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The antinociceptive properties of reboxetine in acute pain

Shaul Schreiber [a], Ruthi Frishtick [b], Ina Volis [b], Vardit Rubovitch [b], Chaim G. Pick [b,*,1], Ronit Weizman [c,1]

[a] *Dept. of Psychiatry, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel*
[b] *Dept. of Anatomy and Anthropology, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel*
[c] *Tel-Aviv Community Mental Health Center and Department of Psychiatry, Tel-Aviv University Sackler Faculty of Medicine, Tel-Aviv, Israel*

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Abstract

The antinociceptive effects of the selective noradrenaline reuptake inhibitor antidepressant reboxetine and its interaction with various opioid and noradrenaline receptor subtypes were evaluated. Reboxetine (i.p.) induced a weak dose-dependent antinociceptive effect in acute pain, using the hotplate model. The reboxetine-induced antinociception was significantly inhibited by the opioid receptor antagonists naloxone, nor-BNI, naltrindole and b-FNA, implying a non-selective role for the opioid receptors in the reboxetine's antinociceptive effect. The adrenergic antagonists yohimbine and phentolamine attenuated to some extent the reboxetine-induced antinociception, implying a minor adrenergic mechanism of antinociception. The addition of opioid or $\alpha 2$ agonists, did not potentiate the antinociception effect of reboxetine. Thus, it seems that reboxetine possesses a weak antinociceptive effect, mediated by non-selective opioid receptors and influenced somewhat by noradrenaline $\alpha 2$ receptors. These results suggest that reboxetine as monotherapy does not have sufficient efficacy in the management of acute pain. However, further research is needed in order to establish its possible use alone or in combination with other antidepressants or analgesics in the amelioration of chronic pain disorders.

1. Introduction

Tricyclic antidepressants have been used for decades in the treatment of severe pain in non-depressed patients (Spiegel et al., 1983; Tura and Tura, 1990; Mattia et al., 2002). They have proven effective both for chronic pain syndromes such as post-herpetic neuralgia (Woodeford et al., 1965; Kishore-Kumar, 1990), peripheral neuropathies (Taub and Collins, 1974;

* Corresponding author. Tel.: +972 36409247; fax: +972 36408287.
E-mail address: pickc@post.tau.ac.il (C.G. Pick).
[1] Equal contribution of senior authors.

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Max, 1987; Sindrup and Jensen, 1999) and chronic low-back pain, and for acute pain episodes with characteristic features such as cancer pain, chronic tension headache and migraine (Couch et al., 1976; Diamond and Baltes, 1971; Foley, 1979) and irritable bowel syndrome (Crowell et al., 2004). Both serotonin and noradrenaline (two neurotransmitters mainly implicated in the pathogenesis of mood disorders) have been recognized to be important mediators in pain conducting pathways (Jensen et al., 1994) (Banks et al., 1988; Sacerdote et al., 1987; Tura and Tura, 1990). Furthermore, these two neurotransmitters apparently also potentiate the endogenous opioid system (Botney and Fields, 1983). Indeed, duloxetine, a serotonin and noradrenaline reuptake inhibitor (SNRI) was the first SNRI approved for the treatment of neuropathic pain (Goldstein et al., 2005; Perahia et al., 2006).

Reboxetine inhibits noradrenaline reuptake in vitro to a similar extent to the tricyclic antidepressant desmethylimipramine. It does not affect dopamine or serotonin reuptake and it has low, both in vivo and in vitro, affinity for adrenergic, muscarinic cholinergic, histaminergic, dopaminergic and serotonergic receptors (Holm and Spencer, 1999). In the present study we have assessed reboxetine's potential antinociceptive properties using the acute pain model of the hotplate analgesia meter in mice.

2. Materials and methods

Male ICR mice from Tel-Aviv University colony (Tel-Aviv, Israel), weighing 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 °C±0.5 °C. Mice were housed in groups of 5 until testing. Mice were used only once. The Sackler Faculty of Medicine Ethical Committee for Animal Experimentation approved the experimental protocol (M-08-076), which complied with the guidelines for animal experimentation of the National Institutes of Health [DHEW Publication (NIH) 85-23, revised, 1995].

2.1. Agents

Morphine was generously donated by Teva (Jerusalem, Israel), naloxone HCL β-FNA, naltrindole, nor-BNI, U50,488H, and DPDPE were obtained from the Research Technology Branch of NIDA. Clonidine, yohimbine, phentolamine and reboxetine were purchased from Sigma-Aldrich Israel Ltd. (Rehovot, Israel).

2.2. 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., 2002a,b), 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 52.0 °C±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 and 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.

2.3. Experimental procedures

The study was broken down into three experiments. In the first stage of the study groups of mice ($n \geq 15$) were injected with increasing doses of reboxetine in order to determine the antinociceptive effect of the drug.

In the second experiment, the sensitivity of reboxetine to four selective opioid antagonists and two noradrenergic antagonists was examined: Five groups of mice ($n \geq 15$) were treated with β-FNA (40 mg/kg, μ antagonist) 24 h before the reboxetine challenge, or with one of the following drugs: naloxone (10 mg/kg, universal opioid antagonist), naltrindole (20 mg/kg, δ antagonist), nor-BNI (10 mg/kg, κ antagonist) or saline immediately before reboxetine (10 mg/kg) was injected. For comparison, the β-FNA effect was tested against morphine, nor-BNI against the U50,488H antinociceptive effect and naltrindole against DPDPE, in separate groups of mice. In addition, two other groups of mice were injected with phentolamine (4 mg/kg α1+α2 adrenergic antagonist) or with yohimbine (4 mg/kg α2 adrenergic antagonist) immediately before reboxetine (10 mg/kg) was injected.

In the third experiment, the influence of reboxetine on opioid and adrenergic antagonists was examined. The antinociceptive effect induced by a fixed sub-threshold dose of morphine (0.5 mg/kg, opioid receptor agonist) or a fixed sub-threshold dose of clonidine (0.1 mg/kg, adrenergic receptor agonist) was tested with increasing doses of reboxetine. All agonists and antagonists were chosen according to our previous studies (Schreiber et al., 2002b). None of the antagonists posses any analgesic effect of their own, nor do they alter blood pressure. The agonists studied were used at sub-threshold doses, and did not manifest any effect on their own.

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. In the agonists–antagonists experiment significance was determined by using the Chi-square test.

3. Results

3.1. Reboxetine antinociceptive effect

Reboxetine induced a weak antinociceptive effect (Fig. 1). Reboxetine reached its maximal effect of 30% analgesia at 10 mg/kg.

Figure 1 Reboxetine antinociceptive effect: groups of mice ($n \geq 15$) received an s.c. injection of reboxetine at the indicated dose and were tested in the hotplate test 30 min late. % Analgesia refers to the proportion of mice tolerating a doubling of their mean latency.