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Antidepressants enhance the antinociceptive effects of carbamazepine in the acetic acid-induced writhing test in mice

Mieko Aoki [a,*], Minoru Tsuji [b,c], Hiroshi Takeda [b,c], Yoichiro Harada [b], Jun Nohara [b], Teruhiko Matsumiya [b], Hiroshige Chiba [a]

[a] *Department of Oral and Maxillofacial Surgery, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan*
[b] *Department of Pharmacology, Tokyo Medical University, 6-1-1 Shinjuku, Shinjuku-ku, Tokyo 160-8402, Japan*
[c] *Division of Pharmacology, School of Pharmaceutical Sciences, International University of Health and Welfare, 2600-1 Kitakanemaru, Ohtawara, Tochigi 324-8501, Japan*

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Abstract

Some antidepressants, as well as antiepileptics, are effective for treating pain of varying etiology. The present study was designed to characterize the antinociceptive effects of imipramine, a tricyclic antidepressant, fluvoxamine, a selective serotonin reuptake inhibitor, milnacipran, a serotonin noradrenaline reuptake inhibitor, and carbamazepine, an antiepileptic drug, using the acetic acid-induced writhing test in mice. Imipramine (1.25–10 mg/kg, i.p.), fluvoxamine (5–40 mg/kg, i.p.) and milnacipran (2.5–20 mg/kg, i.p.) all dose-dependently and significantly reduced the number of writhes induced by the injection of acetic acid (0.8% (v/v)), although the maximal effect of milnacipran was weaker than those of imipramine and fluvoxamine. Similarly, carbamazepine (5–20 mg/kg, i.p.) also showed a dose-dependent and significant antinociceptive effect. In combination studies, the co-administration of a sub-effective dose of carbamazepine (5 mg/kg, i.p.) with imipramine (1.25 and 2.5 mg/kg, i.p.), fluvoxamine (10 mg/kg, i.p.) or milnacipran (1.25 and 2.5 mg/kg, i.p.) significantly reduced the number of writhes. Additionally, the hole-board test revealed that the medications with significant antinociceptive effects barely produced changes in motor activity that could possibly affect writhing behavior. Thus, the present study demonstrated that the antinociceptive effect of carbamazepine is enhanced by combination with imipramine, fluvoxamine and milnacipran. Therefore, the combined therapy using antidepressants and carbamazepine may be useful clinically for the control of pain.

Keywords: Imipramine; Fluvoxamine; Milnacipran; Carbamazepine; Writhing test; (Mouse)

1. Introduction

Nociception is a bi-directional process of ascending and descending neuronal pathways, and these nociceptive circuits are modulated particularly by serotonin and noradrenaline. The descending serotonin and noradrenaline pathways serve to inhibit the input of painful stimuli from the intestines, skeletal muscles and other sensory inputs (Wall and Melzack, 1999), and thus dysfunction of these descending pathways can produce a hypersensitivity to pain and even lower the pain threshold in response to normally non-noxious stimuli (Stahl and Briley, 2004). Furthermore, it is now generally accepted that there is a relationship between pain and depression (Lépine and Briley, 2004). In this sense, dysfunction of the serotonergic and noradrenergic pathways is a common neurological abnormality involved in the etiology of nociceptive and depressive disorders (Basbaum and Fields, 1984; Stahl and Briley, 2004). Therefore, it is expected that antidepressants that increase neuronal transmission in the serotonin and/or noradrenaline systems are likely to produce relief from pain. Indeed, in clinical practice, tricyclic antidepressants have been widely used in several painful conditions, as well as opioids and other analgesics, and have been proven to be effective in the management of pain of diverse etiology, including neuropathic pain, head-ache, fibromyalgia and gastrointestinal pain (O'Malley et al., 1999; Sindrup and

* Corresponding author. Tel.: +81 3 3342 6111.
E-mail address: kokuaoki@tokyo-med.ac.jp (M. Aoki).

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Jensen, 1999). Furthermore, selective serotonin reuptake inhibitor and serotonin noradrenaline reuptake inhibitor, which are newer antidepressants that have been developed with the idea of eliminating the adverse effects of tricyclic antidepressants, have been successfully introduced in the treatment of depression, and are now also used to alleviate pain syndromes (O'Malley et al., 1999; Sindrup and Jensen, 1999; Briley, 2004). The clinical effectiveness of antidepressants as analgesics has recently been confirmed in preclinical studies using various tests of nociceptive activity, which use thermal, mechanical, electrical or chemical stimuli (Korzeniewska-Rybicka and Plaznik, 1998; Schreiber et al., 1999; Otsuka et al., 2001; Yokogawa et al., 2002; Rojas-Corrales et al., 2003; Duman et al., 2004; Mochizuki, 2004), as well as in animal models of chronic pain (Zarrindast et al., 2000; Marchand et al., 2003; Anjaneyulu and Chopra, 2004; Mochizuki, 2004).

In addition to antidepressants, anticonvulsants have also been used in the management of neuropathic pain. Carbamazepine, an iminostilbene derivative that is chemically related to tricyclic antidepressants, is the first of this class of drugs to be studied in clinical trials, and has been used the longest for the treatment of neuropathic pain, especially trigeminal neuralgia, a relatively common disease that is characterized by severe lancinating pain in oral and maxillofacial lesions (Backonja, 2002; Jensen, 2002). However, the use of carbamazepine is often complicated by frequent adverse events including somnolence, dizziness, gait abnormalities and hematological changes (Backonja, 2002; Jensen, 2002). Furthermore, the chronic use of carbamazepine induces microsomal enzyme systems, which effectively reduces its analgesic efficacy (Benedetti et al., 2005).

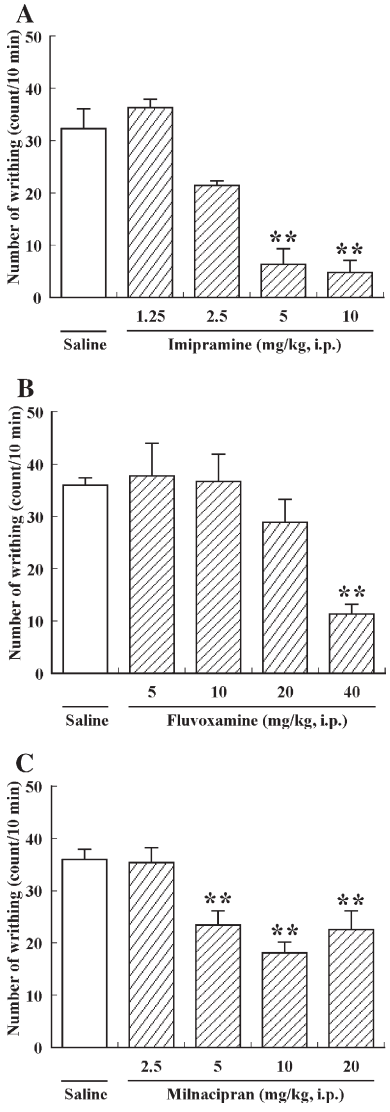

Fig. 1. Effects of imipramine (A), fluvoxamine (B) and milnacipran (C) in the acetic acid-induced writhing test in mice. Each column represents the mean with S.E.M of 8–11 mice. $^{**}P<0.01$ vs. saline-treated group.

Although several animal models of nociceptive tests have been developed to examine and compare the antinociceptive effects of different types of drugs, the antinociceptive effects of antidepressants appear to be test-dependent. Indeed, it has been reported that the acetic acid-induced writhing test, a well-established nociceptive test using a chemical stimulus, is more sensitive to antidepressants than other tests using thermal, mechanical or electrical stimuli (Korzeniewska-Rybicka and Plaznik, 1998; Rojas-Corrales et al., 2003). Therefore, the present study was designed to characterize the antinociceptive effects of the tricyclic antidepressant imipramine, the selective serotonin reuptake inhibitor fluvoxamine, the serotonin noradrenaline reuptake inhibitor milnacipran, as well as the antiepileptic drug carbamazepine using the acetic acid-induced writhing test in mice. Furthermore, the changes in the antinociceptive effects of antidepressants and carbamazepine produced by their co-administration were also evaluated.

2. Materials and methods

The present studies were conducted in accordance with the Guide for Care and Use of Laboratory Animals as adopted by the Committee on Care and Use of Laboratory Animals of Tokyo Medical University, International University of Health and Welfare and The Japanese Pharmacological Society.

2.1. Animals

Male ICR mice (Charles River, Japan) weighing 30–35 g were housed at a room temperature of 22±1 °C with a 12-h light–dark cycle (light on 6:00 a.m. to 6:00 p.m.). Food and water were available *ad libitum*.

2.2. Acetic acid-induced writhing test

Mice were injected intraperitoneally (i.p.) with a 0.8% (v/v) acetic acid solution (10 ml/kg of body weight) as an irritant stimulus and placed in an individual plastic cage (20×30×12 cm high) for observation. After a 5-min period, the number of writhes was recorded for 10 min. A writhe was defined as stretching of the hind limbs accompanied by a contraction of the abdominal muscles. Imipramine (1.25–10 mg/kg, i.p.), fluvoxamine (5–40 mg/kg, i.p.), milnacipran (2.5–20 mg/kg, i.p.), carbamazepine (5–20 mg/kg, i.p.) or vehicle (10 ml/kg, i.p.) was administered 30 min before the injection of acetic acid. In the