Effects of sustained serotonin reuptake inhibition on the firing of dopamine neurons in the rat ventral tegmental area

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Background: Selective serotonin (5-HT) reuptake inhibitors (SSRIs) are efficacious in depression because of their ability to increase 5-HT neurotransmission. However, owing to a purported inhibitory effect of 5-HT on dopamine (DA) neuronal activity in the ventral tegmental area (VTA), this increase in 5-HT transmission might result in a suppression of the firing activity of DA neurons. Since the mesolimbic DA system plays an important role in motivation and reward, a potential decrease in the firing of DA neurons may lead, in some patients, to a lack of adequate response to SSRIs. **Methods:** We administered the SSRIs citalopram or escitalopram in rats. We determined DA neuronal activity using in-vivo electrophysiology. **Results:** Sustained administration of escitalopram robustly decreased the firing rate and burst activity of DA neurons. There was no difference in the mean number of spontaneously active DA neurons per tract among the 3 groups (citalopram, escitalopram, control). This inhibition was reversed by the selective 5-HT_{2C} receptor antagonist SB 242084. Citalopram, however, did not alter the overall firing rate but inhibited the burst activity of DA neurons. **Limitations:** Our experiments were carried out with the rats under general anesthesia. Therefore, under such conditions the absolute changes produced by SSRIs may heve been different from those occurring in freely moving rats. The exact location of the 5-HT_{2C} receptors mediating the inhibitory effects of the SSRIs could not be determined in these studies. **Conclusion:** The difference between escitalopram and citalopram in their effect on DA neuronal activity may be explained by the higher efficacy of escitalopram as a 5-HT reuptake inhibitor. Since the inhibitory effect of escitalopram on DA neuronal activity is mediated via 5-HT_{2C} receptors, antagonists of these receptors might be effective adjuncts in SSRI-resistant depression.

Contexte : Les ISRS, ou inhibiteurs sélectifs du recaptage de la sérotonine (5-HT), sont efficaces dans la dépression en raison de leur capacité d'accroître la neurotransmission sérotoninergique. Toutefois, compte tenu d'un présumé effet inhibiteur de la 5-HT sur l'activité dopaminergique dans l'aire tegmentaire ventrale, cette transmission sérotoninergique accrue pourrait entraîner un ralentissement de la fréquence de décharge des neurones dopaminergiques. Étant donné que le système dopaminergique mésolimbique joue un rôle important dans la motivation et la gratification, un ralentissement potentiel de la fréquence de décharge des neurones dopaminergiques pourrait empêcher une réponse incomplète aux ISRS chez certains patients. **Méthodes :** Nous avons administré les ISRS citalopram ou escitalopram à des rats. Nous avons enregistré in vivo l'activité éléctrophysiologique des neurones dopaminergiques. **Résultats :** L'administration soutenue d'escitalopram a nettement ralenti la fréquence de décharge et diminué l'activité en salve des neurones dopaminergiques. On n'a noté aucune différence quant au nombre moyen de neurones dopaminergiques spontanément actifs parmi les 3 groupes (citalopram, escitalopram, témoins). Cette inhibition a été renversée par le SB242084, un antagoniste sélectif des récepteurs 5-HT_{2C}. Le citalopram n'a cependant pas modifié la fréquence globale de décharge, mais a inhibé l'activité en salve des neurones dopaminergiques. **Limites :** Nos expériences ont été effectuées chez des rats sous anesthésie générale. Compte tenu de cette condition, les changements absolus générés par les ISRS pourraient être différents de ce qui s'observerait chez des rats éveillés. Ces expériences ne démontrent pas la localisation des récepteurs 5-HT_{2C} modulant les effets inhibiteurs des ISRS. **Conclusion :** La différence entre l'escitalopram et le citalopram pour ce qui est de leur effet sur l'activité neuronale dopaminergique pourrait s'expliquer par l'inhibition plus grande du escitalopram sur le recaptage de la 5-HT. Étant donné que l'effet inhibiteur du escitalopram sur l'activité neuronale dopaminergique est modulé par les récepteurs 5-HT_{2C}, les antagonistes de ces récepteurs pourraient être efficaces en traitement d'appoint dans la dépression résistante aux ISRS.

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Introduction

Selective serotonin (5-HT) reuptake inhibitors (SSRIs) are used as first-line drugs in the treatment of depression. However, only about one-third of depressed patients achieve remission within the first medication trial with an SSRI.[1] Different possibilities have been proposed to explain this lack of adequate response to SSRIs. Sustained administration of SSRIs elevates extracellular 5-HT levels, which leads to activation of 5-HT_{1A} receptors on 5-HT neurons in the dorsal raphe nucleus and 5-HT_{2A} receptors on postsynaptic neurons. The activation of these receptors suppresses the firing of 5-HT and norepinephrine (NE) neurons of the locus coeruleus, respectively.[2,3] Although 5-HT neurons regain their firing rate with treatment prolongation, because of the desensitization of 5-HT_{1A} autoreceptors, the firing rate of NE neurons does not recover over time. This persistent suppression of NE neuronal firing activity may contribute to the incomplete or lack of response to SSRIs in some patients.[4,5] Atypical antipsychotics, which are all 5-HT_{2A} receptor antagonists, are effective adjuncts in SSRI-resistant depression.[6]

Dopamine (DA) neurons have received little attention as a possible target of augmentation strategies in treatment-resistant depression. Since the lesion of 5-HT neurons results in an increase of DA neuronal activity in the ventral tegmental area (VTA), it has been proposed that enhanced 5-HT levels inhibit DA neurons.[7] Thus, an increase in the availability of 5-HT owing to SSRIs might result in attenuation of the firing of DA neurons. Because of the critical role of DA neuronal activity in the VTA in motivation, hedonia and reward,[8] the inhibition of this firing might contribute to SSRI resistance in some patients.

It has been previously reported that acute administration of various SSRIs produces a small inhibition or no effect on the firing activity of DA neurons in the VTA.[9–11] However, these observations have little clinical relevance, since the therapeutic effect of SSRIs in depressed patients is observed only after prolonged administration. Only one study assessed the effect of long-term administration of fluoxetine on the firing activity of DA neurons.[9] It showed no significant effect on DA neuronal firing activity in the VTA. Fluoxetine, however, is not entirely selective for the 5-HT transporters.[12]

In the present study, we examined the effects of sustained administration of the SSRIs citalopram and escitalopram on the firing activity of DA neurons in the VTA. We chose these SSRIs because they are potent and have negligible affinity to other transporters and receptors.[13] Citalopram is a racemic compound that contains equal parts of the R and S enantiomers. It has been previously reported that only S-citalopram (escitalopram) acts as a 5-HT reuptake inhibitor, whereas R-citalopram antagonizes this action of escitalopram. As a result, escitalopram has higher efficacy as a reuptake inhibitor than citalopram.[14] The comparison between the effects of citalopram and escitalopram on DA neuronal activity in the VTA was of special interest because of the differential effectiveness of these drugs to inhibit 5-HT reuptake in vivo.[4,5,14]

Methods

Animals

We carried out the experiments in male Sprague–Dawley rats (Charles River, St. Constant, Que.) weighing 300–350 g at the time of the recording. We kept the rats under standard laboratory conditions (12:12 light–dark cycle with free access to food and water). The Ottawa Health Research Institute Animal Care Committee approved all animal procedures, and we carried out the procedures in accordance with the guidelines of the Canadian Council on Animal Care.

Treatments

We dissolved the citalopram and escitalopram (Lundbeck) in distilled water and administered the drugs via osmotic minipumps (Alza) for 2 and 14 days at the daily doses of 20 and 10 mg/kg/d, respectively. We implanted control rats with a minipump containing water. We implanted the pumps subcutaneously with the animals under isoflurane (Abbott) anesthesia; the pumps remained in the rats during the electrophysiological recordings. We injected escitalopram acutely via a lateral tail vein at cumulative doses of 0.5–5.0 mg/kg. We chose these doses and time courses based on the results of previous studies. Since citalopram and escitalopram have a half-life about 10 times shorter in rats than in humans, these drugs reach a steady state brain concentration in rats much faster than in humans.[13] Thus, a 2-day administration period in rats likely corresponds to about a 1-week course of therapy in humans, and a 2-week regimen in rats probably corresponds to a 3- or 4-week course of therapy in humans, a time at which an improvement of the symptoms of depression in humans can be observed.[15,16] The continuous release of the drug from the minipumps therefore more accurately mimics the treatment in humans than do subcutaneous or intraperitoneal injections.

We dissolved the selective antagonist of 5-HT_{2C} receptors 6-chloro-5-methyl-1[(2-[2-methylpyrid-3-yloxy] pyrid-5yl) carbamoyl] indoline (SB 242084; Sigma-Aldrich) in 20% of (2-hydroxypropyl)-β-cyclodextrin (Acros Organics) and administered it subcutaneously at 0.5 and 2.0 mg/kg/d for 2 days, alone or in combination with escitalopram (administered via osmotic minipumps). We administered the first injection of SB 242084 after the minipump implantation, the second 24 hours afterward and the last 1 hour before the recording. The doses of citalopram, escitalopram and SB 242084 were based on those reported in previous studies.[2,4,17]

Electrophysiological experiments

We anesthetized the rats with chloral hydrate (Sigma-Aldrich; 400 mg/kg, intraperitoneally) and mounted them in a stereotaxic apparatus (David Kopf Instuments). We administered supplemental doses to prevent any nociceptive reaction to pinching of the hind paw. We maintained body temperature at 37°C throughout the experiments using a water heating pad. We drilled a 2-mm burr hole, 3.2 mm anterior to

the interaural line and 0.8 mm lateral to the midline for recordings of DA neurons in the VTA. We stopped any bleeding from disruption of the sagittal sinus immediately using bone wax. We conducted extracellular unitary recordings with single-barrelled glass electrodes filled with a 2-M NaCl solution. Their impedance range was between 4 and 6 M. We identified spontaneously active DA neurons of the VTA using the following criteria: a typical triphasic action potential with a marked negative deflection, a characteristic long duration (> 2.5 ms) often with an inflection or "notch" on the initial rising phase and a slow spontaneous firing rate (1–7 Hz) with an irregular single spiking pattern with slow bursting activity (characterized by spike amplitude decrement). In addition, we used a criterion of duration (> 1.1 ms from the start of the action potential to the negative trough). These electrophysiological properties reliably distinguish DA from non-DA neurons.[7,18,19]

Analysis of burst firing

The DA neurons in the VTA demonstrate 2 different types of firing activity: single-spike firing and burst firing. It has been previously shown that burst firing of DA neurons leads to significantly greater DA release than single spikes.[20] Therefore, we analyzed the firing activity of DA neurons in terms of their basal firing rate and their burst activity. We assessed burst firing using interspike interval analysis. We defined the onset of a burst as the concurrence of 2 spikes with an interspike interval shorter than 0.08 seconds. We defined the termination of burst as an interspike interval of 0.16 seconds or longer.[18] We used Spike2 software (Cambridge Electronic Design) for the analysis of burst activity.

Statistical analysis

We expressed results as means and standard errors of the means (SEM) of single neuron values. We carried out statistical comparisons between the differences in DA neuron firing using multivariate analysis of variance (ANOVA). We determined statistically significant differences using the $p < 0.05$ criterion.

Results

The mean firing rate of DA neurons was 4.5 Hz in the control group. We lowered the electrode through the VTA of each animal 4 or 5 times. There was no difference in the mean number of spontaneously active DA neurons per tract between the groups (control: 0.76, SEM 0.24; escitalopram: 0.77, SEM 0.24; $p = 0.99$). There were on average 6 bursts per 10 seconds, each burst contained about 4 spikes, and about a half of the spikes occurred within the bursts. The pattern of the firing (Fig. 1A) was typical for DA neurons, as previously described.[18,19]

Acute, intravenous administration of 0.5–5.0 mg/kg of escitalopram did not alter the firing activity of DA neurons in the VTA (Fig. 2). When escitalopram was administered for 2 (22 recordings from 5 animals) or 14 days (18 recordings

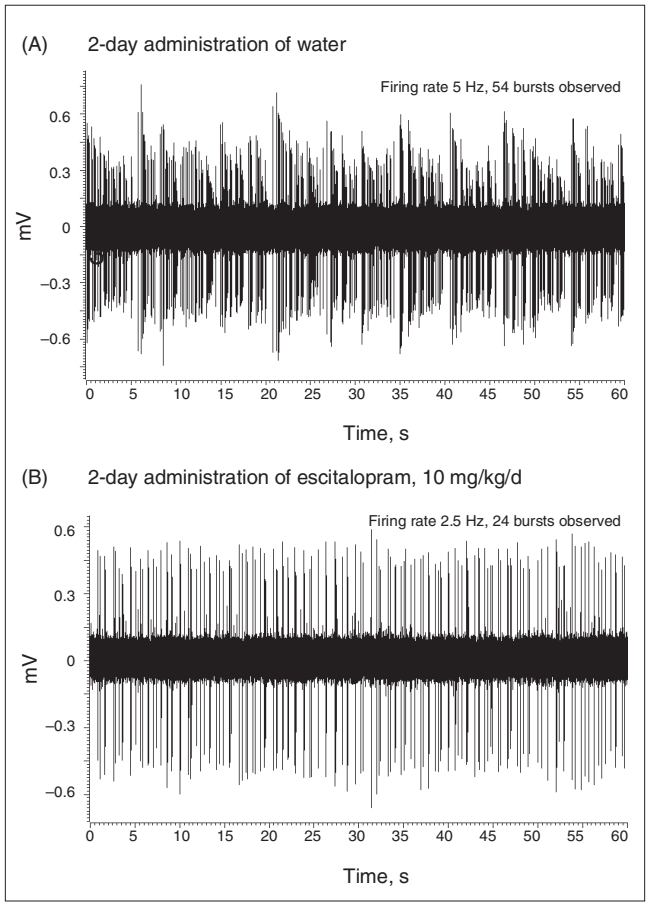

Fig. 1. Representative single-unit extracellular recordings from the ventral tegmental area dopamine neurons in (**A**) a control rat that received water and (**B**) in a rat that received 10 mg/kg/d of escitaloram for 2 days.

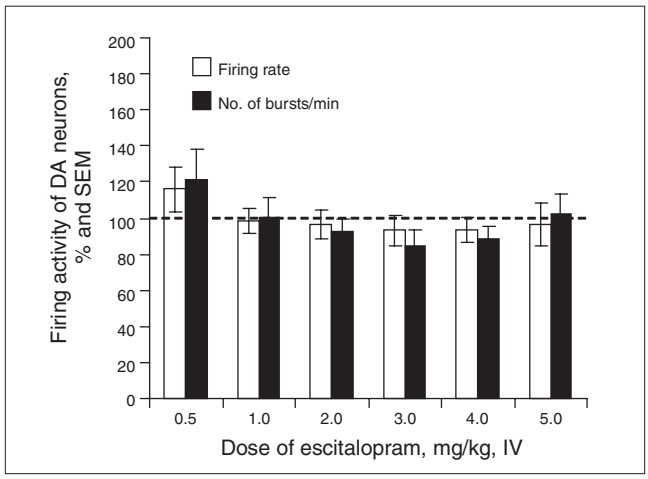

Fig. 2. Lack of the effect of acute administration of escitalopram on the firing activity of dopamine neurons. The animals ($n = 5$) were consecutively given (intravenously) escitalopram at the doses from 0.5 to 5.0 mg/kg. The firing rates and burst activity (mean and standar error of the mean) are presented. The higher doses of escitalopram could not be tested because of their lethal effect on animals.

from 6 animals), it decreased the firing rate and the burst activity of DA neurons by about 50% (Fig. 1). The 2-day citalopram regimen did not alter the firing rate of DA neurons (11 recordings from 4 animals), but decreased the mean number of spikes per burst. After 14 days (15 recordings from 5 animals), citalopram decreased the mean number of bursts per 10 seconds, but not the firing rate of DA neurons (Fig. 3).

The selective 5-HT_{2C} receptor SB 242084 did not alter the firing rate of DA neurons by itself (0.5 mg/kg/d: 15 recordings from 5 animals; 2.0 mg/kg/d: 13 recordings from 4 animals). When it was coadministered with escitalopram for 2 days at 0.5 mg/kg/d (27 recordings from 6 animals), SB 242084 partially antagonized the escitalopram-induced inhibition of DA neuronal firing activity. Administered at the dose of 2 mg/kg/d (11 recordings from 4 animals), SB 242084 completely reversed the escitalopram-induced suppression of the firing rate and of the burst activity of DA neurons (Fig. 4).

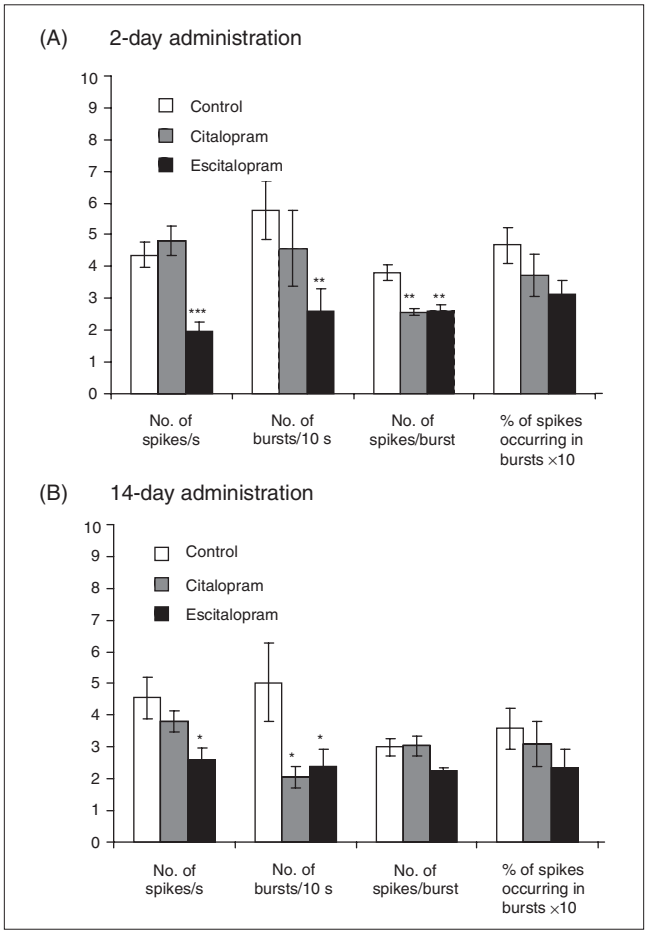

Fig. 3. Effects of citalopram and escitalopram administration on the dopamine neuronal firing rate in the ventral tegmental area. The rats were implanted with minipumps containing vehicle (water), citalopram (20 mg/kg/d) and escitalopram (10 mg/kg/d) for (**A**) 2 and (**B**) 14 days. The firing rates and burst activity (mean and standard error of the mean) are presented. Multivariate analysis of variance showed a significant difference between the groups. For 2 days: Wilks $\Lambda = 0.22$, $F_{8,94} = 12.91$, $p < 0.001$, firing rate $F = 13.19$, $p < 0.001$; number of bursts/10 s $F = 6.95$, $p < 0.01$; number of spikes/burst $F = 9.62$, $p < 001$; for 14 days: Wilks $\Lambda = 0.59$, $F_{8,84} = 12.91$, $p < 0.01$, firing rate $F = 4.50$, $p < 0.05$, number of bursts/10 s $F = 4.39$, $p < 0.05$, number of spikes/burst $F = 3.37$, $p < 0.05$). *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$ in comparison with vehicle, Bonferroni post-hoc test.

Discussion

Our results did not show a significant effect of acute administration of escitalopram on the firing activity of DA neurons in

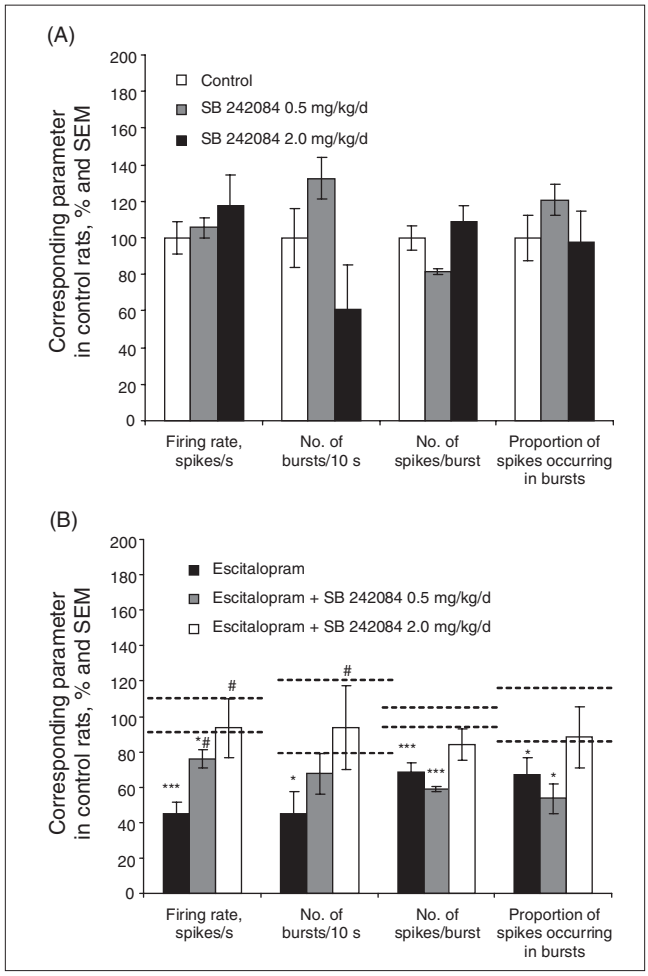

Fig. 4. Effect of SB 242084 administration on the dopamine neuronal firing rate in the ventral tegmental area. The selective 5-HT_{2C} receptor antagonist SB 242084 was given (0.5 and 2.0 mg/kg/d for 2 days, subcutaneously) to rats that received (**A**) vehicle and (**B**) escitalopram. The firing rates and burst activity (mean and standard error of the mean [SEM]) are presented. The ranges of control animals are shown using dotted lines (mean–SEM, bottom line; mean+SEM, upper line). When SB 242084 was coadministered with escitalopram, multivariate analysis of variance showed significant difference between the groups: Wilks $\Lambda = 0.53$, $F_{12,196} = 4.38$, $p < 0.001$, firing rate $F = 5.83$, $p = 0.001$; number of spikes/burst $F = 12.47$, $p < 001$, proportion of spikes occurring in bursts $F = 3.22$, $p < 0.05$). *$p < 0.05$ and ***$p < 0.001$ in comparison with vehicle; #$p < 0.05$ in comparison with escitalopram, Bonferroni post-hoc test.

the VTA. In contrast, sustained administration of escitalopram (for 2 and 14 days), but not of citalopram, decreased the mean firing rate of DA neurons. Citalopram administration for 2 days decreased the number of spikes per burst, whereas after a 14-day regimen it attenuated the occurrence of burst activity. The selective 5-HT_{2C} receptor antagonist SB 242084 did not alter the firing activity of DA neurons by itself, but reversed the escitalopram-induced inhibition of DA neuronal firing activity.

Serotonin exerts an inhibitory action on DA neuronal firing since, in rats with lesioned 5-HT neurons, the overall firing of DA neurons and their burst activity were increased.[7] It has been previously reported that acute administration of 1–4 mg/kg of escitalopram dose-dependently increases extracellular 5-HT levels in the prefrontal cortex in rats.[14] We therefore expected that such acute doses of escitalopram would produce a dose-dependent inhibition of the firing of DA neurons in the VTA. However, we observed no effect of acute administration of 0.5–5.0 mg/kg of escitalopram on DA neuronal firing activity (Fig. 2). Thus, it is possible that the escitalopram-induced elevation of extracellular 5-HT levels in the VTA is smaller than in the prefrontal cortex.

Results of previous studies[9,10] have shown that the acute administration of various SSRIs produces small inhibitions of DA neuronal firing activity in the VTA (paroxetine: mean inhibitory effect 10, standard error [SE] 11%; sertraline: 10, SE 7%; citalopram: 14, SE 7%; fluvoxamine: 17, SE 12). The acute administration of fluoxetine significantly inhibited the firing of DA neurons to a greater extent (mean inhibitory effect 34, SE 7%).[9] However, another study reported no effect of acute administration of fluoxetine on DA neuronal firing activity.[11] Thus, it appears paradoxical that the SSRI with the greatest potency, escitalopram, was ineffective in dampening the firing of DA neurons whereas the relatively weaker SSRIs did so.[21,22] Therefore, it is conceivable that the ability of these SSRIs to acutely inhibit DA neuronal firing activity may result from the additional properties of these drugs at a variety of other receptors.[23]

In sharp contrast to the lack of effect of acute escitalopram on the firing of DA neurons, sustained administration over 2 days produced a mean inhibitory effect of 66 (SE 7%), also attenuating their burst firing activity (Fig. 3). Thus it is possible that only an elevated steady state brain concentration of escitalopram achieved by its sustained administration was necessary. This possibility would be consistent with the observation that SSRIs are eliminated from the brain more slowly than from the plasma.[24,25] The time necessary to reach steady state and time of elimination of any given drug are essentially similar. Presumably, escitalopram did not achieve an optimal level in the brain until 2 days of sustained administration.

In an attempt to determine the 5-HT receptor subtype involved in mediating the decrease in firing of DA neurons by escitalopram, we used the 5-HT antagonist SB 242084. Only 5-HT_{2C} receptors had an inhibitory effect on DA tone, whereas an activation of other receptors led to an increase in DA release in the nucleus accumbens.[26] We initially co-administered SB 242084 with escitalopram at a dose of 0.5 mg/kg/d because the same dose of this compound, administered in a single injection, was previously reported to potentiate the citalopram-induced increase in 5-HT levels in the hippocampus in rats.[27] This dose of SB 242084 partially antagonized the inhibitory effect of escitalopram. When we increased the dose of SB 242084 to 2 mg/kg/d, it completely reversed escitalopram-induced suppression of firing of DA neurons in the VTA (Fig. 4). These results indicate that the effect of escitalopram on DA neuronal firing activity in the VTA is mediated via 5-HT_{2C} receptors. These receptors, in fact, are probably excitatory and located on γ-aminobutyric acid (GABA) neurons innervating the DA neurons in the VTA. Thus, their activation leads to the suppression of firing of DA neurons. We did not examine other 5-HT receptors since 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_3 and 5-HT_4 receptors facilitate DA release in postsynaptic regions, whereas only 5-HT_{2C} receptor mediates an inhibitory effect on terminal DA release.[26]

We observed that sustained solo administration of SB 242084 for 2 days did not alter the firing rate of DA neurons in the VTA. The results of previous studies showed that acute administration of various agents with 5-HT_{2C} antagonistic properties increased the firing rate of DA neurons in the VTA.[26] Since in our study we started recording from the DA neurons 1 hour after the last injection of SB 242084, it is possible that the activation of DA neuronal firing activity by SB 242084 observed in other studies was transient. However, the ability of SB 242084 to antagonize the inhibitory effect of escitalopram on DA neuronal firing activity appeared sustained.

It is noteworthy that the regimen of escitalopram used in our study produces a robust decrease of the firing rate of 5-HT neurons in the dorsal raphe nucleus and of NE neurons in the locus coeruleus.[2,4,5] However, whereas 5-HT neurons regain their normal firing after 14 days of sustained administration,[2] we observed no recovery of the firing rate of DA neurons with the same escitalopram regimen (Fig. 3). Similarly, no recovery of initial inhibition of firing by the same regimen of escitalopram was previously observed for NE neurons.[4,5] The recovery of the normal firing rate of 5-HT neurons is explained by desensitization of 5-HT_{1A} autoreceptors in the dorsal raphe nucleus.[28] It therefore can be suggested that the 5-HT_{2C} receptors regulating the firing activity of DA neurons in the VTA do not desensitize after long-term administration of escitalopram. Similarly, 5-HT_{2A} receptors regulating NE neuronal firing activity in the locus coeruleus do not desensitize.[4]

Unlike escitalopram, sustained administration of citalopram did not alter the firing rate of DA neurons. However, it attenuated certain characteristics of their burst activity: after 2 days, the mean number of spikes per burst was decreased, and after 14 days, the occurrence of the bursts was suppressed (Fig. 2). These alterations of the firing pattern of DA neurons could still lead to a decrease in DA transmission, since the burst firing contributes to a significant increase in DA release.[20] However, we expected the escitalopram-induced inhibition of DA transmission to be much higher than that of citalopram because escitalopram attenuated both the firing rate and burst activity of DA neurons, whereas citalopram attenuated only the burst activity.

It was recently reported that the chronic administration of

citalopram decreased the mean number of spontaneously active DA neurons in the VTA in rats.[29] Unfortunately, firing rates were not reported. Merely reporting the number of neurons per tract is not a clear indication of their activity. In addition, the citalopram regimen used (1 mg/kg/d) was extremely low and did not mimic the levels achieved in humans.[13] It was also recently observed that the long-term administration of monoamine oxidase inhibitors doubles the number of neurons per tract, but decreases the mean firing rate by 30% and the number of bursts per minute by 80%.[30] These results indicate that to reliably estimate the effect of a treatment on DA neuronal firing, all the above-mentioned parameters must be taken into consideration.

The other difference between escitalopram and citalopram is that escitalopram attenuates the firing activity of both DA and NE neurons with a brief delay. Citalopram, however, has a time-independent effect on DA, but a time-dependent effect on NE neuronal firing activity. Thus a 2-day regimen of citalopram did not alter the firing of NE neurons even if it was given at a dose 4 times higher than that of escitalopram.[4,17] A significant inhibition of NE neurons becomes apparent only after 14 days of citalopram administration, and it increases over the next 7 days.[17] These differences between the effects of citalopram and escitalopram on DA and NE neuronal firing activity can be explained by higher efficacy of escitalopram as a reuptake inhibitor, as previously suggested.[4] It was observed in microdialysis studies that escitalopram produces greater elevations in extracellular 5-HT levels than those achievable with racemic citalopram.[14] Consistently, escitalopram was 5 times more potent in suppressing the firing of 5-HT neurons in the dorsal raphe nucleus than racemic citalopram, an effect taking place as a result of the inhibition of 5-HT reuptake.[2]

Limitations

Our experiments were carried out with the rats under general anesthesia. Therefore, under such conditions the absolute changes produced by SSRIs may have been different from those occurring in freely moving rats. The exact location of the 5-HT_{2c} receptors mediating the inhibitory effects of the SSRIs could not be determined in these studies.

In conclusion, 5-HT reuptake inhibition can attenuate the firing activity of DA neurons in the VTA, although only escitalopram does so in a robust fashion. This inhibition might result in suppression of mesolimbic and mesocortical DA neurotransmission. On the one hand, because of the critical role of these DA pathways in the regulation of motivation and reward, such an effect may account, in some patients, for the lack of adequate response to SSRIs. On the other hand, since escitalopram showed greater remission rates than racemic citalopram in 2 head-to-head, double-blind studies,[31,32] the marked potency of escitalopram to enhance 5-HT levels above that of other SSRIs might partially offset this attenuation of DA tone. Nevertheless, the present results suggest that 5-HT_{2C} receptor antagonism, as well as DA receptor agonism, may be effective augmentation strategies in SSRI-resistant depressed patients.

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Contributors: All authors contributed to study design and data analysis and approved publication of the article. Dr. Dremencov acquired the data and wrote the article. Drs. El Mansari and Blier reviewed the article.

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