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Acute and long-term administration of citalopram desensitizes α_2-adrenoceptors in the rat vas deferens

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Abstract

The aim of this study was to investigate the effect of citalopram, a selective serotonin reuptake inhibitor, on the sensitivity of rat vas deferens α_2-adrenoceptors and to compare it with the effects of serotonin and the dual noradrenaline–serotonin uptake inhibitor duloxetine. To this end, we studied the inhibitory effect of the α_2-adrenoceptor agonist bromoxidine on the electrically induced contraction of the vas deferens. Citalopram (1, 3×10^3 and 3×10^4 nM) applied in-vitro significantly attenuated the concentration–response inhibition induced by activation of α_2-adrenoceptors on the electrically evoked contraction of the vas deferens (concentration of the agonist required to promote 50% of the maximal effect, EC50, for bromoxidine increased by 232%, 421% and 818%, respectively). Similarly, serotonin also attenuated the concentration–response inhibition mediated by presynaptic α_2-adrenoceptors (96% increase in EC50). Acute and long-term systemic administration of citalopram and duloxetine also produced a loss in the sensitivity of α_2-adrenoceptors to bromoxidine (EC50 for bromoxidine increased by 97% and 144%, respectively, after citalopram, and by 214% and 167% after duloxetine). In addition, we observed that an increased fraction of receptors was required to be occupied to yield 50% of the inhibitory effect of bromoxidine after long-term administration of citalopram and duloxetine (K_E increased by 142% and 83%). These results are indicative of early-onset and persistent down-regulation of peripheral α_2-adrenoceptors by citalopram, which may account for some of its side effects.

Introduction

Selective serotonin reuptake inhibitor (SSRI) antidepressant drugs are widely prescribed and, in many cases, effective for the treatment of clinical depression (Wagstaff et al 2002). Due to the delayed onset of the therapeutic effects, it has been suggested that adaptation of several neurotransmitter systems may take place. The noradrenergic system is one such candidate system that may adapt in response to SSRI administration, since altered noradrenergic synaptic components have been found in depression and they are modulated by antidepressant treatment (Farvolden et al 2003). In addition, some side effects associated with the use of SSRIs could be due to their action on noradrenergic transmission.

One of the common side effects of SSRIs is sexual dysfunction (Holsboer 2001; Cassano & Fava 2004). This could be related to the peripheral effects of antidepressants on noradrenergic transmission in the vas deferens (Busch et al 1999; Kalyoncu et al 1999; Yaris et al 2003). The rat vas deferens is characterized by a predominantly sympathetic innervation. It possesses α_{2A}-autoreceptors located presynaptically (Smith & Docherty 1992; Cleary et al 2002). Activation of these presynaptic α_2-adrenoceptors results in inhibition of transmitter release (Starke et al 1989) and subsequently leads to inhibition of the electrically evoked contraction of the vas deferens (García-Sevilla & Zubieta 1986). Only a small fraction of these receptors needs to be occupied to elicit a near maximal response, meaning that a large reserve pool of these presynaptic α_{2A}-adrenoceptors exists in the rat vas deferens (Pineda et al 1997). In addition, the vas deferens also contains serotonin, which may act as a modulatory neurotransmitter (Fuenmayor et al 1976; Celuch & Sloley 1988). Exogenous serotonin accumulates in the neuronal noradrenaline store (Etcheverry & Zieher 1968; Thoa et al 1969) and it modulates electrically evoked contraction (Seong et al 1990; Smith & Bennett 1990) in the vas deferens. Thus, noradrenergic and serotonergic neurotransmitters seem to functionally interact in the vas deferens and this interaction may

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underline some acute and chronic effects of SSRIs. In fact, in-vitro studies have shown that SSRIs potentiate the rat vas deferens response to noradrenaline without significantly altering the response to serotonin (Busch et al 2000; Yaris et al 2003). In addition, long-term treatment with fluoxetine induced an increase of the vas deferens response to noradrenaline (Busch et al 1999).

Therefore, the aim of this study was to characterize the effect of citalopram, an SSRI widely used in the treatment of depression, on the sensitivity of presynaptic α_2-adrenoceptors, which mediate inhibition of electrically evoked contraction of the vas deferens. To this end we examined the concentration–response curves for the α_2-adrenoceptor agonist bromoxidine in the vas deferens from control rats in the presence of citalopram and from rats after acute or prolonged treatment with the SSRI citalopram and we compared the results with those obtained in the presence of serotonin and after acute and prolonged administration of the dual noradrenaline and serotonin uptake inhibitor duloxetine.

Materials and Methods

Drugs

The following drugs were used: bromoxidine (5-bromo-6-[2-imidazolina-2-ylamino]-quinoxaline) and serotonin HCl (both from RBI), citalopram (generously supplied by Lundbeck), duloxetine (generously supplied by Lilly), chloral hydrate (Fluka Chemika) and EEDQ (*N*-ethoxicarbonyl-2-ethoxy-1,2 dihydroxyquinoline) (Sigma Chemical Co).

For in-vitro applications, all drugs were dissolved in Krebs bicarbonate solution. For the administration of antidepressant via minipumps, citalopram was dissolved in ethanol and NaCl (1:1) and duloxetine was dissolved in mQ water and NaCl (1:1). EEDQ was dissolved in absolute ethanol, propylene glycol and Krebs bicarbonate solution (1:1:2).

Animals and treatments

Male Sprague-Dawley rats, 220–350 g, received a standard diet with freely available water and were housed at 22 ± 2°C with a 12-h light–dark cycle. The rats were treated subcutaneously with minipumps containing either citalopram (20 mg kg^{-1} daily, s.c.) or duloxetine (20 mg kg^{-1} daily, s.c.) for 1 or 14 days. Controls received vehicle via minipumps. Doses of citalopram and duloxetine were calculated for a mean body weight of 250 g. Experiments were carried out 24 h after minipump removal. All the procedures involving rats and their care were approved by the ethical committee of the UPV/EHU and are in compliance with the relevant Spanish Legislation and the European Community Council Directive on Protection of Animals Used in Experimental and Other Scientific Purposes of 24 November 1986 (86/609/EEC).

The rat vas deferens

Experiments were carried out as described previously (García-Sevilla & Zubieta 1986). Control and treated rats were anaesthetized with chloral hydrate (400 mg kg^{-1}, i.p.), decapitated and both vasa deferentia were set up between platinum electrodes in a 7-mL organ bath at 31 ± 1°C containing Krebs bicarbonate solution with the following composition (in mM): NaCl 112, KCl 4.7, KH_2PO_4 1.1, $NaHCO_3$ 25, glucose 11.1, $CaCl_2$ 2.5 and $MgSO_4$ 1.2. The solution was bubbled with 95% O_2–5% CO_2. Contractile responses were recorded by means of an isometric transducer attached to an OmniScribe pen recorder. At the beginning of each experiment, a 15-min stabilization period was allowed before a resting tension of 0.5 g was applied to each tissue. Neurogenic tissue contractions were elicited by field stimulation at a supra-maximal voltage (20–30 V) with square wave electrical pulses of 3-ms duration, at a frequency of 0.1 Hz delivered via a Cibertec model CS-14 stimulator. Constant isometric tension changes of the vas deferens were recorded as individual contractile responses. Tissues were stimulated for 10 min to allow for equilibration of the contractile responses before drug application. All drug additions were performed cumulatively without washout.

Irreversible receptor inactivation

To assess α_2-adrenoceptor reserve, experiments were conducted as described previously by Pineda et al 1997. Both vasa deferentia from each rat were used; one was incubated with a single concentration of the irreversible adrenoceptor α_2-antagonist EEDQ (300 nM, for 30 min). The other was incubated with the vehicle in which EEDQ was dissolved. After this period of incubation, excess EEDQ was removed by means of changing the Krebs solution in the organ bath several times. Once stable responses to electrical stimulation were reproducible, agonist concentration–effect curves were constructed by cumulative addition of bromoxidine.

Analysis of data

All mathematical calculations were performed following the methodology described by Pineda et al 1997 using nonlinear regression with the aid of the Graph Pad program. Electrically evoked contractions were measured before (basal contraction) and after each concentration of bromoxidine. Effects are expressed as the percentage inhibition of the basal electrically evoked contraction. Only a single curve was elaborated with each tissue sample. Agonist concentration–effect curves based on individual experimental data were fitted to the logistic equation of Parker & Waud (1971):

$$E = E_{max}[A^n]/([A^n] + EC50^n) \quad (1)$$

in which E and [A] are the observed effect and the concentration of the agonist (bromoxidine), respectively, E_{max} is the maximal inhibitory effect expressed in percentage values; EC50 is the concentration of the agonist required to promote, in each case, 50% of the maximal effect and n represents the slope factor of the function.

To estimate the affinity constant of the agonist–receptor complex, bromoxidine concentration–effect curves obtained with data from the saline-incubated tissue were fitted to the equation described above and the data obtained from the

EEDQ-incubated tissues were simultaneously fitted to the following equation:

$$E = E_{max}/[\{EC50 \times (K_A + [\{A'\])\}/ \{q \times K_A \times [A']\} \times (1-q) + 1]^n \quad (2)$$

in which [A′] is the concentration of the agonist (bromoxidine) in the EEDQ-preincubated tissue; K_A is the dissociation constant of the agonist from the receptor and q is the fraction of functional receptors remaining (non-inactivated) after administration of EEDQ. Other parameters are as described above.

Finally, to analyse the occupancy–effect relation, the fraction of receptor occupancy (R_A/R_T) for each concentration of the agonist ([A]) was calculated by substituting the value of K_A previously estimated (see above) in the following equation derived from the mass action law:

$$R_A/R_T = [A]/([A] + K_A) \quad (3)$$

Thus, all experimental sets of data of the occupancy–effect relation were then fitted by nonlinear regression to the hyperbolic equation described by Black & Leff (1983):

$$E = [E'_{max} + (R_A/R_T)]/[(R_A/R_T)^{n'} + K_E{}^{n'}] \quad (4)$$

in which E'_{max} and n′ are the maximal effect and the slope factor, respectively, for this equation and K_E is the fraction of receptors needed to be occupied to promote 50% of the maximal effect (the maximal value of K_E would be 1).

Statistics

Data are shown as mean ± s.e.m. The parameters of the concentration–response curves were compared using Student's *t*-test. To compare more than two groups, we used one-way analysis of variance followed by the Newman–Keuls test. $P < 0.05$ was taken as significant.

Results

Effect of citalopram and serotonin on α_{2A}-adrenoceptor sensitivity in the rat vas deferens

To determine whether citalopram induces changes in the sensitivity of presynaptic α_{2A}-adrenoceptors, concentration–response curves were constructed with cumulative increasing concentrations of the α_{2A}-adrenoceptor agonist bromoxidine (0.1–3×10^4 nM). Initial experiments were carried out under control conditions; as expected, bromoxidine inhibited the electrically evoked contraction in a concentration-dependent manner with an EC50 of 0.66 ± 0.06 nM (n = 5) and a maximal response of 100%.

The addition of increasing concentrations of citalopram (1, 3×10^3 and 3×10^4 nM) 15 min before bromoxidine resulted in a progressive shift to the right of the concentration–effect curves (Figure 1A) and significantly increased the EC50 values by 232% (n = 6), 421% (n = 7) and 818% (n = 5),

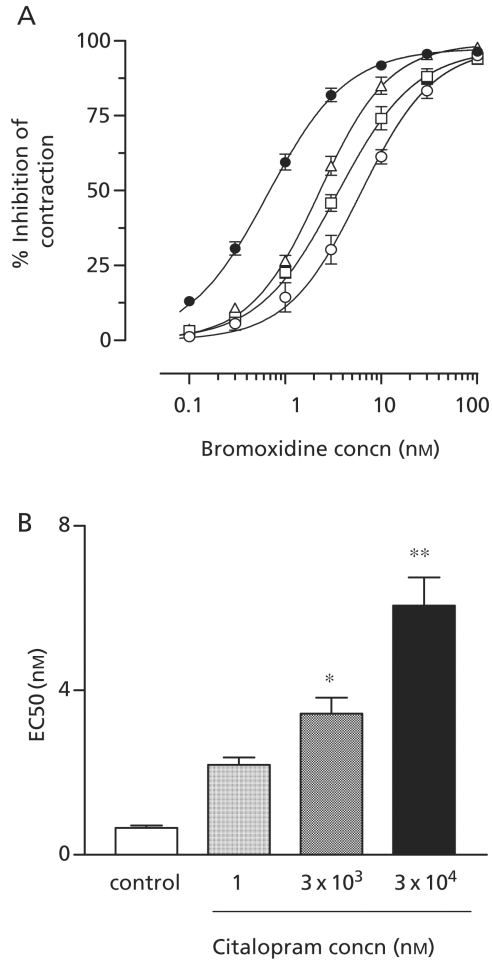

Figure 1 A. Concentration–effect curves for inhibition of the electrically evoked contractions of the rat vas deferens by bromoxidine in control rats (●) and after application of citalopram at concentrations of 1 (△), 3×10^3 (□) and 3×10^4 (○) nM. Each symbol represents the mean ± s.e.m. of 5–7 experiments. The vertical axis represents the percentage decrease of the electrically evoked contraction. B. Bar histogram showing the mean ± s.e.m. of the EC50 of the bromoxidine concentration–effect curve at different concentrations of citalopram. *$P < 0.01$, **$P < 0.001$, compared with control (Newman–Keuls test, post one-way analysis of variance).

respectively ($P < 0.01$ and $P < 0.001$, Newman–Keuls test post one-way analysis of variance, Figure 1B). However, the effect of direct application of citalopram on electrically evoked contractions was different, depending on drug concentration. Thus 1 nM and 3×10^3 nM caused inhibition (−13 ± 4% and −40 ± 6%), whereas 3×10^4 nM caused stimulation (+69 ± 14%), indicating that the distinct citalopram effects were not directly related.

Since the effect of citalopram could be explained by an increase in the concentration of serotonin in synapses, we studied also the effect of serotonin on α_{2A}-adrenoceptor sensitivity to bromoxidine. The presence of serotonin (1 nM) in the bath solution also significantly increased the corresponding EC50 value by 96% (n = 6, $P < 0.05$, Student's *t*-test). Under these circumstances, serotonin alone

caused a slight inhibition (−9 ± 2%) of the basal electrically evoked contraction.

Effect of treatment with citalopram and duloxetine on α_{2A}-adrenoceptor sensitivity in the rat vas deferens

The clinical effects of antidepressants become evident only after long-term exposure to these drugs. Therefore, we evaluated the sensitivity of presynaptic α_2-adrenoceptors after 14 days of sustained administration of citalopram and the dual noradrenaline and serotonin uptake inhibitor, duloxetine. After 1 or 14 days of citalopram administration (20 mg kg^{-1} daily, s.c., via minipump) and duloxetine (20 mg kg^{-1} daily, s.c., via minipump), no significant changes in the intensity of the basal electrically evoked contraction of the rat vas deferens were observed. However, treatments with either antidepressant for 1 or 14 days shifted the concentration–effect curve for bromoxidine to the right (Figure 2A, B) and consequently increased the corresponding EC50 values. Thus, treatment with citalopram increased the EC50 by 97% (n = 5) and 144% (n = 5), respectively ($P < 0.001$ and $P < 0.001$, Newman–Keuls test post one-way analysis of variance, Figure 2C), and treatment with duloxetine by 214% (n = 4) and 167% (n = 6), respectively ($P < 0.001$ and $P < 0.001$, Newman-Keuls test post one-way analysis of variance, Figure 2D).

Effect of treatment with citalopram and duloxetine on α_{2A}-adrenoceptor reserve in the rat vas deferens

To determine whether changes in presynaptic α_2-adrenoceptor sensitivity were due to changes in the affinity or the efficiency of the agonist–receptor interaction, one of the two vas deferens from an individual rat was incubated with the irreversible α_2-adrenoceptor antagonist EEDQ and the other with the corresponding vehicle. Subsequently, we measured the fraction of receptors needed to be occupied to yield 50% of the maximal effect (K_E). As expected, preincubation of the vas deferens with EEDQ (300 nM) for 30 min induced a shift to the right of the concentration–effect curve for bromoxidine. EC50 values were dramatically increased both in experiments carried out using tissue from control rats and in those carried out using rats treated with citalopram (20 mg kg^{-1} daily, s.c., via minipump) or

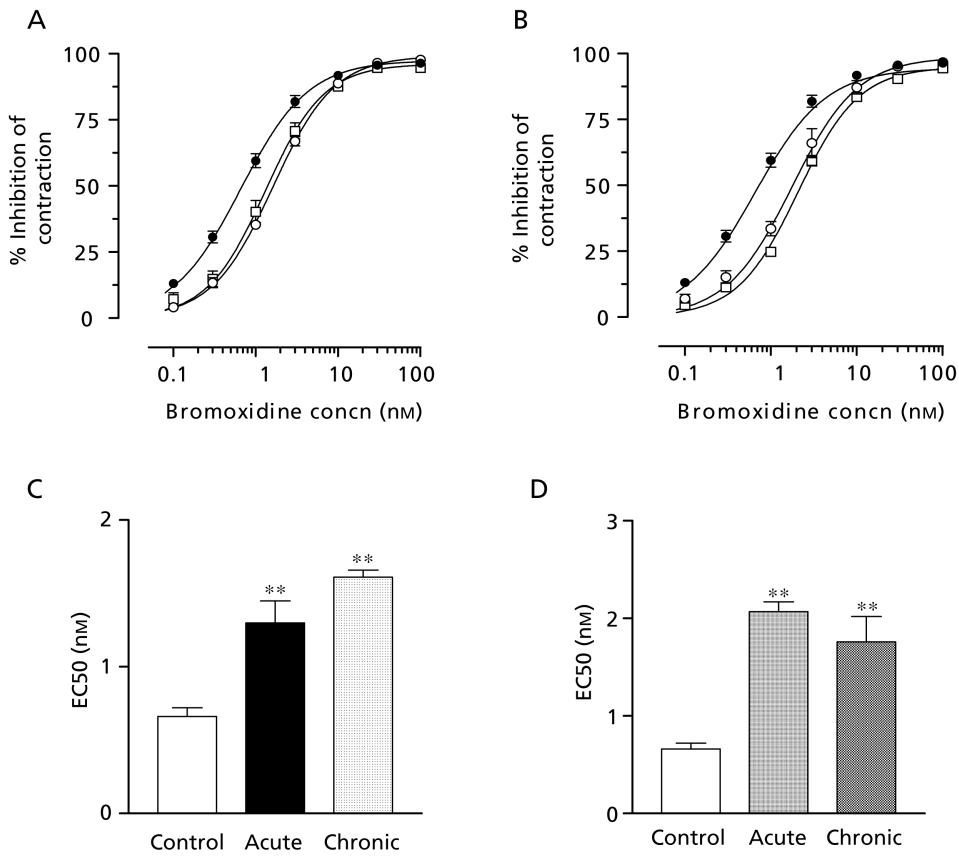

Figure 2 Concentration–effect curves for inhibition of the electrically evoked contractions of the vas deferens by bromoxidine in control rats (●) and in rats treated with citalopram (A) and duloxetine (B) (both at 20 mg kg^{-1} daily, s.c., via minipump) for 1 (□) and 14 days (○). Each symbol represents the mean ± s.e.m. of 4–7 experiments. The vertical axis represents the percentage decrease of the electrically evoked contraction. Also shown are bar histograms showing mean ± s.e.m. of the EC50 of the bromoxidine concentration–effect curve after treatment with citalopram (C) or duloxetine (D) (both at 20 mg kg^{-1} daily, s.c., via minipump, for 1 and 14 days). **$P < 0.001$ compared with control (Newman–Keuls test post one-way analysis of variance).

duloxetine (20 mg kg^{-1} daily, s.c., via minipump) (Table 1). The affinity constant (K_A) was estimated by analysing concentration–response curves simultaneously from both situations. Table 1 shows the mean values of the EC50 and the affinity constant of the agonist–receptor complex for bromoxidine (K_A) for all experimental groups. By plotting receptor occupancy against the bromoxidine effect (Figure 3), we were able to estimate that only a small fraction of total receptors was needed to be occupied to yield 50% of the maximal effect of bromoxidine ($K_E = 1.39 \pm 0.14\%$, n = 7). However, this fraction of total receptors was increased after treatment with citalopram (K_E values increased by 142%, n = 7 ($P < 0.001$, Newman–Keuls test post one-way analysis of variance)) and with duloxetine (K_E values increased by 83%, n = 7 ($P < 0.01$, Newman–Keuls test post one-way analysis of variance)) (Figure 3, Table 1).

Table 1 Effect of treatment with antidepressants on the parameters of the bromoxidine concentration–effect curves in EEDQ-preincubated rat vas deferens

Treatment	E_{max} (%)	EC50 (nM)	K_A	K_E (%)
Control	97 ± 1	0.66 ± 0.06	—	1.39 ± 0.14
Control + EEDQ	81 ± 4	27 ± 4	47.5 ± 15	—
Citalopram + EEDQ	93 ± 2	32 ± 3	46.2 ± 18	3.37 ± 0.11**
Duloxetine + EEDQ	86 ± 3	19 ± 4	62.6 ± 19	2.54 ± 0.37*

Rats were treated with vehicle, citalopram or duloxetine (both at 20 mg kg^{-1} daily, s.c.) via minipumps. The parameters of the concentration–effect curves for bromoxidine were estimated in each experiment using the Parker & Waud equation. Values are shown as mean ± s.e.m. of 5–7 experiments per group. *$P < 0.01$, **$P < 0.001$ vs control (Newman-Keuls test post one-way analysis of variance).

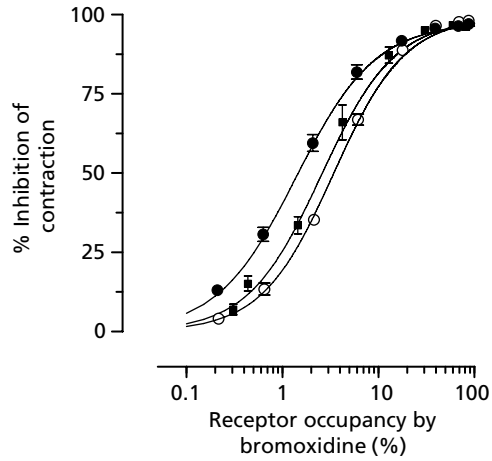

Figure 3 Receptor occupancy–effect relationship for inhibition of the electrically evoked contractions of the rat vas deferens by bromoxidine in control rats (●), and those treated with citalopram (○) or duloxetine (■), both at 20 mg kg^{-1} daily, subcutaneously, via minipumps, for 14 days. Each symbol represents the mean ± s.e.m. of 5–7 experiments. The vertical axis represents the percentage decrease of the electrically evoked contraction.

Discussion

Our results show that citalopram induces a loss of sensitivity of presynaptic α_2-adrenoceptors of the vas deferens, both when it is applied in-vitro and when it is systemically administered for a short or a prolonged period of time. In addition, the effect of citalopram after bath application is similar to the effect of serotonin and prolonged administration of citalopram or duloxetine cause similar changes.

In this study, citalopram attenuates the response mediated by presynaptic α_2-adrenoceptors, indicating that citalopram may elicit a modulatory action on these receptors. Several findings indicate that this effect is probably due to an increase in the levels of synaptic serotonin. Firstly, the principal action of citalopram is to block serotonin uptake from the synaptic cleft (Popik 1999). Secondly, the vas deferens is known to contain serotonin (Fuenmayor et al 1976; Celuch & Sloley 1988) and exogenous serotonin has been reported to accumulate in the neuronal noradrenaline store in the vas deferens (Etcheverry & Zieher 1968; Thoa et al 1969). Finally, we show here that serotonin application in-vitro also causes a decrease in sensitivity to the α_2-adrenoceptor agonist, as occurs with citalopram. In keeping with these findings, it has previously been shown that serotonin also attenuates other α_2-adrenoceptor-mediated responses (Kostowski et al 1981) and that paroxetine, which is another SSRI inhibitor, can inhibit exogenous noradrenaline-induced contraction of the vas deferens (Yaris et al 2003). On the other hand, the effects of high concentrations of citalopram (stimulation and inhibition) may be due to a direct interaction of citalopram with a 5-HT-receptor subtype present on the vas deferens, which mediates stimulation of contraction of the vas deferens. The 5-HT_2 receptor is a good candidate subtype (Seong et al 1990). Indeed, an interaction between 5-HT_2 receptors and citalopram has already been found in some functional studies (Pälvimäki et al 1996). Nevertheless, these effects observed with high concentrations may not have clinical relevance, since such a high concentration is probably not reached when used in patients.

We observed that systemically applied citalopram caused a loss in sensitivity to the α_2-adrenoceptor agonist. Since both bath application and subcutaneous administration of citalopram were found to lead to a loss of sensitivity to the α_2-adrenoceptor agonist, it could be argued that the observed desensitization in response to systemic citalopram may be due to the presence of drug in the tissue at the time of the experiment. However, as minipumps were removed 24 h before assay, it is unlikely that this is the reason for the loss of sensitivity according to the kinetics of citalopram (Hyttel et al 1984), but to an adaptation mechanism that develops at the beginning of citalopram administration.

We did not find differences between the effects of citalopram, which as mentioned above is a very highly efficient SSRI, and those of duloxetine, which is a dual noradrenaline and serotonin uptake inhibitor (Kasamo et al 1996). Both antidepressants induced a loss in sensitivity to the α_{2A}-adrenoceptor agonist. These results suggest that both antidepressants may share a similar mechanism to induce α_{2A}-adrenoceptor desensitization. Previous studies have also shown a desensitization of α_2-adrenoceptors in the vas deferens after prolonged administration

of noradrenaline uptake inhibitor antidepressants (García-Sevilla & Zubieta 1986). It is thus conceivable that citalopram increases not only the levels of serotonin, but also of noradrenaline, either by means of serotonin uptake inhibition or by directly inhibiting the uptake of noradrenaline, as has been found in-vitro (Hughes & Stanford 1998), leading therefore to a sustained activation of α_2-adrenoceptors. In addition, our results show that the loss of sensitivity to the α_2-adrenoceptor agonist is associated with a loss in the efficiency of receptor activation, since a higher fraction of receptors was needed to be occupied to yield a given effect. This finding could also be the consequence of an increase in the bioavailability of noradrenaline, since precisely opposite results have been reported after noradrenaline depletion (Pineda et al 1997). However, noradrenaline uptake inhibitor antidepressants do not induce changes in α_2-adrenoceptor sensitivity when they are administered acutely (García-Sevilla & Zubieta 1986), whereas we observed a loss in α_2-adrenoceptor sensitivity after only 24 h of citalopram and duloxetine administration. Thus, serotonin uptake inhibition must be responsible for the early desensitization. This may be relevant to the side effects related to sexual dysfunction associated with the use of citalopram and other SSRIs (Farvolden et al 2003) and, less frequently, with classical antidepressant drugs. Since α_2-adrenoceptors participate in the control of sexual function (Andersson 2001) and since sexual dysfunction occurs early and persists during SSRI use (Cassano & Fava 2004), in a manner which is similar to the receptor changes which we observed, it is likely that presynaptic α_2-adrenoceptor desensitization accounts for these side effects.

The results of this study corroborate those of reports that show an attenuation of the response to noradrenaline in the vas deferens after treatment with citalopram (Petersen & Mork 1996), paroxetine (Yaris et al 2003) and fluoxetine (Busch et al 1999). In a previous study conducted in our laboratory, which employed an identical protocol to that used in this study, but focusing on central α_2-adrenoceptors, we did not find any changes in the sensitivity of α_2-adrenoceptors in the locus coeruleus (Grandoso et al 2005). Moreover, Gobbi et al (1997) did not find any changes in serotonin uptake binding sites in the central nervous system after 14 days of citalopram treatment. This differential regulation of the central and peripheral α_2-adrenoceptor by citalopram may underlie the discrepancy between the onset of the therapeutic effects of antidepressants, which usually takes several weeks, and the sexual dysfunction side effects, which can appear at the beginning of treatment and can even be associated with citalopram withdrawal (Adson & Kotlyar 2003; Cassano & Fava 2004). Taking into account the results of a recent clinical trial in which the combination of the α_2-adrenoceptor antagonist yohimbine with an SSRI appears to hasten the antidepressant response (Sanacora et al 2004), and that yohimbine also seems potentially useful for the management of SSRI-induced sexual dysfunction (Cassano & Fava 2004), our results may help to clarify the role of α_2-adrenoceptor antagonists in the management of depression.

Conclusion

These results demonstrate that citalopram produces a desensitization of α_2-adrenoceptors in the peripheral nervous system, which may contribute to the sexual dysfunction produced by SSRIs. However, previous studies by our group revealed that the same treatment protocol did not change α_2-adrenoceptor sensitivity in the central nervous system (Grandoso et al 2005). This differential modulation of peripheral and central α_2-adrenoceptors may underlie the differences between the onset of the side effects, and in particular those associated with sexual dysfunction, and the antidepressant effect. Overall, these finding may contribute to the elaboration of better-tolerated strategies for the treatment of depression.

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