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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 ED_{50} 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.

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

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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 skilful 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; Shimodozono 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 reconfirmed as "purest SSRI", and this is valid also for its *S*(+)-enantiomer (escitalopram), where the 5-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 κ_3-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 δ-opioid receptor subtype, and the κ_1- and κ_3-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 (Bomholt 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: escitalopram and citalopram were a generous gift from Lundbek (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 determinate 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.