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Interaction between venlafaxine and caffeine on antinociception in mice

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This study was conducted in order to evaluate whether or not caffeine has any effect on venlafaxine antinociception in mice in acute application. Swiss albino mice, both male and female, were tested with hot plate analgesiameter set at 52.5 ± 0.1 °C. The mice were divided into four groups receiving saline + saline, caffeine (5 mg/kg) + saline, saline + venlafaxine (70 mg/kg) and caffeine (5 mg/kg) + venlafaxine (70 mg/kg) intraperitoneally. Each animal was tested on hot plate before treatment and 30, 45, 60 min after injections. Venlafaxine produced a significant antinociceptive effect at 30 and 45 min and the effect decreased at 60 min. Caffeine alone showed no significant antinociceptive effect at the applied dose however, it significantly antagonized the antinociceptive effect of venlafaxine at 30 min. As a result, caffeine inhibits the antinociceptive effect of venlafaxine in acute application in mice and this observation provides new evidence that the adenosinergic system may play a significant role in the mechanism of antinociceptive action of venlafaxine. This study raises the possibility that caffeine consumption might influence the effectiveness of venlafaxine in the treatment of pain in humans.

1. Introduction

To remove drawbacks of classical analgesics several approaches have been made, such as to use analgesic adjuvants (Tekol et al. 1994), to develop new methods directed to the use of parasympathomimetics as an analgesic (Tekol and Eminel 2002) and to apply antidepressants in painful conditions (Sawynok et al. 2001).

Antidepressants' analgesic effects have been known for a long time and currently tricyclic antidepressant drugs are frequently used in the treatment of various chronic pain syndromes (Korzeniewska and Plaznik 1998; Lynch 2001). Venlafaxine is a novel antidepressant drug that is chemically unrelated to tricyclic or other available antidepressants (Marchand et al. 2003c; Horst and Preskorn 1998). Animal studies have shown that venlafaxine has antinociceptive effects in acute and chronic pain models (Marchand et al. 2003a, b, c; Lang and Denson 1996; Schreiber et al. 1999). Clinical trials indicate that venlafaxine is effective in chronic pain patients (Sumpton and Moulin 2001; Rowbotham et al. 2004), some of whom are insensitive to other analgesics (Lithner 2000). Pharmacologically, venlafaxine inhibits neuronal reuptake of norepinephrine and serotonin and, to a minor degree, of dopamine (Bymaster et al. 2001; Horst and Preskorn 1998). It is believed that venlafaxine exerts analgesic effects preferentially via supraspinal and spinal mechanisms, however, the precise mechanisms are still unclear (Marchand et al. 2003c, Schreiber et al. 1999).

Due to antidepressants' multiple pharmacological actions it is important to consider the potential interactions with other agents that may influence their efficacy (Sawynok et al. 2001). Of particular interest in our study is the potential interaction with caffeine. Caffeine is the most widely used psychoactive substance and has been shown to inhibit antinociception induced by a number of tricyclic antidepressant drugs in animal models (Sawynok et al. 2001; Esser and Sawynok 2000). Our study is the first one to investigate the effect of caffeine on venlafaxine induced antinociception.

2. Investigations and results

Caffeine did not induce any significant antinociceptive effect for 5 mg/kg i.p. in mice ($P > 0.05$). Venlafaxine showed significant antinociceptive effect for 70 mg/kg at 30 and 45 min compared to saline or caffeine administered groups ($P < 0.05$) and the effect was decreased at 60 min. Venlafaxine induced antinociception was signifi-

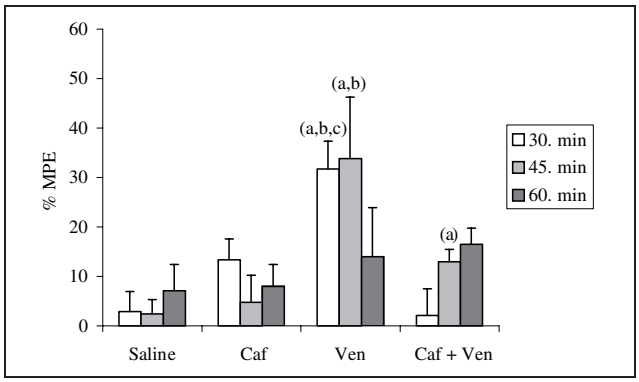

Fig.: The effects of saline, caffeine (Caf,5 mg/kg), venlafaxine (Ven, 70 mg/kg) and caffeine + venlafaxine (5 + 70 mg/kg) administration (i.p) in hot plate test (n = 8) at 30, 45 and 60 min in mice. Latencies were converted to mean ± S.E.M. percentage of maximal possible effect (% MPE). $P < 0.05$ as compared to saline (a), caffeine (b) and caffeine + venlafaxine (c) treated groups

cantly antagonised by caffeine at 30 min ($P < 0.05$). The antinociceptive effect of venlafaxine was significant at only 45 min ($P < 0.05$) in caffeine combined group. Results are presented in the Fig.

3. Discussion

The tricyclic antidepressant drugs which have been used for decades in the treatment of chronic pain have many side effects such as orthostatic hypotension, tachycardia, urinary retention, visual problems and sedation which often limit the tolerability of these drugs. Unlike the tricyclic antidepressant drugs, venlafaxine is devoid of anticholinergic, antihistaminergic and antiadrenergic effects thus, it may potentially be better tolerated than tricyclic antidepressant drugs (Lang et al. 1996; Horst and Preskorn 1998).

However, there is little information about the mechanism of analgesic action of venlafaxine compared to tricyclic antidepressant drugs. Animal studies indicate that adrenergic, serotonergic and opioidergic mechanisms may be involved in venlafaxine induced antinociception (Schreiber et al.1999; Marchand et al. 2003a, b, c), however, to our knowledge there is no information about possible mediation of adenosine.

Adenosine, acting at both spinal and supraspinal sites, can produce analgesia through the activation of adenosine A_1 receptors (Sawynok 1998; Sawynok et al. 2001). Adenosine administration not only produced the antinociceptive effect but also enhanced the effects of amitriptyline and imipramine in the tail flick test (Pareek et al. 1994). Biochemical studies showed that some antidepressants can inhibit the uptake of adenosine into neuronal preparations (Phillis and Wu 1982). In animal nociceptive tests coadministration of caffeine with amitriptyline reduced the antinociceptive effects of amitriptyline but does not alter the activity of desipramine. Adenosine thus contributes to analgesia produced by some, but not all, antidepressants (Esser and Sawynok 2000; Sawynok et al. 2001; Sawynok 1998).

Caffeine is a nonselective adenosine receptor antagonist being equally effective at both adenosine A_1 and A_2 receptors. Although caffeine has been extensively used as an analgesic adjuvant, it is now accepted that caffeine increases the analgesic response to nonsteroidal antiinflammatory drugs only in certain pain states and at certain dose ratios (Granados-Soto and Castaneda-Hernandez 1999). Caffeine exerts its pharmacological effects through the antagonism of adenosine receptors at low doses and the inhibition of phosphodiesterase enzyme at higher doses (Esser and Sawynok 2000). In our study we found that venlafaxine induced antinociception is antagonized by 5 mg/kg caffeine in mice. Several studies have revealed that caffeine at low doses inhibits the analgesic effects of some drugs. A study in mice showed that low caffeine doses (10–25 mg/kg) inhibit the analgesic effects of morphine while higher (75–100 mg/kg) doses potentiate it (Malec and Michalska 1988). In another study in rats, the thermal antihyperalgesic effect of amitriptyline was completely blocked by 3.75 mg/kg caffeine (Esser and Sawynok 2000). The antinociceptive effects of carbamazepine was inhibited by caffeine in stressed rats (Mashimoto et al.1998). There are some *in vitro* and *in vivo* studies that deal with the effect of venlafaxine and other antidepressants on CYP1A2, the main enzyme involved in caffeine metabolism, showing that venlafaxine appears to have a low potential for drug interactions based on CYP1A2 inhibition (Amchin et al. 1999).

We thought that endogenous adenosine or adenosine receptors may partly contribute the antinociceptive effect of venlafaxine, but there is a need for detailed studies to decide about interaction mechanism. This study raises the possibility that caffeine consumption might influence the effectiveness of venlafaxine in the treatment of pain in humans.

4. Experimental

4.1. Animals

Experiments were conducted on Swiss albino mice (25–35 g) from our own breeding facilities and each group consisted of the equal number of male and female animals ($n = 8$). Animals were allowed free access to food (Aytekinler standard pellets, Turkey) and tap water and were kept under artificial light for 12 h day (lights on at 7.00 a.m.) in a room with controlled temperature (22 ± 2 °C) and humidity ($50 \pm 10\%$). This study was approved by Erciyes University's Local Ethical Committee for Animal Experimentation.

4.2. Hot plate test

Mice were tested with hot plate analgesia meter (MAY 9601, Turkey) which was set at 52.5 ± 0.1 °C. Each animal was tested on hot plate before treatments (baseline latency) and at 30, 45, 60 min after injections (postdrug latencies). Baseline latencies were between 10–20 s. The end point was the withdrawal or licking response of the hindpaws or jumping response and the cut-off time was 45 s to minimize tissue damage. Hot plate latencies were converted into the Percent Maximal Possible Effect (% MPE) according to the formula (Yamamoto et al. 1997):

$$\% \text{ MPE} = (\text{Postdrug Latency-Baseline Latency})/(\text{Cutoff Latency-Baseline Latency}) \times 100$$

4.3. Drugs and administration route

There were 4 groups of mice ($n = 8$) receiving saline + saline, caffeine (5 mg/kg) + saline, saline + venlafaxine (70 mg/kg) and caffeine (5 mg/kg) + venlafaxine (70 mg/kg). All solutions were freshly prepared by dissolving the drugs in saline and were injected intraperitoneally (i.p) in a volume of 10 ml/kg. In experiments caffeine anhydrous (Sigma Chemicals, USA) or saline was injected 5 min. before venlafaxine HCl (Wyeth Pharmaceuticals, USA).

4.4. Statistical analysis

For the testing differences in terms of % MPE between groups Student's t Test was used. For the test, a P value <0.05 was considered statistically significant

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