Available online at www.sciencedirect.com
SCIENCE DIRECT®
Pharmacology, Biochemistry and Behavior 77 (2004) 391–398
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

R-citalopram inhibits functional and 5-HTP-evoked behavioural responses to the SSRI, escitalopram

Connie Sánchez*, Mads Kreilgaard

Neuropharmacological Research, H. Lundbeck, Ottiliavej 9, DK 2500 Copenhagen–Valby, Denmark

Received 3 July 2003; received in revised form 30 November 2003; accepted 3 December 2003

Abstract

Escitalopram mediates the serotonin re-uptake inhibitory and antidepressant effect of citalopram racemate. However, recent studies have shown that R-citalopram inhibits the escitalopram-induced increase of extracellular 5-HT levels in the frontal cortex of rats. Here, we investigated the inhibitory effect of R-citalopram on the escitalopram-induced increase of 5-HT neurotransmission at the behavioural [potentiation of 5-hydroxytryptophan (5-HTP)-induced behavioural changes in mice and rats] and functional (increase in serum corticosterone in rats) levels. The effect of escitalopram was inhibited by R-citalopram in all three models, and R-citalopram, given alone, was inactive. The effects were more pronounced using an escitalopram to R-citalopram ratio of 1:4 than ratios of 1:2 and 1:1, suggesting a dose-dependent effect. The ED_{50}-value of escitalopram in mouse 5-HTP potentiation studies corresponded to a serum concentration of approximately 50 ng/ml, which can be considered to be in the range of clinically relevant serum concentrations.

In conclusion, R-citalopram inhibited the escitalopram-induced increase of 5-HT activity in functional, as well as behavioural, animal models. The mechanism involved in this interaction is currently unknown, but may be related to an improved clinical effect seen with escitalopram in comparison with citalopram.

Keywords: 5-Hydroxytryptophan potentiation; Corticosterone; Serum concentration; Citalopram enantiomers; Mice; Rat

1. Introduction

The selective serotonin (5-HT) re-uptake inhibitor (SSRI), citalopram, is a racemic mixture of S-(+)- and R-(−)-enantiomers (escitalopram and R-citalopram, respectively) in a 1:1 ratio. The in vitro and in vivo 5-HT re-uptake inhibitory and the antidepressant and anxiolytic activity of citalopram, was reported to reside in the S-enantiomer and the R-enantiomer was reported to be practically devoid of pharmacological activity (Hyttel et al., 1992; Sánchez et al., 2003a). During the last few years, escitalopram has demonstrated its therapeutic benefit in treating major depressive and anxiety disorders (e.g., Burke et al., 2002; Wade et al., 2002). Interestingly and unexpectedly, escitalopram appeared to be clinically superior to an equivalent dose of citalopram in clinical studies (Burke et al., 2002; Colonna et al., 2002; Lepola et al., 2003; Montgomery et al., 2001), suggesting a negative influence of R-enantiomer on the clinical outcome. Recently published pharmacological studies support these observations by demonstrating that R-citalopram inhibits escitalopram-induced increase of extracellular 5-HT levels in the frontal cortex of freely moving rats (Mørk et al., 2003). R-citalopram also inhibits anxiolytic- and antidepressant-like effects of escitalopram in rats, that is, the inhibition of footshock-induced ultrasonic vocalisation (Sánchez, 2003), the reversal of conditioned suppression of exploratory behaviour (Sánchez et al., 2003b) and the reversal of chronic mild stress-induced hedonic deficits (Sánchez et al., 2003c).

The present study was designed to assess whether the inhibitory effect of R-citalopram on escitalopram-induced increase of extracellular 5-HT concentration in the brain was correlated to decreased responses in functional and behavioural models of 5-HT neurotransmission. We used potentiation of 5-hydroxytryptophan (5-HTP)-induced changes in mice and rats as a behavioural (Ortman et al., 1980), and the increase in serum corticosterone in rats as a functional index of enhanced 5-HT activity (Fuller et al.,

* Corresponding author. Tel.: +45-36-30-13-11; fax: +45-36-30-10-79.
E-mail address: cs@lundbeck.com (C. Sánchez).

0091-3057/$ – see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2003.12.001

1996). Furthermore, we related the behavioural responses in mice to escitalopram serum concentrations.

2. Experimental

2.1. Animals

Male NMRI/BOM mice (18–25 g; Bomholtgaard, Denmark) were housed in plastic cages (35 × 30 × 12 cm) in groups of four and were habituated to the animal facilities for at least a week before testing. Male Wistar rats (200–250 g; Møllegaard, Denmark) were housed in groups of two to four in Macrolon cages type III and were habituated to the animal facilities for at least 2 weeks before testing. The room temperature (21 ± 2 °C), relative humidity (55 ± 5%) and air exchange (16 times per hour) were automatically controlled, and the dark/light cycle was lights on at 6 a.m. and off at 6 p.m. The animals had free access to commercial food pellets and tap water.

Ethical permissions for the studies were granted by the animal welfare committee, appointed by the Danish Ministry of Justice, and all animal procedures were carried out in compliance with the EC Directive 86/609/EEC and with the Danish law regulating experiments on animals.

2.2. 5-HTP potentiation

2.2.1. Mice

The test was carried out as described in detail by Hyttel et al. (1992). Briefly, 5, 15 or 30 min after the subcutaneous administration of test compound(s), the mice were given 5-HTP (100 mg/kg iv). Thereafter, the animals were evaluated in their home cage during a 15-min observation period with respect to stereotypy (lateral head movements), tremor and hind limb abduction. The behavioural changes were scored as 0 = not present, 1 = present in mild to moderate degree, 2 = present in a marked degree. A total of 8–16 mice were used per dose. The drug response was calculated as mean (% of maximum score) ± S.E.M. score.

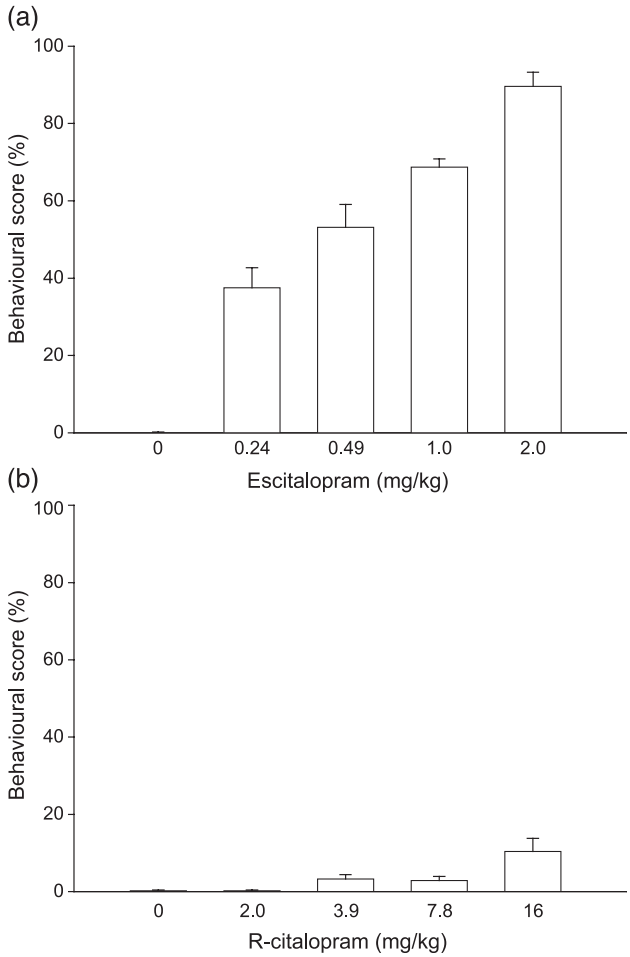

Fig. 1. Effect of (a) escitalopram and (b) R-citalopram in the mouse 5-HTP potentiation test. Mice were given 5-HTP (100 mg/kg iv) 30 min after the subcutaneous administration of escitalopram or R-citalopram, and were evaluated with respect to stereotypy (lateral head movements), tremor, and hind limb abduction (scores 0–2; $n = 8–16$ per dose group). Responses are presented as mean total score (% of the maximum score of 6) ± S.E.M.

2.2.2. Rats

Test compound(s) and vehicle were administered 30 min before the injection of L-5-HTP (87.3 mg/kg sc). The rats were placed singly in observation cages and the number of head twitches (wet dog shakes) was counted during a time interval of 30–40 min after L-5-HTP. A total of eight rats was used per treatment group.

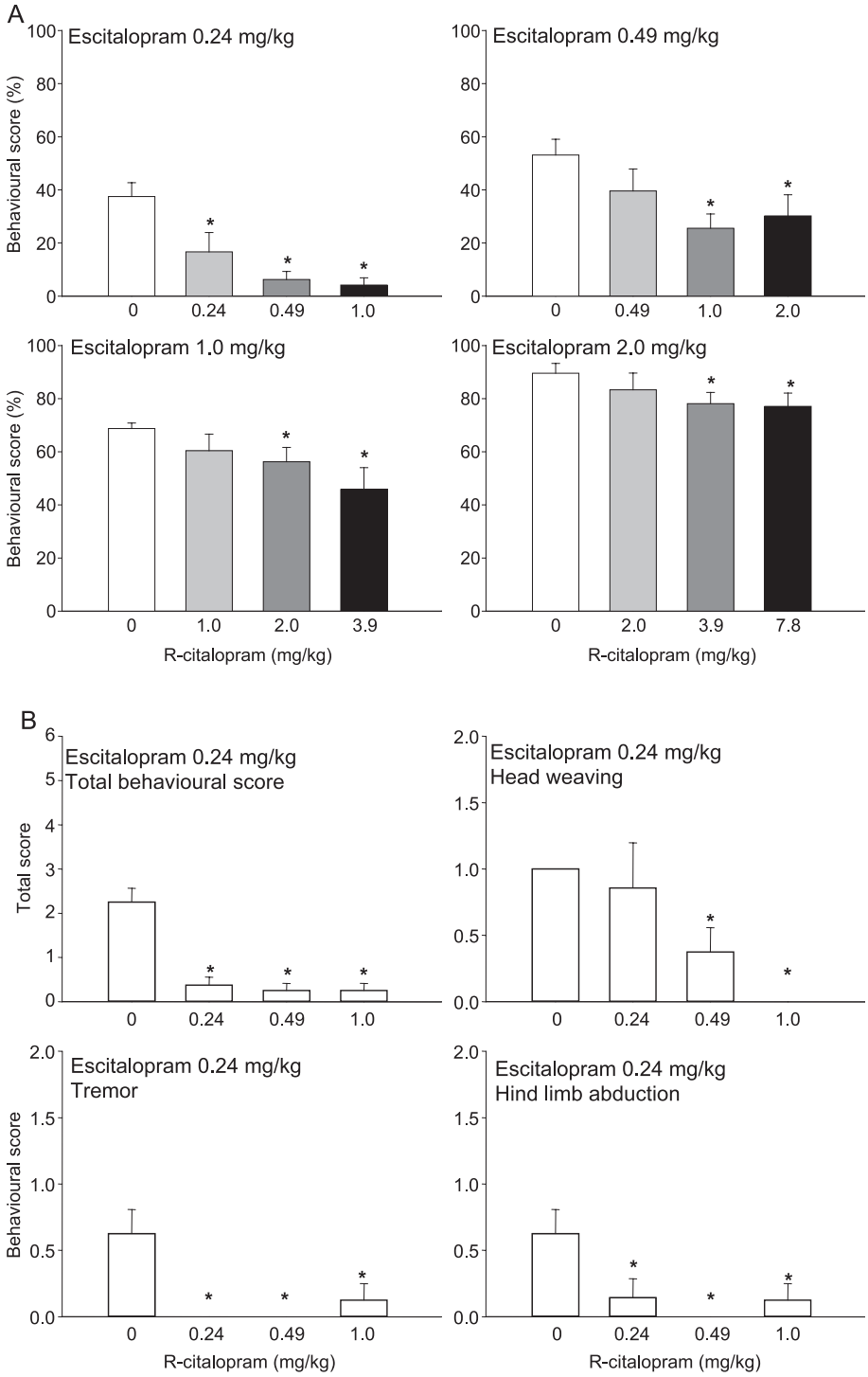

Fig. 2. Effect of R-citalopram on escitalopram-induced potentiation of behavioural response to 5-HTP in mice. Mice were given 5-HTP (100 mg/kg iv) 30 min after the subcutaneous administration of test compounds and were evaluated with respect to stereotypy (lateral head movements), tremor, and hind limb abduction (scores 0–2; $n = 8–16$ per dose group). Responses are presented as mean total score (% of the maximum score of 6) ± S.E.M. in Panel A and the individual behavioural signs are shown in Panels B–E. * $P < .05$ compared with escitalopram-treated group (F test followed by Student's t test comparison of means).

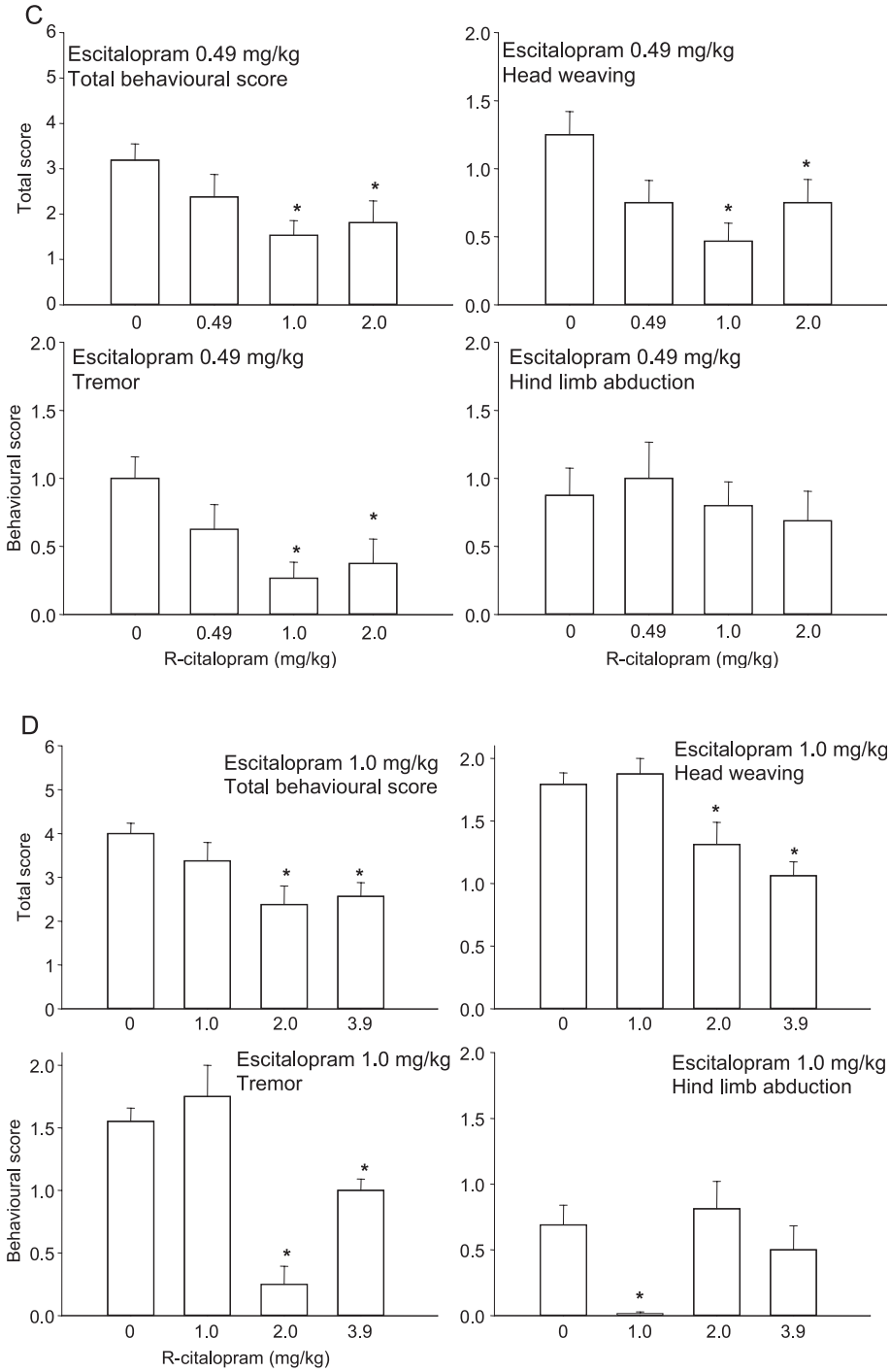

Fig. 2 (*continued*).

2.3. Serum corticosterone

Experiments were conducted between 10:00 and 11:30 a.m. to reduce the influence of circadian variation. Furthermore, drug treatments were conducted by consecutive treatment across groups to avoid a systematic bias, for example, by treating all animals in the vehicle group at the start of the experiment. The rats were sacrificed by decapitation 30 min after drug treatment, and trunk blood was collected and allowed to clot for at least 30 min at room temperature. The blood was then centrifuged at $1000 \times g$ for 10 min, and the supernatant was removed and stored at -80 °C until analysis. Serum corticosterone concentrations were determined using a commercially available ^{125}I-corticosterone radio immunoassay kit, with a lower level of detection of approximately 50 ng/ml and

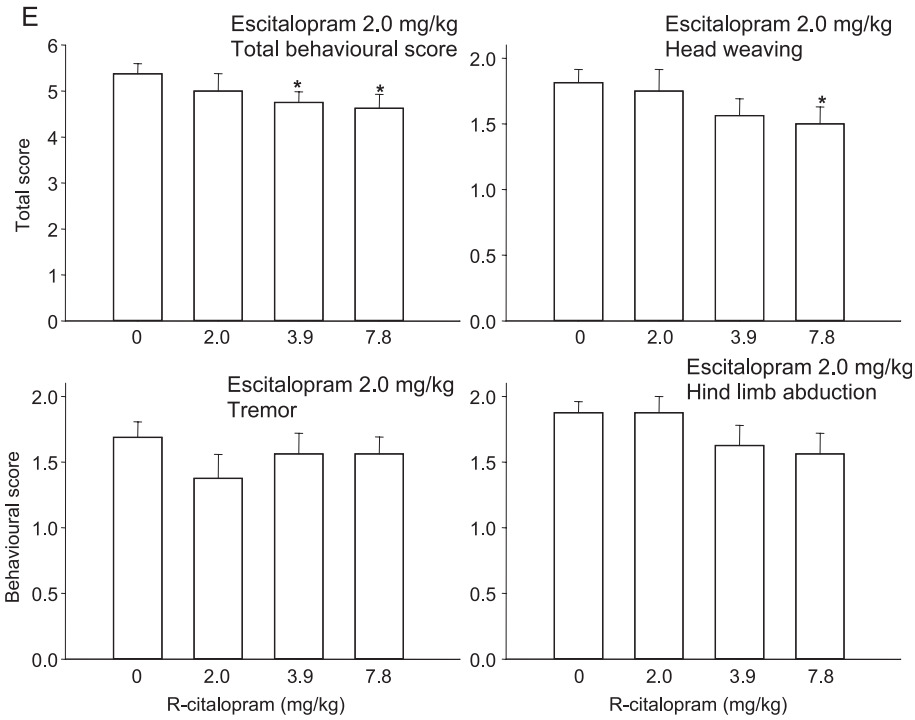

Fig. 2 (*continued*).

intra- and interassay variations of 5–10% (Amersham International, Bucks, England). The results were expressed as nanogram corticosterone per milliliter serum.

2.4. Escitalopram serum concentration

The mice were sacrificed by cervical dislocation 30 min after subcutaneous drug administration; trunk blood was collected, and serum was isolated and frozen at −80 °C until analysis.

Serum escitalopram content was determined by liquid chromatography/tandem mass spectrometry (LC–MS/MS). On-line sample preparation and liquid chromatography were performed with turbulent flow chromatography (Cohesive Technologies, Franklin, MA, USA), using a dual column configuration, according to a modified methodology described by Herman (2002).

Samples and calibration standards were precipitated with a ratio of 1:1, with methanol containing 20 ng/ml sertindole (Department of Medicinal Chemistry, H. Lundbeck, Copenhagen, Denmark) as internal standard. Following centrifugation for 40 min at 3200 × *g*, 10 μl sample was injected onto a Cohesive 2300 system (Cohesive Technologies) consisting of a quaternary pump for sample extraction and a binary pump for sample elution with a two-valve switchboard. Ammonium (0.1%) in water and methanol was used as eluents.

Extraction of escitalopram was achieved by loading the sample onto a Cyclone HTLC with a 1 × 50-mm (60 μm) column with pure aqueous, and by flushing the column for 30 s at 5 ml/min. Thereafter, the compound was transferred to a C18 HiRes 2.1 × 50-mm (10 μm) analytical column by switching 100 μl methanol onto the extraction column, followed by a gradient from 0% to 90% methanol over 2.5 min at 1 ml/min, maintaining 90% methanol for 60 s. Both columns were then reequi-

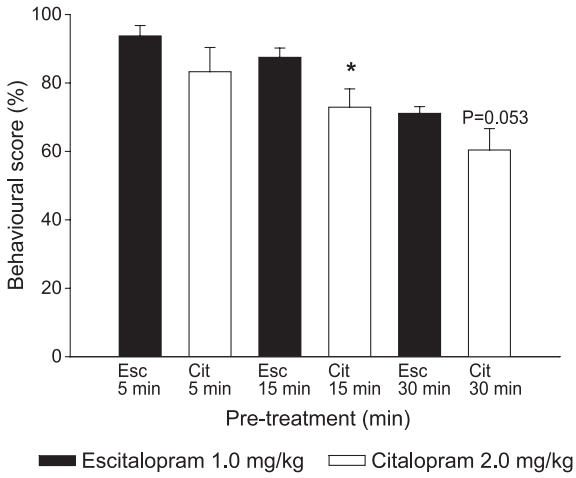

Fig. 3. Comparison of escitalopram- and citalopram-induced (1.0 and 2.0 mg/kg, respectively) potentiation of behavioural response to 5-HTP in mice. Mice were given 5-HTP (100 mg/kg iv) 5, 15 or 30 min after the subcutaneous administration of test compounds and were evaluated with respect to stereotypy (lateral head movements), tremor, and hind limb abduction (scores 0–2; $n = 8–16$ per dose group). Responses are presented as mean total score (% of the maximum score of 6) ± S.E.M. $^*P < .05$ compared with escitalopram-treated group (F test followed by Student's t test comparison of means).

librated with 100% aqueous for 60 s. MS/MS detection was done with a Quattro Ultima (Micromass, UK) in positive-ion electrospray ionization mode. Escitalopram and sertindole were detected at parent > daughter molecular mass of 324.99 > 108.95 and 440.96 > 112.96 Da, using a cone voltage of 50 and 48 V and a collision energy of 25 and 30 eV, respectively. Nitrogen was used for the auxiliary and nebulizer gases, and argon was used for the collision gas. Retention times were 3.44 min for escitalopram and 3.40 min for sertindole. The peak area correlated linearly with the serum concentration of escitalopram ($r^2 > .99$) in the range of 1–500 ng/ml. The lower limit of quantification was 1.0 ng/ml ($S/N > 10$).

2.5. Drugs

Citalopram HBr, escitalopram oxalate and R-citalopram oxalate (Department of Medicinal Chemistry, H. Lundbeck) were dissolved in saline and were injected subcutaneously using an injection volume of 5 and 10 ml/kg in rats and mice, respectively. Doses are expressed as mg/kg base.

3. Results

R-citalopram alone was practically inactive, whereas escitalopram showed a potent effect in the mouse 5-HTP potentiation test (Fig. 1). When given in combination, the effect of 0.24, 0.49, 1.0 and 2.0 mg/kg escitalopram was significantly inhibited by R-citalopram (Fig. 2A and B–E show the total score and individual behavioural signs, respectively). With respect to total score, the escitalopram to R-citalopram dose ratios of 1:2 and 1:4 showed

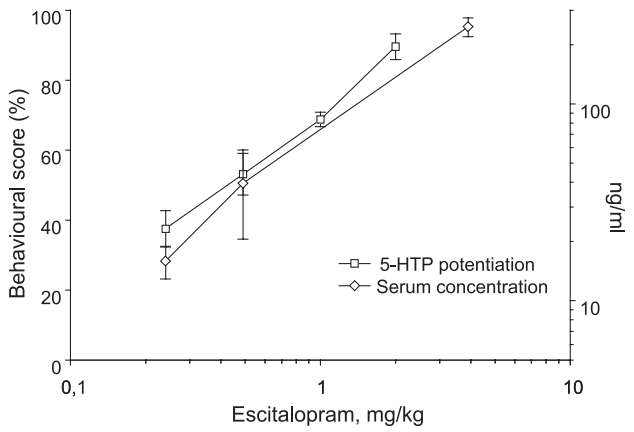

Fig. 4. Relation between escitalopram-induced potentiation of behavioural response to 5-HTP in mice and serum concentration. The mice were given 5-HTP (100 mg/kg iv) 30 min after the subcutaneous administration of test compounds and were evaluated with respect to stereotypy (lateral head movements), tremor, and hind limb abduction (scores 0–2; $n = 8–16$ per dose group). Responses are presented as mean total score (% of the maximum score of 6) ± S.E.M. Serum levels were determined in separate groups of mice treated with escitalopram subcutaneously 30 min before sacrifice ($n = 3$ per dose group).

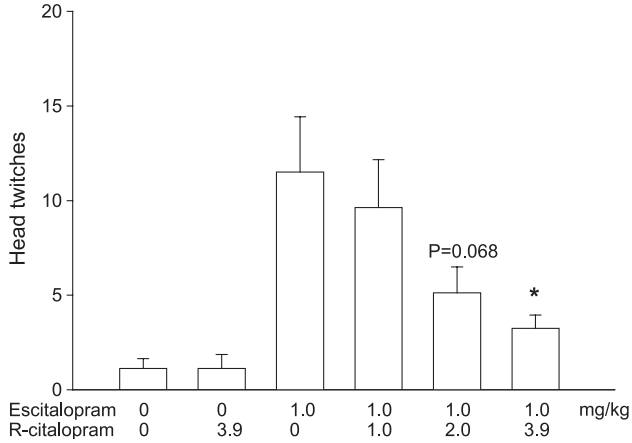

Fig. 5. Effect of R-citalopram on escitalopram-induced potentiation of behavioural response to L-5-HTP in rat. The test compound(s) and vehicle were administered 30 min before L-5-HTP (87.3 mg/kg sc). The rats were placed singly in observation cages, and the number of head twitches (wet dog shakes) were counted 30–40 min after L-5-HTP ($n = 8$ per dose group). * $P < .05$ compared with the escitalopram-treated group (F test followed by Student's t test comparison of means).

significantly lower behavioural response compared with escitalopram alone at all assessments, whereas a ratio of 1:1 (corresponding to citalopram) showed a consistent, but not always significant, trend towards a lowered response (Fig. 2). A similar trend was observed in a comparative study of 1.0 mg/kg escitalopram and 2.0 mg/kg citalopram at different pretreatment times (Fig. 3). The individual behavioural signs induced by escitalopram were all attenuated significantly by the coadministration of R-citalopram, whereas hind limb abduction appeared as the least sensitive and head weaving the as most sensitive behavioural measure (Fig. 2B–E). The maximum effect of escitalopram and citalopram was achieved fast, that is, 5 min or earlier after injection (Fig. 3). The escitalopram doses used in the 5-HTP potentiation studies corre-

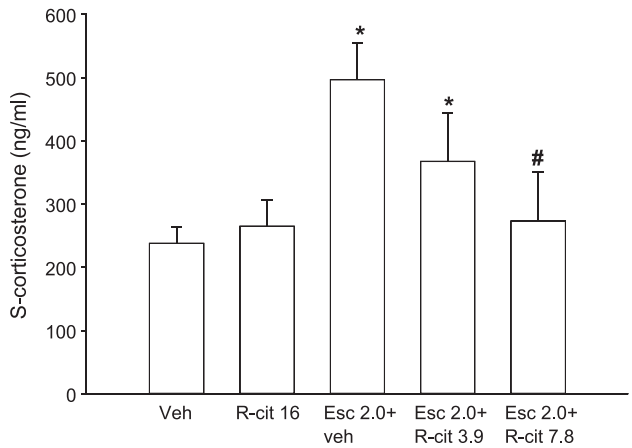

Fig. 6. Effects of escitalopram and R-citalopram, and escitalopram + R-citalopram, on serum corticosterone levels in rats. Drugs were administered subcutaneously 30 min before the isolation of serum. * $P < .05$ compared with the vehicle control and $P < .05$ compared with escitalopram + vehicle (F test followed by Student's t test comparison of means).

sponded to serum concentrations in the range of approximately 20–200 ng/ml (Fig. 4).

R-citalopram did also inhibit escitalopram (1.0 mg/kg)-induced potentiation of L-5-HTP-induced head twitches in rats (Fig. 5). The effect of R-citalopram appeared to be dose-dependent, although a significant effect was only achieved at an escitalopram to R-citalopram ratio of 1:4.

Escitalopram, but not R-citalopram, significantly increased serum corticosterone compared with the controls (Fig. 6). R-citalopram seemed to attenuate the effect of escitalopram (2.0 mg/kg) in a dose-dependent manner, although a significant effect was only achieved at an escitalopram to R-citalopram ratio of 1:4.

4. Discussion

Previous investigations suggested that escitalopram was approximately 3- and 2-fold more potent than citalopram, and 50- and 40-fold more potent than R-citalopram in the mouse and rat 5-HTP potentiation tests, respectively (Sánchez et al., 2003a). Taking the variation in the behavioural models into account, this was originally considered compatible with the notion that R-citalopram has no or very weak effect, and that escitalopram was twice as potent as citalopram.

The results of the present mouse 5-HTP potentiation study point towards a more than twofold potency difference between citalopram and escitalopram and an inhibitory role of R-citalopram. This is further substantiated by the consistent and significant inhibitory effect of R-citalopram on escitalopram at two and four times higher doses. It is highly relevant to study the 5-HT-enhancing properties of escitalopram using escitalopram to R-citalopram ratios of 1:2 and 1:4, as repeated dosing of racemic citalopram results at steady-state conditions in a higher (twofold and, in some cases, even higher) serum level of R-citalopram than escitalopram (Foglia et al., 1997; Sidhu et al., 1997; Zheng et al., 2000). Furthermore, the inhibitory effect of R-citalopram on escitalopram appears to be maintained during chronic treatment, as shown in the rat chronic mild stress model of depression, where the administration of an escitalopram to R-citalopram ratio of 1:2 failed to produce an antidepressant-like effect after 5 weeks (Sánchez et al., 2003c). In contrast, escitalopram produced a significant effect from week 1 and throughout the study. These findings support that the inhibitory effect of R-citalopram on escitalopram may be of clinical relevance after repeated dosing.

The escitalopram doses used in the mouse 5-HTP potentiation studies correspond to serum concentrations ranging from approximately 20 to 200 ng/ml. The ED_{50} – value corresponds to a serum concentration of approximately 50 ng/ml, which can be considered to be in the range of clinically relevant serum concentrations. Thus, a clinical repeated-dosing study in healthy volunteers of escitalopram 10 and 30 mg per day report Cmax-values of 21 and 64 ng/ml, respectively (Gutierrez and Mengel, 2002). Moreover, 5-HT transporter occupancies calculated from recent in vivo binding affinity studies in mice using [^{3}H]MADAM [*N*,*N*-dimethyl-2-(2-amino-4-methylphenyl thio)benzylamine; Brennum et al., 2002] indicate that approximately 80% occupancy of the 5-HT transport is required to produce a significant effect of escitalopram in the 5-HTP potentiation model. These occupancy levels are comparable with the approximately 80% SERT occupancy in depressed patients treated with clinically active doses of SSRIs as determined by PET (Meyer et al., 2001).

The maximum effect is achieved very fast in the mouse 5-HTP potentiation model, and the time-effect patterns are very similar for escitalopram and citalopram, suggesting that the metabolic rate of escitalopram is unaffected by the presence of R-citalopram. It has previously been reported that the escitalopram brain concentration is unaffected by the coadministration of a fourfold higher R-citalopram dose (Mørk et al., 2003). Interestingly, the maximum effect with other SSRIs, for example, paroxetine and sertraline, is not achieved until after 15–30 min (Sánchez, unpublished observation).

The inhibitory effect of R-citalopram on escitalopram-induced 5-HT enhancement is also observed in the rat L-5-HTP potentiation model and the serum corticosterone measurements. These models seem to be less sensitive to the inhibitory effect of R-citalopram, as significant effects were only observed at an escitalopram to R-citalopram ratio of 1:4. However, in a microdialysis study measuring extracellular 5-HT levels in the frontal cortex, this is not a general finding in the rat, as ratios of 1:1 and 1:2 differed significantly from escitalopram (Mørk et al., 2003). The effects were more pronounced using an escitalopram to R-citalopram ratio of 1:4 than ratios of 1:2 and 1:1, suggesting a dose-dependent effect.

The mechanism by which R-citalopram inhibits escitalopram-induced increase of 5-HT activity is not fully understood. Of the 144 targets tested in in vitro binding affinity studies (Sánchez et al., 2003a), the only site for which citalopram and R-citalopram, but not escitalopram, showed appreciable affinity was the histamine H_1 receptor. In vitro studies in isolated guinea pig ileum show that R-citalopram is a weak histamine H_1 receptor antagonist (unpublished observation). However, histamine H_1 antagonists, for example, mepyramine, do not modulate the effect of escitalopram in the 5-HTP-potentiation test (Sánchez, unpublished observations). Similarly, there is no experimental evidence that this mechanism modulates the 5-HT-induced increase of serum corticosterone, and mepyramine does not affect the 5-HT-induced increase of ACTH (Jørgensen et al., 1996).

It is unlikely, but cannot be excluded, that R-citalopram modulates the effect of escitalopram via a hitherto unidentified receptor. Another probable and more likely explanation is that R-citalopram modulates the interaction of escitalopram with the 5-HT transporter protein and thereby affects 5-HT neurotransmission at the synapse. R-citalopram

is 30- to 100-fold less potent than escitalopram in its ability to inhibit 5-HT re-uptake in vitro (Owens et al., 2001; Sánchez et al., 2003a). A recent in vitro study measuring the inhibition of 5-HT elicited ion-current in Xenopus oocytes-expressing human 5-HT transporter showed that R-citalopram inhibited the response of escitalopram (Stórustovu et al., in press). Furthermore, in vivo binding studies in mice using [^{3}H]MADAM suggest that R-citalopram bind, to some extent, to the 5-HT transporter at the doses used in the present study, for example, 2.0 mg/kg, which correspond to approximately 30% occupancy (Brennum et al., 2002).

In conclusion, R-citalopram inhibited dose-dependently the escitalopram-induced increase of 5-HT activity in functional, that is, serum corticosterone response, as well as behavioural animal models, that is, the potentiation of 5-HTP-induced behaviours. Furthermore, the effects were measurable at escitalopram serum concentrations that are comparable to clinically relevant levels. Thus, although the mechanism involved is unknown, these observations may be related to the improved clinical effect observed with escitalopram relative to citalopram.

Acknowledgements

The excellent technical skills of Karin Larsen, Ulla Østerby Mønsted and Christian Spang Pedersen are gratefully acknowledged.

References

Brennum LT, Larsen AK, Sánchez C, Halldin C. Escitalopram—the most selective SSRI; in vitro data and in vivo binding studies using the new selective SERT ligand 3H-MADAM. Poster presented at the 15th ECNP Congress, October 5–9, Barcelona, Spain; 2002.

Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. J Clin Psychiatry 2002;63:331–6.

Colonna L, Reines EH, Andersen HF. Escitalopram is well tolerated and more efficacious than citalopram in long-term treatment of moderately depressed patients. Int J Psychiatry Clin Prac 2002;6:243–4.

Foglia JP, Pollock BG, Kirshner MA, Rosen J, Sweet R, Mulsant B. Plasma levels of citalopram enantiomers and metabolites in elderly patients. Psychopharmacol Bull 1997;33:109–12.

Fuller RW, Perry KW, Hemrick-Luecke SK, Engleman E. Serum corticosterone increases reflect enhanced uptake inhibitor-induced elevation of extracellular 5-hydroxytryptamine in rat hypothalamus. J Pharm Pharmacology 1996;48:68–70.

Gutierrez M, Mengel H. Pharmacokinetics of escitalopram. Poster presented at the 42nd Annual New Clinical Drug Evaluation Unit Meeting June 10–13, Boca Raton, FL, USA; 2002.

Herman JL. Generic method for on-line extraction of drug substances in the presence of biological matrices using turbulent flow chromatography. Rapid Commun Mass Spectrom 2002;16:421–6.

Hyttel J, Bøgesø KP, Perregaard J, Sánchez C. The pharmacological effect of citalopram resides in the (S)-(+)-enantiomer. J Neural Transm 1992;88:157–60.

Jørgensen H, Knigge U, Kjaer A, Warberg J. Interactions of histaminergic and serotonergic neurons in the hypothalamic regulation of prolactin and ACTH secretion. Neuroendocrinology 1996;64:329–36.

Lepola UM, Loft H, Reines EH. Escitalopram (10–20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. Int Clin Psychopharmacol 2003;18:211–7.

Meyer JH, Wilson AA, Ginovart N, Goulding V, Hussey D, Hood K, et al. Occupancy of serotonin transporters by paroxetine and citalopram during treatment of depression: a [^{11}C]-DASB PET imaging study. Am J Psychiatry 2001;1588:1843–9.

Montgomery SA, Loft H, Sánchez C, Reines EH, Papp M. Escitalopram (S-enantiomer of citalopram): clinical efficacy and onset of action predicted from a rat model. Pharmacol Toxicol 2001;88:282–6.

Mørk A, Kreilgaard M, Sánchez C. The R-enantiomer of citalopram counteracts escitalopram-induced increase in extracellular 5-HT in the frontal cortex of freely moving rats. Neuropharmacology 2003;45:167–73.

Ortmann R, Waldmeier PC, Radeke R, Felner A, Delini-Stula A. The effect of 5-HT uptake- and MAO-inhibitors on L-5-HTP-induced excitation in rats. Arch Pharmacol 1980;311:185–92.

Owens MJ, Knight DL, Nemeroff CB. Second-generation SSRIs: human monoamine transporter binding profile of escitalopram and R-fluoxetine. Biol Psychiatry 2001;50:345–50.

Sánchez C. R-citalopram attenuates anxiolytic effects of escitalopram in a rat ultrasonic vocalisation model. Eur J Pharmacol 2003;464:155–8.

Sánchez C, Bergqvist PBF, Brennum LT, Gupta S, Hogg S, Larsenm AK, et al. Escitalopram, the S-(+)-enantiomer of citalopram, is a selective serotonin reuptake inhibitor with potent antidepressant and anxiolytic activities. Psychopharmacology 2003a;167:353–62.

Sánchez C, Gruca P, Bien E, Papp M. R-citalopram counteracts the effect of escitalopram in a rat conditioned fear stress model of anxiety. Pharmacol Biochem Behav 2003b;75:903–7.

Sánchez C, Gruca P, Papp M. R-citalopram counteracts the antidepressant-like effect of escitalopram in a rat chronic mild stress model. Behav Pharmacol 2003c;14:465–70.

Sidhu J, Priskorn M, Poulsen M, Segonzac A, Grollier G, Larsen F. Steady-state pharmacokinetics of the enantiomers of citalopram and its metabolites in humans. Chirality 1997;9:686–92.

Stórustovu S, Sánchez C, Pörzgen P, Brennum LT, Larsen AK, Pulis M, Ebert B. R-citalopram functionally antagonizes escitalopram in vivo and in vitro: evidence for kinetic interaction at the serotonin transporter. Br J Pharmacol, in press.

Wade A, Lemming O, Bang Hedegaard K. Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. Int Clin Psychopharmacol 2002;17:95–102.

Zheng Z, Jamour M, Klotz U. Stereoselective HPLC-assay for citalopram and its metabolites. Ther Drug Monit 2000;22:219–24.