

## ANTINOCICEPTIVE ACTIVITY OF ANTIDEPRESSANTS AND CORRELATION WITH NEUROTRANSMITTER INHIBITORY POTENCY

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### ABSTRACT

Antidepressant agents inhibit the neuronal reuptake of monoamines such as serotonin (5-HT), noradrenaline (NA), and dopamine (DA). Several clinical and animal studies have advocated the use of these agents in the management of pain. In this study, therefore, the possibility of a correlation between the analgesic activity of six serotonin specific reuptake inhibitor (SSRI) antidepressants and their reported relative inhibitory potencies on monoamine reuptake was studied. The antidepressants studied were citalopram, fluoxetine, fluvoxamine, sertraline, and zimelidine.

Male ICI-WSP mice were given a 30 min pretreatment with antidepressants, subcutaneously before challenge with 1% intraperitoneal acetic acid. Abdominal constrictions were evaluated over 20 min and percentage inhibition compared to vehicle controls was calculated as a measure of analgesia. All the antidepressants yielded linear log dose-analgesic response relationships from which  $ED_{50}$  values were converted into relative potencies against fluoxetine as unity. Spearman's rank correlations between relative potencies for analgesia and inhibition of monoamine reuptake were examined. It was found that the correlation coefficients between analgesia and 5HT, NA and DA reuptake were -0.54, -0.54 and -0.43, respectively, suggesting that there was no overall rank correlation between these parameters. This is somewhat surprising since monoamines are involved in the expression of analgesia and their reuptake is considered to be a major component of the pharmacology of these compounds. It is probable, however, that other differing pharmacological properties such as opioid-like activity or diversity of pharmacokinetic characteristics may disrupt any straightforward correlation between monoamine reuptake and analgesia for the compounds examined.

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### INTRODUCTION

Antidepressant drugs have been integrated into the management of pain syndromes for several years.<sup>11</sup> Numerous open and controlled studies have taken place

evaluating the antinociceptive efficacy of antidepressants. In animal studies also, several laboratories have reported the antinociceptive activity of this group of agents.<sup>15,19</sup>

Modulation of nociceptive processing seems to depend on the recruitment of intrinsic systems, which mediate their

effects by opiate and non-opiate systems. Emphasis has been put on the role played by opioids and the monoamines, 5-hydroxytryptamine (5-HT), and noradrenaline (NA) in mediating the effects of intrinsic antinociceptive systems.<sup>1,10,20</sup>

Reuptake of monoamines is considered to be a major known component of the pharmacology of antidepressants.<sup>7</sup> Therefore, attempts to explain the direct antinociceptive effect of antidepressants in pharmacological terms center mostly on how these compounds interact with neurotransmitter systems in the brain and spinal cord.<sup>3,11,17</sup>

It has been suggested that antidepressants with higher selectivity for NA reuptake inhibition may have more antinociceptive activity compared to antidepressants with selectivity for 5-HT reuptake,<sup>2</sup> which have been designated serotonin specific reuptake inhibitors (SSRIs).

Hwang and Wilcox<sup>5</sup> have also reported a different mode of antinociceptive action of SSRIs from that of non-SSRIs in the spinal cord of mice. They demonstrated that intrathecal (i.t.) fluoxetine and citalopram had no antinociceptive activity in tail-flick (T.F.) assay, whilst protriptyline and desipramine, two noradrenaline reuptake inhibitors, were active in this test.

Moreover, Fasmer et al.<sup>2</sup> also claimed that there might be a correlation between 5-HT reuptake inhibitory potency of antidepressants and their antinociceptive activities. This hypothesis was studied further, by six accepted SSRIs, to establish any potential correlation between antidepressant antinociception and reported relative inhibitory potencies on monoamine reuptake inhibition derived from the literature. The possibility that other factors, such as differing inherent opioid-like activities, might influence the correlations, was also investigated and this aspect is considered in the discussion.

## MATERIALS AND METHODS

Male ICI-WSP derived mice (22-25g) were employed throughout. Animals were allowed food and water *ad libitum* and they were maintained at a temperature of  $22.0 \pm 1.0^\circ\text{C}$  on a 12/12h light/dark cycle, the experiments being performed between 9.00 and 17.00 h.

Antinociceptive activity in mice was assessed using the abdominal constriction assay.<sup>15</sup> Briefly, abdominal constrictions (writhes) were elicited by intraperitoneal (i.p.) injection of 1% acetic acid and their incidence recorded over a 20 min period. Any decrease in abdominal constrictions compared to vehicle controls was calculated as a percentage of control values and designated % protection (as a criteria for antinociceptive activity of compound).

$$\% \text{ Protection} = 100 - \frac{\text{Writhes in drug group}}{\text{Writhes in control group}} \times 100$$

Acetic acid (BDH, UK) was administered i.p. 5 min before the test. SSRIs including fluoxetine (Lilly),

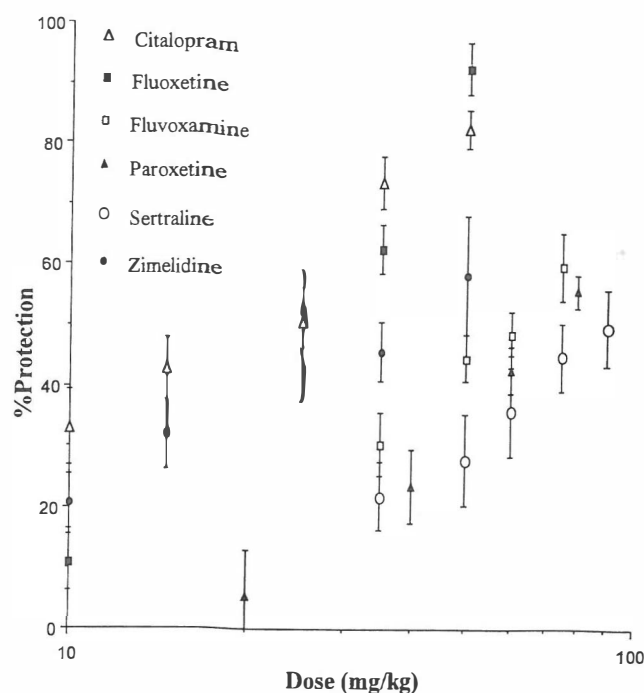


Fig. 1. Dose response antinociceptive activity of SSRI antidepressants in the abdominal constriction assay. All SSRIs were administered subcutaneously 30 min before the test. Values are mean  $\pm$  S.E.M. (n=8-10).

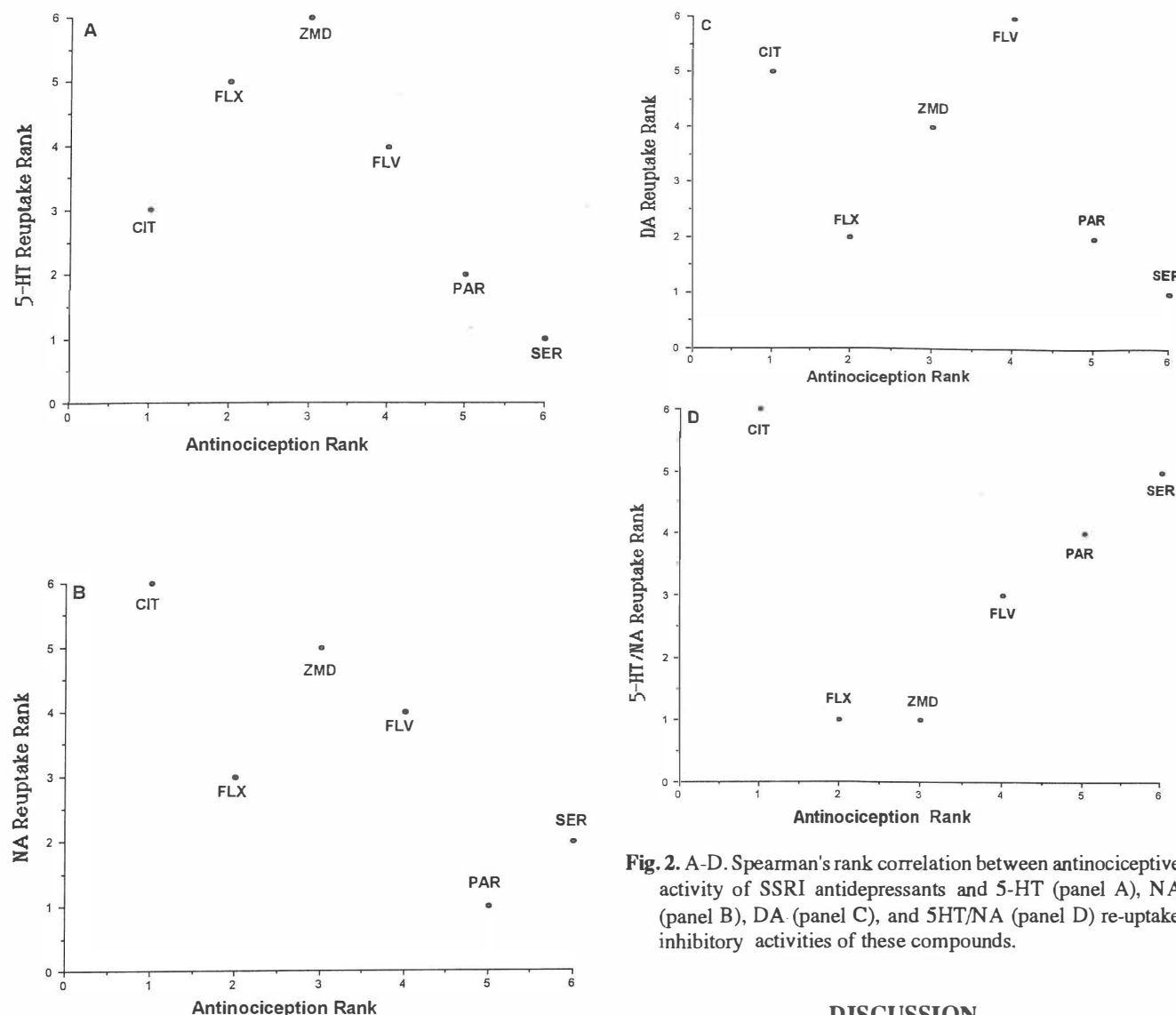
fluvoxamine (Duphar), sertraline (Pfizer), paroxetine (Smith Kline Beecham), citalopram (Lundbeck) and zimelidine (Astra) were all dissolved in Tween 80 (5% in saline) and injected s.c. 30 min before the test.

To measure the antinociceptive activity of SSRIs, different doses of each compound were administered s.c. and their antinociception calculated as mentioned above. Then, their  $ED_{50}$  values were converted into relative potencies against fluoxetine as unity. Correlations between antinociceptive activity of antidepressants and serotonin (5HT), dopamine (DA), noradrenaline (NA), and 5HT/NA reuptake inhibitory potencies were calculated employing Spearman's rank correlation method.

## RESULTS

### Antinociceptive activity of SSRIs in the abdominal constriction test

Citalopram (10-50 mg/kg), fluoxetine (10-50 mg/kg), zimelidine (10-50 mg/kg), fluvoxamine (35-75 mg/kg), paroxetine (20-80), and sertraline (35-90 mg/kg) all produced dose-related inhibition of acetic acid-induced abdominal constriction in mice (Fig. 4.1). Their log dose-antinociceptive relationships possessed positive linear trends with respective correlation coefficients of 0.98, 0.93, 0.97, 0.99, 0.99, and 0.92. Their  $ED_{50}$  values (with confidence intervals) were 21.74 (14.4-27.3), 27 (19.7-36.1), 38.65 (27-75), 60.46 (54-



**Fig. 2.** A-D. Spearman's rank correlation between antinociceptive activity of SSRI antidepressants and 5-HT (panel A), NA (panel B), DA (panel C), and 5HT/NA (panel D) re-uptake inhibitory activities of these compounds.

## DISCUSSION

All antidepressant compounds tested demonstrated dose-related inhibition of acetic acid-induced abdominal constrictions. Several clinical and laboratory studies also report inherent antinociceptive activity for antidepressants.<sup>12,16</sup> Others have reported a potentiation of opioid analgesia by these compounds,<sup>16,19</sup> whilst some laboratories dispute any antinociceptive effects whatsoever.<sup>4,8</sup> In addition, Lund and colleagues<sup>9</sup> reported that the antinociceptive effect of antidepressants in the tail flick assay was due to a reduction of tail skin temperature rather than through pain pathways. Hence, some discrepancy at the laboratory level exists as to the precise nature of antidepressant antinociception.

Each of the above studies was conducted using different laboratory nociceptive behavioural assays such as the tail flick or hot plate tests. The study of Shaw et al.<sup>15</sup> provides good evidence for involvement of stimulus intensity as a

68), 71 (64.7-80), and 87.7 (81.3-97.3) mg/kg and their slopes were comparable, possessing values of 73.3, 109.8, 51.9, 86.6, 83.7, and 71.5, respectively.

### Rank correlation tests between antinociceptive activity of SSRIs and their neurotransmitter inhibitory activities

The antinociceptive activity as well as the monoamine reuptake inhibitory potencies of six serotonin specific reuptake inhibitors citalopram, fluoxetine, zimelidine, fluvoxamine, paroxetine and sertraline were ranked according to potency.<sup>7</sup> Subsequently Spearman's rank correlation values between analgesia and inhibition of monoamine reuptake were tested. It was found that the correlation coefficient between analgesia and 5-HT (Fig. 2A), NA (Fig. 2B), DA (Fig. 2C) and 5HT/NA (Fig. 2D) were -0.6, -0.77, -0.49, and 0.15, respectively.

complicating factor in evaluating the antinociceptive response. The use of a 55°C thermal stimulus, for instance, yields a model which, although retaining the ability to detect morphine, is insensitive to many other analgesic compounds. This implies that the stimuli employed in such assays exceed those encountered in clinical pain and that some antinociceptive activities would not be therefore detected thus limiting the predictive validity of these assays. In the present study, the abdominal constriction assay was chosen as the most appropriate test for detection of the weaker antinociceptive activity induced by antidepressants.

The mean group-antinociceptive values ( $ED_{50}$ s) of SSRI antidepressants was 51 mg/kg. Spearman's rank correlations between relative potencies for antinociception and inhibition of monoamine reuptake were studied. This revealed that the correlation coefficients between analgesia and 5-HT, NA, DA, and 5HT/NA reuptake were surprisingly low or even negative, suggesting that there was no overall rank correlation between these parameters following acute administration of antidepressants.

The lack of rank group correlation (and inevitably a lack of absolute correlation) between antinociceptive potencies and *in vitro* brain tissue monoamine reuptake inhibitory activity is in contrast to Fasmer and colleague's hypothesis<sup>2</sup> who claimed that there might be a correlation between these parameters. This discrepancy in conclusion may be due to the limited number of compounds employed by Fasmer et al. (four compounds from different groups of antidepressants). These findings are somewhat surprising since monoamines are involved in the expression of analgesia.<sup>13,20</sup> and it is well established that antidepressant agents inhibit the neuronal reuptake of monoamines such as 5-HT, NA and DA.<sup>7</sup> It must be emphasized, however, that these findings do not diminish the view that monoamine mechanisms are implicated in antidepressant antinociception, since differing pharmacological or pharmacokinetic properties might disrupt any group correlation *in vivo*. Thus, antidepressants have been shown to have differing activities, some laboratories reporting an implication of opioid pathways.<sup>10</sup>

Another significant factor which may disrupt the correlation between antidepressant reuptake-potency and their antinociceptive activity is their metabolic profile. This is exemplified by citalopram and its metabolites desmethyl citalopram, didesmethyl citalopram or citalopram-N-oxide which have selectivity for 5-HT reuptake.<sup>6</sup>

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