SHORT COMMUNICATION

From selective to highly selective SSRIs: A comparison of the antinociceptive properties of fluoxetine, fluvoxamine, citalopram and escitalopram

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Abstract Most Serotonin Selective Reuptake Inhibitors (SSRIs) have been found to possess secondary binding properties, while citalopram and its S-enantiomer (escitalopram) have been reconfirmed “purest SSRIs”. Using the mouse model of acute pain hotplate analgesia meter, we evaluated the antinociceptive properties of fluoxetine, fluvoxamine, citalopram and escitalopram, injected i.p. Fluvoxamine induced a dose-dependent clear antinociceptive effect (with an ED50 value of 6.4 mg/kg). Both fluoxetine and citalopram induced (separately) only a weak antinociceptive effect with an inverse “U” shape curve. All three drug’s effects were not abolished by naloxone. Escitalopram did not elicit any effect at quasi-equipotent doses. These findings show that fluoxetine, fluvoxamine and citalopram given i.p. are weak antinociceptors, (not mediated through opioid mechanisms), while escitalopram possesses no antinociceptive properties when injected i.p. This difference between citalopram and escitalopram calls for further studies in order to assess the various differences between the two enantiomers of citalopram, and between each enantiomer and the racemic mixture.

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1. Introduction

The serotonin-selective reuptake inhibitors (SSRIs) are a structurally heterogeneous group of drugs introduced at the end of the 1980s and during the 1990s as ‘a new class of antidepressants’. Due to their favorable side-effect profile
when compared with the traditional tricyclic antidepressants, they have replaced the older antidepressants as first-line therapy. Nowadays, the SSRIs consist of 6 compounds: fluvoxamine (the first of the family) available since 1988; fluoxetine, launched a couple of weeks later (in a particularly skillful advertisement campaign that used a paradoxical approach, that revolutionized the general negative attitude towards depression and anxiety); paroxetine; sertraline; citalopram and the latest of the family — escitalopram.

During the last decade, fluoxetine, sertraline, paroxetine and fluvoxamine have been found to possess secondary binding properties (i.e. dopamine reuptake inhibition, muscarinic cholinergic antagonism, noradrenaline reuptake inhibition, nitric oxid synthase inhibition etc.), thus ‘not so selective’ as initially thought (Stahl, 1998a). These various interactions of the SSRIs allowed for their use in a more sophisticated way (Stahl, 1998b), including various clinical settings outside psychiatry, e.g. some neurological disorders (Schreiber and Pick, 1995, 1997) and in the pain clinic (Aragona et al., 2005; Freeman et al., 2002; Shimodzono et al., 2002; Schreiber et al., 2001; Mattia et al., 2002; Saper et al., 1994; Power-Smith and Turkington, 1993; Sindrup et al., 1990). Only citalopram has been confirmed as “purest SSRI”, and this is valid also for its S(+)-enantiomer (escitalopram), where the S-HT reuptake inhibitory activity of the racemic mixture citalopram resides (Chen et al., 2005).

When assessed in an acute model of nociception in mice (the hotplate analgesia meter), fluvoxamine elicited antinociceptive effect in a dose-dependent manner following i.p., i.t. and i.c.v. injection, not abolished by naloxone. When administered together with various opioid agonists, fluvoxamine significantly augmented analgesia at the \( \kappa_2 \)-opioid receptor subtype (Schreiber et al., 1996a). Fluoxetine assessed in the same laboratory model (the hotplate) was found to induce a dose-dependent antinociceptive effect following s.c., i.t. and i.c.v. injections, not abolished by naloxone. When administered in an inactive dose together with various opioid agonists, fluoxetine was found to significantly potentiate the \( \delta \)-opioid receptor subtype, and the \( \kappa_2 \) and \( \kappa_1 \)-opioid subtypes (Schreiber et al., 1996b). When paroxetine (injected i.p.) was evaluated with the hotplate assay, it was found to induce a significant antinociception effect, reversible by naloxone (Duman et al., 2004). This finding indicated a possible involvement of paroxetine with the opioid system. Sertraline injected i.p., was found to augment morphine analgesia in the mouse hotplate assay. Following multiple doses, sertraline alone, increased pain reaction (Pakulska, 2004). When citalopram injected i.p. was assessed in the hotplate assay, it was found ineffective (Bonholt et al., 2005).

We found no data regarding the possible antinociceptive properties of escitalopram. The findings regarding the inhibitory effects of the R(−)−enantiomer on the S(+)−enantiomer effect (Sanchez et al., 2004), imply possible differences between citalopram and escitalopram as far as their main clinical effect (i.e. the serotonin reuptake inhibition properties). We conducted the present study in order to assess further possible differences between the “purest SSRIs” (citalopram and escitalopram), regarding antinociception, and compared it with those of the first two drugs of the family (fluvoxamine and fluoxetine). We’ve done so using the same mouse model of acute pain (the hotplate analgesia meter), the same way of administration (i.p.) and the same strain of mice (Pick, 1996) for all four drugs.

2. Experimental procedures

2.1. Subjects and surgery

Male ICR mice from Tel-Aviv University colony (Tel-Aviv, Israel), weight 25−35 g were used. The mice were maintained on a 12 h light : 12 h dark cycle with Purina rodent chow and water available ad libitum. Animals were housed five per cage in a room maintained at 22 ± 0.5 °C. Mice were housed in groups of 5 until testing. Mice were used only once. The experimental protocol was approved by the local ethics committee of the Sackler Faculty of Medicine (no. M-03-010) and complied with the guidelines for animal experimentation of the National Institutes of Health [DHEW Publication (NIH) 85-23, revised, 1995].

2.2. Agents

Several agents were generously donated as follows: citalopram and clozapine were a generous gift from Lundbeck (Copenhagen, Denmark). Fluoxetine HCL was a generous gift from Eli-Lilly and Company (Indianapolis, IN). Fluvoxamine HCL was a generous gift from Agis Laboratories (Yeruham, Israel). All the drugs were dissolved in saline.

2.3. Analgesia/antinociception assessment

Mice were tested with the hotplate analgesia meter Model 35D, (IITC INC. Woodland Hills, CA. USA) as previously described (Schreiber et al., 2002), to determine the nociceptive threshold. The device consists of a metal plate (40×35 cm) heated to a constant temperature, with a plastic cylinder placed on top. The analgesic meter was set to a plate temperature of 55.5 ± 0.5 °C. The time of latency was recorded i.e., between the second the animal was placed on the hotplate surface till it licked its back paw or jerked it strongly or jumped out. Baseline latency was determined before experimental treatment for each mouse as the mean of two trials. All baselines were between 5−10 s. Post-treatment latencies were determined after 30 min. The analgesic/antinociceptive effect was defined quantitatively as doubling of the baseline value for each mouse. The quantitative (yes/no) definition of analgesia/antinociceptive is presented as percentage of effect in each treatment group. We used double baseline scores as a cut point value in our experiments, in order to minimize tissue damage, during the post-treatment measurements.

2.4. Statistic analysis

Dose-response curves were analyzed, using a SPSS computer program. This program maximizes the log-likelihood function to fit a parallel set of Gaussian normal sigmoid curves to the dose−response data.
3. Results

3.1. Fluvoxamine antinociceptive effect

Groups of mice (n ≥ 15) were injected with various doses of fluvoxamine, and fluvoxamine was found to induce a clear antinociceptive effect in the hotplate assay. Following i.p. injection, fluvoxamine elicited analgesia in a dose-dependent manner, with an ED₅₀ value of 6.4 mg/kg (3.1, 14.6; 95% CI: Fig. 1). This effect was not abolished by naloxone 1 mg/kg.

3.2. Fluoxetine antinociceptive effect

When groups of mice (n ≥ 15) were injected with various doses of fluoxetine i.p., fluoxetine was almost inactive (at a dose as high as 25 mg/kg only 30% of the mice were analgesic: Fig. 1). This very weak effect was not affected by naloxone 1 mg/kg.

3.3. Citalopram antinociceptive effect

Citalopram injected i.p. (in groups of mice, n ≥ 15), induced a weak antinociceptive effect with a maximal effect of only 40% analgesia at 5 mg/kg. Increasing doses of citalopram decreased its antinociceptive effect, leading to an inverted U-shape curve, suggestive of a “therapeutic window effect” (Fig. 2). The antinociceptive effect was not abolished by naloxone 1 mg/kg.

3.4. Escitalopram antinociceptive effect

When injected i.p., at doses from 0.25 to 50 mg/kg (in groups of mice, n ≥ 15), escitalopram did not elicit any antinociceptive effect at all. Even when injected at extremely high doses, escitalopram elicited only a weak antinociceptive effect in a dose-dependent manner, reaching a maximal effect of 50% analgesia following 150 and 200 mg/kg (200 mg/kg was lethal for 20% of the mice) escitalopram (Fig. 2). At these extreme doses, naloxone 1 mg/kg abolished the antinociceptive effect.

4. Discussion

The results of the present study demonstrate some very interesting differences between 4 different SSRIs (all administered i.p. and tested in the same mouse hotplate assay), regarding their antinociceptive properties. We found fluvoxamine to induce a clear antinociceptive effect, while fluoxetine and citalopram tested in the same assay yielded only a weak antinociceptive effect. All these three SSRIs' antinociception was not antagonized by naloxone, implying no involvement of the opioid system in the effect. Escitalopram, in the same conditions, was totally inactive, and only at extremely high doses (far beyond any quasi-equivalent range, and partially lethal for mice) elicited weak antinociception (Figs. 1 and 2), abolished by naloxone.

The weak antinociceptive effect of fluvoxamine, fluoxetine and citalopram is not mediated through opioid mechanisms, but rather serotonergic pathways. Data emerging from studies in animal antinociception models suggest an important role for some 5-HT receptors in pain modulation (Suzuki et al., 2005; Sawynok and Reid, 1994), complying with old findings that both serotonin (Taylor et al., 1982) and noradrenaline (Max et al., 1992) are separately important links in tricyclic antidepressants' analgesia.

There are some more possible explanations to the different antinociceptive properties of the various SSRIs studied, beyond the involvement of serotonin and noradrenalin pathways. One possibility is the differential interaction...
of each drug with other neurotransmitter systems, i.e. the noradrenaline reuptake inhibitory properties of fluoxetine (Cryan et al., 2004) and the \( \sigma \) (sigma) interaction of fluvoxamine (Walker et al., 1990; Tulloch et al., 1995). For that reason, we preferred not to assess paroxetine (an SSRI with moderate noradrenaline reuptake inhibition properties) (Nemeroff and Owens, 2003; Nemeroff and Owens, 2004; Cryan et al., 2004), or sertraline, with both \( \sigma \) (sigma) interaction (Gundlach et al., 1986; Tulloch et al., 1995; Faherty et al., 1998) and dopamine reuptake inhibitory properties (Nemeroff and Owens, 2003; Nemeroff and Owens, 2004; Dansma et al., 2004).

Another possibility may arise from the indirect involvement of some SSRIs with the dopaminergic system (Schreiber and Pick, 1995, 1997). This interaction may mediate a weak direct antinociceptive effect (Altier and Stewart, 1999), or an indirect effect, through activation of the reward system (Bergman et al., 2000). However, describing those mechanisms is beyond the scope of the present study.

Of interest is the difference between the positive antinociceptive properties of citalopram and the lack of antinociceptive properties of escitalopram. Citalopram is a racemic (1:1) mixture of \( S^+ \)- and \( R^- \)-enantiomers. The 5-HT reuptake inhibitory activity of the racemic mixture has been found to reside in the \( S^- \) -enantiomer while the \( R^- \) -enantiomer is lacking this activity (Hyttel et al., 1992). Furthermore, studies have shown that \( R^- \)-citalopram counteracts escitalopram’s antidepressant and anxiolytic effects in animal models, in a dose-dependent manner (Mork et al., 2003; Sanchez et al., 2004), suggesting a possible antagonistic effect of the \( R^- \)-enantiomer. In another study, escitalopram was found to increase inhibitor binding to the human serotonin transporter by an allosteric mechanism, suggesting some degree of stereoselectivity (Plenge and Mellerup, 1997; Chen et al., 2005). The difference between the positive antinociceptive properties of citalopram and the failure of escitalopram to induce antinociception (at quasi-equivalent dosages) may be attributed to a need of the presence of both enantiomers for antinociception properties to manifest. In that matter, it would be interesting to evaluate the \( R^- \)-enantiomer in the same antinociception model.

It would be difficult to draw possible clinical conclusions from our findings due to some limitations of our study: neither fluoxetine nor fluvoxamine or citalopram manifested a strong enough antinociceptive property to indicate a possible clinical use as analgesics, and the nociception found with escitalopram was only at extremely high doses, much beyond those used in clinical settings and partially lethal for the mice. One of the interesting findings of the present work is that although all four drugs are part of the SSRIs family, each one of them expresses its antinociceptive effect in a different manner. One of the more intriguing findings is that fluoxetine, and separately citalopram expressed their effects in a biphasic manner, which may indicate that some additional intrinsic systems are involved in each drug’s antinociceptive effects. Clearly, more work must be done in order to discover which systems are actually involved here.

In conclusion, the findings of this study show that fluoxetine, fluvoxamine and citalopram administered i.p. are weak antinociceptors, and this effect is not mediated through opioid mechanisms. Escitalopram (i.p.) possesses no antinociceptive properties, unless administered at extremely high (lethal to mice) doses, where any interpretation of findings is not possible. This difference between citalopram and escitalopram calls for future studies in order to assess the various differences between the two enantiomers and between each enantiomer and the racemic mixture.

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References


