressant-induced inhibition of GVRs in female rabbits.

Pharmacological treatments that improve depressive symptoms in patients with depression sometimes disrupt normal sexual function. Sexual dysfunction affects the patient’s quality of life and represents the main side effect that leads to the discontinuation of treatment (Wang et al., 2000). Antidepressant-induced sexual dysfunction affects men and women and includes orgasm delay, anorgasmia, and impotence (Labbate et al., 1998), which usually disappear when the treatment is discontinued (Rothschild, 1995); however, the likelihood of producing sexual side effects varies between individuals. Sexually stimulating stimuli—vaginal and clitoral vasodilator responses (genital vascular responses; GVRs) to pelvic nerve electrical stimulation—are measurable physiological responses to sexual stimulation in females and are therefore important for the study of female sexuality. Indeed, several techniques are currently used to assess female sexual function by measuring indices of genital blood flow in women (Berman et al., 1999; Mendels et al., 2000), whereas citalopram has been shown to produce significantly fewer alterations of sexual function (Mendels et al., 1999; Hovorka et al., 2000). In fact, we have previously reported that acute as well as chronic administration of paroxetine, but not citalopram, inhibit erectile responses in male rats by inhibiting nitric oxide (NO) production (Angulo et al., 2001b). Venlafaxine (a mixed 5-HT and NE reuptake inhibitor) is also among the drugs that are associated with the highest incidence of sexual dysfunction (over 50% in some studies) (Zajecka et al., 1997; Kennedy et al., 2000).

Sexual function in women is also altered by the treatment with antidepressants, but little is known about the mechanisms involved in this effect. Increases of blood flow into the vagina and clitoris is a measurable physiological response to sexual stimulation in females and is therefore important for the study of female sexuality. Indeed, several techniques are currently used to assess female sexual function by measuring indices of genital blood flow in women (Berman et al., 1999; Mendels et al., 2000), whereas citalopram has been shown to produce significantly fewer alterations of sexual function (Mendels et al., 1999; Hovorka et al., 2000). In fact, we have previously reported that acute as well as chronic administration of paroxetine, but not citalopram, inhibit erectile responses in male rats by inhibiting nitric oxide (NO) production (Angulo et al., 2001b). Venlafaxine (a mixed 5-HT and NE reuptake inhibitor) is also among the drugs that are associated with the highest incidence of sexual dysfunction (over 50% in some studies) (Zajecka et al., 1997; Kennedy et al., 2000).

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Studies were performed to investigate the basic mechanisms that regulate female genital vascular response (GVR) to PNES and to investigate the effects of acute administration of antidepressants that have selective 5-HT or NE reuptake inhibitory activity on GVRs in female rabbits (Angulo et al., 2003). On the other hand, it has been suggested that the adrenergic system could play a functional antagonistic role to the NO pathway in female sexual responses (Giuliano et al., 2001), as occurs in males. The aims of the present study were to investigate the basic mechanisms that regulate female genital vascular response (GVR) to PNES and to investigate the effects of acute administration of antidepressants that have selective 5-HT or NE reuptake inhibitory activity on GVRs in female rabbits (Angulo et al., 2003), as occurs in males.

Vaginal and clitoral blood flow responses to PNES were similar and reproducible in the same animal. For instance, after application of PNES at 8 Hz, the mean standard error could represent 40% of the mean value for vaginal blood flow response (n = 8; maximum was 15.9-fold the minimum value) and near 30% of the mean value for clitoral blood flow (n = 6; maximum was 6.8-fold the minimum value). When expressed as a percentage of the control response in the same animal, the mean standard error for the responses to PNES in the same group of animals was less than 7% for both vaginal and clitoral blood flow responses. These data reflect the fact that, although an appreciable variability between different animals was observed, repetition of PNES in the same animal yielded similar responses.

The adrenergic receptor agonist NE was infused at a rate of 0.2 μg/min for 15 min before and during the next PNES application to determine the effects of adrenergic stimulation on PNES-induced responses after first obtaining an adequate control PNES and waiting for an equilibration period. The infusion was then stopped, and 20 min later, PNES-induced responses were again evaluated. Similarly, the effects of 5-HT on PNES-induced responses were also determined by infusing 5-HT at a rate of 0.2 and 1 μg/min for 15 min before and during the evaluation of PNES-induced responses. Data analysis. Blood flow recordings were obtained in arbitrary flow units. Increases of vaginal and clitoral blood flow induced by PNES were measured as the area under the curve (AUC) of the response, taking into account amplitude and duration of the response. Data were expressed as the percentage of the control response (control PNES) before the treatment was applied. Comparison of vehicle- and drug-induced effects on vagina and clitoris blood flow responses to PNES was performed by a two-factor analysis of variance (ANOVA) test.

Drugs and Materials. NE (arterenol), serotonin (5-hydroxytryptamine), HPSCD, N3-nitro-l-arginine methyl ester (l-NAME), and l-arginine were obtained from Sigma-Aldrich (St. Louis, MO). Phentolamine mesylate (Regitine) was obtained from Novartis (Basel, Switzerland). Paroxetine, venlafaxine, and duloxetine were provided by Forest Laboratories, Inc. (New York, NY). NE and 5-HT solutions (2 μg/ml) for intravenous infusions were supplemented with 0.01% ascorbic acid to prevent oxidation.

Results

Effects of Treatments on Blood Pressure. Intravenous administration of vehicle to female rabbits did not significantly modify blood pressure (a transient, nonsignificant increase of 1.6 ± 3.0% compared with baseline values). When compared with vehicle-induced effects, blood pressure was significantly increased by l-NAME (20.7 ± 4.4%, p < 0.001), NE infusion (15.2 ± 5.4%, p < 0.05), paroxetine at 1 and 5 mg/kg (17.4 ± 3.7%, p < 0.05 and 26.8 ± 3.2%, p < 0.001, respectively), venlafaxine (13.2 ± 2.3%, p < 0.05), and duloxetine (15.1 ± 1.8%, p < 0.01). Except for the infusion of NE, these effects were always transient; blood pressure returned to baseline after 5 to 15 min in most cases. l-NAME-induced increase in blood pressure lasted for approximately 20 min. Administration of phentolamine produced a significant decrease in blood pressure (−17.1 ± 2.2%, p < 0.001) that lasted for 20 to 25 min. The other treatments (l-argi-
nine, 5-HT infusion at 0.2 and 1 μg/min/kg, paroxetine at 0.5 mg/kg, and escitalopram) did not significantly modify blood pressure in female rabbits.

**Effects of NO Synthesis Inhibition, Norepinephrine, or 5-HT Administration on GVRs in Female Rabbits.** Application of PNES caused consistent increases of blood flow into the vagina and clitoris in anesthetized female rabbits. The amplitude and duration of responses were dependent on the frequency applied and were not affected by vehicle (20% HPβCD) administration (Fig. 1). At 8 Hz, blood flow increments were more rapid and had a biphasic component in the clitoris when compared with responses in the vagina (see Fig. 1).

Administration (i.v.) of the NO synthase inhibitor L-NAME (1 mg/kg) significantly reduced PNES-induced blood flow increases in the vagina and clitoris (Fig. 2). Intravenous infusion of NE (0.2 μg/min for 15 min) caused a significant inhibition of vaginal and clitoral blood flow increases in response to PNES. This inhibitory effect was transient, as it disappeared 20 min after stopping NE infusion (Fig. 3). In the vagina, NE infusion seemed to have a larger inhibitory effect at 4 Hz than at 8 Hz (54.0 ± 8.5% versus 78.5 ± 17.1% of control response, respectively), whereas the NE-induced inhibition in the clitoris was less frequency-dependent (66.9 ± 7.2% versus 61.5 ± 3.1% of control response at 4 and 8 Hz, respectively); however, intravenous infusion of 5-HT (0.2 and 1 μg/min for 15 min) did not inhibit vaginal or clitoral blood flow increases to PNES. In fact, the higher dose of 5-HT produced a slight but significant potentiation of vaginal blood flow responses to PNES (128.9 ± 21.6% and 122.6 ± 15.3% of control response at 4 and 8 Hz, respectively, p < 0.05), whereas this potentiation was not evident in the clitoris (Fig. 4).

**Effects of Escitalopram, Paroxetine, Venlafaxine, and Duloxetine on GVRs in Female Rabbits.** The intravenous administration of the SSRI escitalopram (5 mg/kg i.v.) did not significantly alter the PNES-induced increase in blood flow in the clitoris or vagina (Fig. 5). In contrast, treatment with another SSRI, paroxetine, significantly and dose-dependently inhibited GVRs. This inhibitory effect was observed at 5 and 1 mg/kg paroxetine. At a dose of 0.5 mg/kg, paroxetine caused a significant inhibition of PNES-induced vascular responses in vaginal blood flow but not in clitoris blood flow (Fig. 6). The mixed 5-HT and NE reuptake inhibitors venlafaxine (5 mg/kg i.v.) and duloxetine (1 mg/kg i.v.)
both caused significant inhibition of GVRs induced by PNES (Fig. 7).

**Effects of L-Arginine and Phentolamine on Inhibition of GVRs Induced by Paroxetine, Venlafaxine, and Duloxetine.** Neither the NO synthase substrate L-arginine (10 mg/kg i.v.) nor the α-adrenergic receptor blocker phentolamine (1 mg/kg i.v.) had a significant effect on PNES-induced GVRs (Fig. 8); however, the administration of L-arginine prevented paroxetine (5 mg/kg)-induced inhibition of vaginal and clitoral blood flow responses to PNES. Phentolamine failed to modify the inhibitory effect of paroxetine on GVRs (Fig. 9).

Conversely, the inhibitory effect of venlafaxine (5 mg/kg) on clitoral and vaginal blood flow responses to PNES was not affected by L-arginine (10 mg/kg) but was fully prevented by phentolamine (1 mg/kg) (Fig. 10). Finally, both L-arginine and phentolamine partially reversed GVRs in female rabbits treated with duloxetine (1 mg/kg). Combined administration of L-arginine and phentolamine completely prevented the inhibitory effects of duloxetine on GVRs (Fig. 11).

**Discussion**

In our rabbit model, electrical stimulation of the pelvic nerve resulted in frequency-dependent increases of vaginal and clitoral blood flow, consistent with vascular responses associated with sexual stimulation in women (Berman et al., 2000). The role of NO in neurogenic relaxation and blood flow control in the clitoris and vagina is supported by substantial evidence (Cellek and Moncada, 1998; Ziessen et al., 2002; Angulo et al., 2003). Our study provides further support for a key role of the NO/cGMP pathway in GVRs since the inhibition of NOS greatly inhibits GVRs to PNES.

Sympathetic input to female rat genitalia has been shown to inhibit vascular sexual responses (Giuliano et al., 2001). α1- and α2-adrenoceptors have been characterized at biochemical and functional levels in rabbit vagina, where they mediate contraction (Kim et al., 2002). α-adrenergic agonists also cause contraction of rabbit clitoral corpus cavernosum (Cellek and Moncada, 1998). In women with sexual arousal difficulties, positive effects on sexual responses were ob-
Fig. 5. Effects of intravenous administration of the selective 5-HT reuptake inhibitor escitalopram (5 mg/kg) on vaginal (A) and clitoral (B) blood flow increases in response to PNES in anesthetized female rabbits. Data are expressed as mean ± S.E.M. of the percentage of control responses previously obtained in the same animal in the absence of the drug. The responses were measured as the area under the curve of the blood flow increase to PNES at each frequency;  \( n \) indicates the number of animals used for the experiments.

Fig. 6. Effects of intravenous administration of the selective 5-HT reuptake inhibitor paroxetine (0.5, 1, and 5 mg/kg) on vaginal (A) and clitoral (B) blood flow increases in response to PNES in anesthetized female rabbits. Data are expressed as mean ± S.E.M. of the percentage of control responses previously obtained in the same animal in the absence of the drug. The responses were measured as the area under the curve of the blood flow increase to PNES at each frequency;  \( n \) indicates the number of animals used for the experiments.  

\[ p < 0.05; \]  
\[ p < 0.01; \]  
\[ p < 0.001 \] versus vehicle-treated group.

†  
\[ p < 0.05 \] versus paroxetine 5 mg/kg by a two-factor ANOVA test.

Fig. 7. Effects of intravenous administration of the 5-HT and NE reuptake inhibitors venlafaxine (5 mg/kg) (A and B) and duloxetine (1 mg/kg) (C and D) on vaginal (A and C) and clitoral (B and D) blood flow increases in response to PNES in anesthetized female rabbits. Data are expressed as mean ± S.E.M. of the percentage of control responses previously obtained in the same animal in absence of the drug. The responses were measured as the area under the curve of the blood flow increase to PNES at each frequency;  \( n \) indicates the number of animals used for the experiments.  

\[ p < 0.001 \] versus vehicle treated group by a two-factor ANOVA test.
served after the treatment with the $\alpha$-adrenoceptor blocker phentolamine (Rosen et al., 1999) and the combination of 1-arginine and the $\alpha_2$-adrenoceptor antagonist yohimbine (Meston and Worcel, 2002). In our model, PNES-induced responses were significantly reduced by stimulation of the adrenergic system with NE. Therefore, our results support the hypothesis that the generation of NO facilitates genital blood flow responses to PNES, although these responses are antagonized by the activation of the adrenergic system. Thus, drugs interfering with the synthesis of NO or adrenergic neurotransmission could have an impact on female sexual function.

The mechanism underlying increased incidence of sexual dysfunction in patients under treatment with SSRIs is not thoroughly understood. The known mechanism of action of these drugs involves the inhibition of 5-HT reuptake by neurons, which increases the levels of this neurotransmitter at the synapse. High levels of 5-HT are generally thought to inhibit sexual behavior (Hull et al., 1999); however, opposite effects can be observed depending on the type of receptor activated by serotonin, since activation of the 5-HT$_{2A}$ receptor subtype is associated with increased sexual motivation in female rats (Nedergaard et al., 2004). Although all SSRIs enhance serotonin levels in the brain, not all of them produce the same effects on sexual function. Indeed, an increase of incidence of erectile dysfunction in patients treated with paroxetine has often been reported, whereas a lesser effect on sexual function is reported for citalopram (Mendels et al., 1999).

The three antidepressants paroxetine, venlafaxine, and duloxetine, which cause inhibition of GVRs in our model, share the ability to inhibit 5-HT reuptake; however, escitalopram, the active $S$-enantiomer of citalopram, a potent and highly selective inhibitor of 5-HT reuptake (Owens et al., 2001; Sanchez et al., 2003), does not affect GVRs in this model at a dose several times higher than those proven to be effective in rats (Mork et al., 2003) or than those effective in humans (Lepola et al., 2003). This would suggest that inhibition of 5-HT reuptake is not the mechanism underlying inhibition of GVRs to PNES by paroxetine, venlafaxine, or duloxetine. The observation that intravenous administration of 5-HT does not inhibit GVRs in female rabbits further.

**Fig. 8.** Effects of intravenous administration of the substrate of nitric oxide synthesis l-arginine (10 mg/kg) or the $\alpha_2$-adrenoceptor antagonist phentolamine (1 mg/kg) on vaginal (A) and clitoral (B) blood flow increases in response to PNES in anesthetized female rabbits. Data are expressed as mean ± S.E.M. of the percentage of control responses previously obtained in the same animal in absence of the drug. The responses were measured as the area under the curve of the blood flow increase to PNES at each frequency; $n$ indicates the number of animals used for the experiments.

**Fig. 9.** Effects of intravenous administration of the substrate of nitric oxide synthesis l-arginine (10 mg/kg) or the $\alpha_2$-adrenoceptor antagonist phentolamine (1 mg/kg) on the inhibitory effect induced by the selective 5-HT reuptake inhibitor paroxetine (5 mg/kg) on vaginal (A) and clitoral (B) blood flow increases in response to PNES in anesthetized female rabbits. Data are expressed as mean ± S.E.M. of the percentage of control responses previously obtained in the same animal in absence of the drug. The responses were measured as the area under the curve of the blood flow increase to PNES at each frequency; $n$ indicates the number of animals used for the experiments. ++, $p < 0.01$ versus vehicle-treated group, and †††, $p < 0.001$ versus paroxetine-treated group by a two-factor ANOVA test.
supports this concept. In fact, the infusion of 1 μg/min (the higher dose tested) of 5-HT for 15 min caused a slight but significant potentiation of blood flow increases to PNES in the vagina. This effect could be due to interaction with some type of vascular 5-HT receptor mediating vasocongestion or with prejunctional 5-HT receptors modulating the release of another neurotransmitter that facilitates vasodilation in rabbit vagina. Thus, the inhibitory effects of paroxetine, venlafaxine, and duloxetine on GVRs must be related to the interference of these drugs with other regulatory mechanisms of GVRs.

Inhibition of NOS activity by paroxetine could explain the impairment of GVRs. In support of this hypothesis is the observation that l-arginine, a substrate for NOS in NO production, fully prevented the inhibitory effects of paroxetine on GVRs at a dose that did not modify GVRs under control conditions. Paroxetine caused erectile dysfunction associated with decreased NO production and NOS expression in male rats (Angulo et al., 2001b) and reduced NO production in hamster brain and depressed patients, where it inhibits NOS activity (Finkel et al., 1996). Paroxetine is a potent inhibitor of the activity of cytochrome P450 (P450) isozymes (Preskorn, 1993), which are structurally related to NOS, whereas citalopram and escitalopram are known to have no or negligible activity on P450 isozymes (Greenblatt et al., 1998; von Moltke et al., 2001). With respect to mixed 5-HT and NE reuptake inhibitors, no or weak inhibition of P450 activity by venlafaxine has been reported (Ereshefsky, 1996), but duloxetine has been shown to inhibit CYP2D6, a P450 isozyme also inhibited by paroxetine (Skinner et al., 2003).

Venlafaxine seems to inhibit GVRs by enhancing adrenergic input while not affecting the NO/cGMP pathway. These conclusions are based on the complete reversal of its inhibitory effects by the α-adrenergic blocker phentolamine and the lack of effect of L-arginine treatment. Venlafaxine, although having relatively low affinity for the 5-HT and NE transporters (Table 1), has been shown to inhibit the reuptake of 5-HT and NE in humans (Harvey et al., 2000). In addition, prejunctional α2-adrenergic receptors inhibit ni-
trergic neurotransmission in various organs (Angulo et al., 2001a) and may represent an additional mechanism for the inhibition of GVRs by venlafaxine. A direct effect of venlafaxine on α-adrenoceptors is not likely, since this compound shows low affinity for these receptors (Table 1).

Duloxetine is also a mixed inhibitor of 5-HT and NE reuptake, as demonstrated in vitro and in vivo (Kasamo et al., 1996; Chalon et al., 2003), and is more potent than venlafaxine (Table 1). Duloxetine is currently being evaluated for the treatment of depression (Detke et al., 2002) and stress urinary incontinence (Norton et al., 2002), but sexual side effects of duloxetine have not yet been fully characterized (Detke et al., 2003). In our female rabbit model, duloxetine potently inhibited GVRs. Phentolamine significantly improved GVRs in the presence of duloxetine. Since, like venlafaxine, duloxetine does not have significant affinity for α-adrenoceptors (Table 1), the inhibitory effects of duloxetine on GVRs could be related to the increased availability of NE subsequent to inhibition of NE transporters; however, in contrast to our observations with venlafaxine, treatment with phentolamine failed to completely reverse duloxetine-induced inhibition of GVRs, suggesting that additional mechanisms contribute to the inhibitory effects of this compound. Duloxetine may interfere with NO production, as suggested by the partial prevention of its inhibitory effects by L-arginine. The involvement of both adrenergic stimulation and interference with NO production in the inhibitory effects of duloxetine was further confirmed by the complete prevention of such effects by the coadministration of L-arginine and phentolamine.

Although the results obtained in the vagina generally paralleled those obtained in the clitoris, some subtle differences in response to treatments do exist. In this regard, norepinephrine seems to produce a greater reduction in vaginal blood flow at 4 Hz compared with its effect at 8 Hz. This frequency-dependent effect of NE was not evident in the clitoris. In addition, serotonin only significantly increased GVRs in the vagina, and the lowest dose of paroxetine only significantly reduced GVRs (also in the vagina). The interpretation of these differences based on our results could be rather speculative; however, it has been observed that the neurogenic relaxation involves different neurotransmitter profiles in the vagina and clitoris. Although neurogenic relaxation of the clitoral corpus cavernosum is largely mediated by NO release from nitricergic nerves (Cellek and Moncada, 1998), in vaginal tissue, in addition to NO, the neurogenic relaxation is also mediated by another unknown neurotransmitter (Ziessen et al., 2002). The participation of this unknown neurotransmitter in the vascular responses induced by pelvic nerve stimulation in the vagina could account for the differences observed between the vagina and clitoris. The divergences could also be related to a different expression of prejunctional or postjunctional receptors in the vagina and clitoris or in the arteries supplying each tissue. The pattern of neurotransmitter release and thus the functional response can be dependent on the frequency applied (Morris and Gibbins, 1992). This could explain the different shape of response observed at 8 Hz in the clitoris.

In conclusion, vaginal and clitoral blood flow increases in response to PNES in female rabbits are mediated, at least to a great extent, by NO and regulated by activation of the adrenergic system. Paroxetine reduces GVRs in this model by inhibiting NO synthesis, whereas the inhibitory effect of venlafaxine is related to its ability to increase NE levels. Inhibition of GVRs by duloxetine involves both—interference with the NOS pathway and activation of the adrenergic system. Administration of 5-HT or the SSRI escitalopram does not affect PNES-induced responses in female rabbits, suggesting that the increase in 5-HT availability is not responsible for inhibition of GVRs induced by SSRIs or 5-HT and NE reuptake inhibitors in female rabbits. These observations could be relevant for the development of therapeutic strategies to minimize sexual side effects in patients under treatment with antidepressants.

**References**


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**TABLE 1**

Reported affinity (Kᵢ) of antidepressants for inhibiting monoamine transporters and receptors

Data are from Owens et al., 1997 (paroxetine and venlafaxine) and 2001 (escitalopram and paroxetine); Sanchez et al., 2003 (escitalopram); and Bymaster et al., 2001 (duloxetine and venlafaxine).

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SERT, serotonin transporter; NET, norepinephrine transporter.


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