



BRIEF COMMUNICATION

Chlomipramine Differently Affects Inflammatory Edema and Pain in the Rat

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BIANCHI, M., P. SACERDOTE AND A. E. PANERAI. *Chlomipramine differently affects inflammatory edema and pain in the rat.* PHARMACOL BIOCHEM BEHAV 48(4) 1037-1040, 1994.—In the rat, the acute administration of the antidepressant drug chlomipramine significantly reduces the edema and the hyperalgesia induced by yeast injection in the paw. However, the intensity and time course of the two effects differ. Moreover, adrenalectomy enhances the antinociceptive effect, whereas it does not affect the antiedema action of chlomipramine. Our data suggest a dissociation between the antiinflammatory and the analgesic effect of acute chlomipramine.

Chlomipramine Edema Hyperalgesia Inflammation

SEVERAL studies have demonstrated that tricyclic antidepressant drugs (TCAs) can induce analgesia both in rat and humans (3,9,13,18). Clinical data indicate that the antinociceptive action of these agents is independent from their antidepressant effect (9). This hypothesis is supported by the observation that, in humans, TCAs are effective, after acute administration, in the treatment of postoperative pain (16), while it is well known that, in psychiatric patients, 2-3 weeks are needed to unveil their therapeutic effectiveness (10). The analgesic effect of TCAs seems due to an increase in amine concentrations in the central nervous system (8). Other studies have demonstrated that TCAs can reduce both acute and chronic experimental inflammation (1,2,4). Thus, the question arises on the role of the antiinflammatory action of these drugs in their ability to reduce acute inflammatory pain.

We compared the effects of the proserotonergic TCA drug chlomipramine (12) on the inflammatory edema and inflammatory pain in the rat. Moreover, with the aim to clarify the mechanisms of action of chlomipramine (CIM), we measured its effects also in adrenalectomized animals, in order to evaluate the possible involvement of steroids in the antiinflammatory effects of the drug. It is well known, in fact, that corticosteroids released from the adrenal gland induce a potent inhibition of inflammatory processes (15) and that seroto-

nin represents a stimulatory input to the corticotropin-releasing hormone (CRH) neurosecretory system (19) and, therefore, to the activation of the hypothalamic-pituitary-adrenal axis (HPA).

METHOD

Sprague-Dawley CD male rats (Charles River, Calco, Italy), eight in each of 16 experimental groups, were used in all experiments. The animals, 200-250 g body weight, were housed at 22°C with a 14 L : 10 D cycle, with food and water ad lib. All experiments began between 0900-0930 h. Chlomipramine (Ciba-Geigy, Origgio, Italy) was dissolved in 0.9% NaCl and injected intraperitoneally at doses of 10, 20 and 40 mg/kg. These doses were chosen on the basis of results obtained in the experiments previously conducted with the drug (13,17).

The edema was induced by the injection of 0.1 ml of a 10% yeast solution in the left hindpaw. The intensity of hindpaw swelling was assessed by measuring the paw volume (ml) by a 7150 Plethysmometer (Basile, Comerio, Italy). The results are expressed as the algebraic difference between the volume of the treated and untreated hindpaw.

The Randall-Selitto paw-withdrawal test (11) was used to

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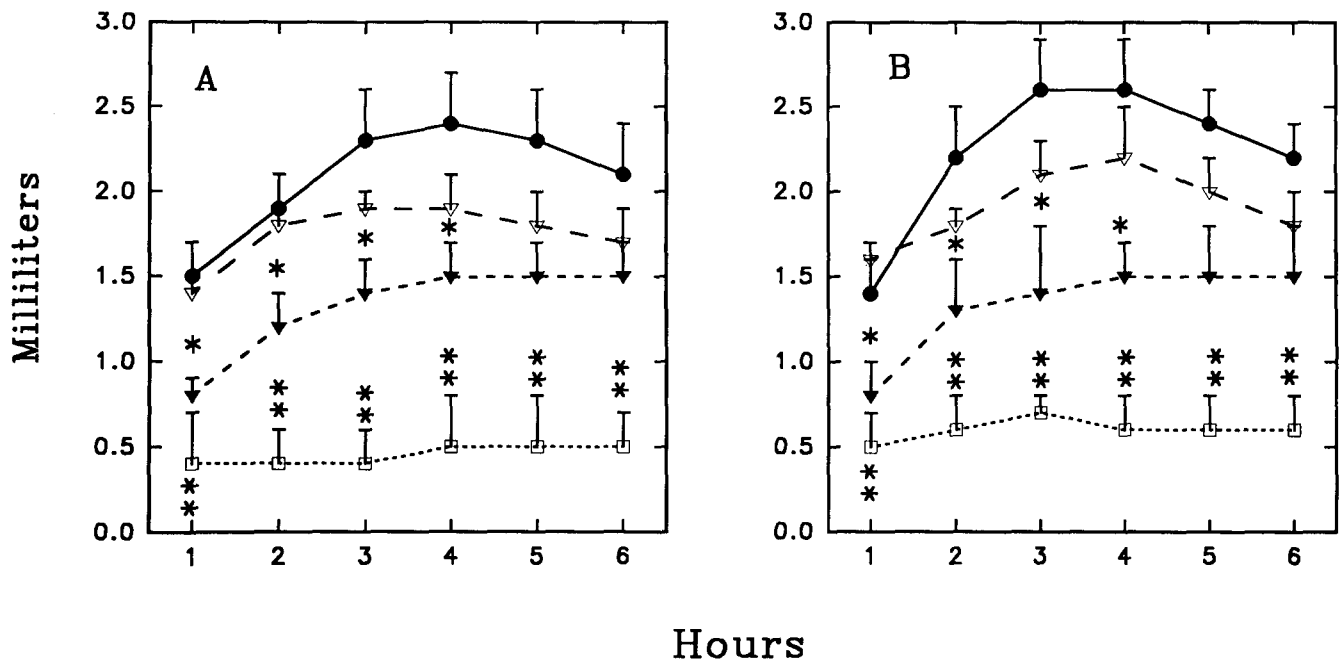


FIG. 1. Antiedema effect of chlorimipramine in sham-operated (Panel A) and adrenalectomized (Panel B) rats. Each point represents the mean \pm SEM of the algebraic difference between the volume of treated and untreated paw. (●) Saline; (▽) CIM 10 mg/kg; (▼) CIM 20 mg/kg; (□) CIM 40 mg/kg. * p < 0.05 vs. saline; ** p < 0.01 vs. saline.

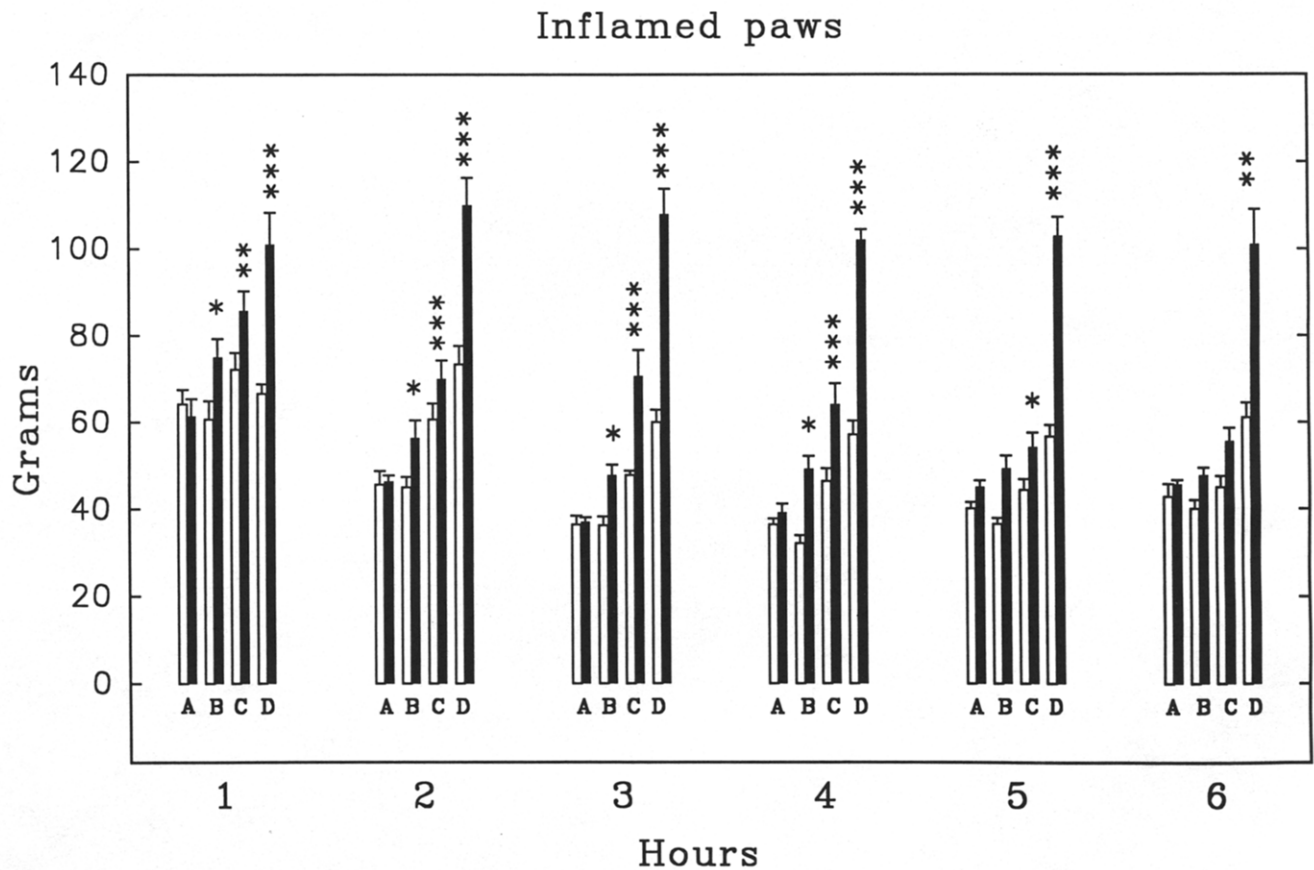


FIG. 2. Effect of chlorimipramine in the Randall-Selitto test performed on the inflamed paws of sham-operated (open bars) and adrenalectomized (filled bars) rats. A = saline; B = CIM 10 mg/kg; C = CIM 20 mg/kg; D = CIM 40 mg/kg. Values are grams, mean \pm SEM. * p < 0.05 vs. saline; ** p < 0.005 vs. saline; *** p < 0.001 vs. saline.

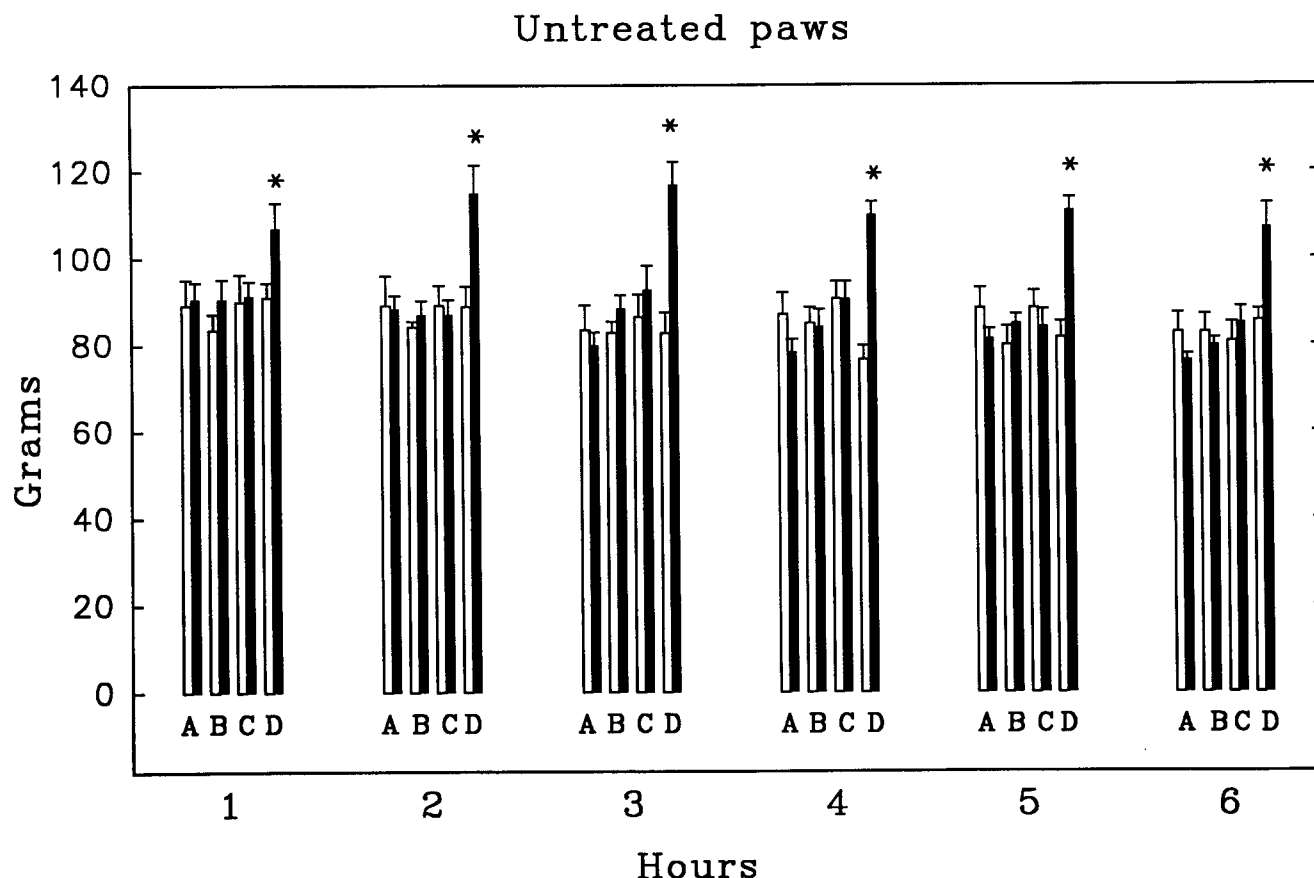


FIG. 3. Effect of chlomipramine in the Randall-Selitto test performed on the untreated paws of sham-operated (open bars) and adrenalectomized (filled bars) rats. A = saline; B = CIM 10 mg/kg; C = CIM 20 mg/kg; D = CIM 40 mg/kg. Values are grams, mean \pm SEM. * p < 0.005 vs. sham-operated animals.

measure mechanical nociceptive thresholds. The stimulus was applied with an analgesymeter (Basile, Comerio, Italy) which generates a linearly increasing mechanical force, applied by a conical piece of plastic with a dome-shaped tip on the dorsal surface of the rat's hindpaw. The animals were trained in the test procedure for 3 days before data collection. The results represent the maximal pressure (expressed in grams) tolerated by the animal. To avoid tissue damage, only a trial was performed at each time point.

Adrenalectomy was performed bilaterally through a dorsal incision under pentobarbital (42 mg/kg IP) anesthesia. After surgery, the rats were returned to their cages with free access to drink, but water was substituted by saline (0.9% NaCl), to maintain physiological sodium plasma concentrations. A group of rats was sham operated and allowed free access to water. One week was allowed for recovery from surgery.

The data were analyzed by means of analysis of variance (ANOVA) followed by Tukey's test for multiple comparisons.

RESULTS

Figure 1 shows the dose-related antiedema effect of CIM in sham-operated (Panel A) and adrenalectomized rats (Panel B). The results refer to the first 6 h of observation, but the antiedema action of the drug is still evident after 24 h. The adrenalectomy does not change the baseline paw edema (data

not shown). The development of the inflammatory edema is similar in the two groups of animals; moreover, the adrenalectomy does not modify the effect of CIM.

Figures 2 and 3 report the results of the Randall-Selitto test. Also in this test, the responses of the controls animals are similar in the adrenalectomized and sham-operated group; however, the effect of CIM is significantly more evident in adrenalectomized rats, where also the lower dose (10 mg/kg) of the drug becomes effective. Moreover, in the adrenalectomized group, the nociceptive thresholds measured in the non-inflamed paws of the rats treated with 40 mg/kg of CIM are significantly higher than those of normal animals treated with the same dose of the antidepressant drug.

The comparison between the results obtained by plethysmometer and the Randall-Selitto test in sham-operated rats indicate that the antiedema action of the drug is more rapid than the antinociceptive action.

DISCUSSION

Our data suggest that different mechanisms are involved in the antiedema and antinociceptive effects induced by the acute administration of CIM during experimental inflammation of the paw. In fact, the time course of the antiinflammatory effect is different from that of the analgesic effect. The observation that adrenalectomy affects only the antinociceptive ef-

fect of the drug further support our hypothesis. At present, we have not a fully satisfactory explanation of the effect of adrenalectomy on the action of CIM in the Randall-Selitto test. However, it is interesting to remember that corticosteroids exert an important inhibitory activity on serotonergic cells in the rat brain (5-7). Thus, we can suppose that the increase of the serotonergic tone induced by CIM is of greater magnitude in adrenalectomized than in normal animals. This hypothesis is consistent with the observation that the lowest dose of CIM is ineffective in sham-operated rats, while it increases nociceptive thresholds in the adrenalectomized animals. In the same line, only in the adrenalectomized rats the higher dose of CIM enhances nociceptive thresholds also in the noninflamed hindpaw.

Thus, as well as in other experimental models of pain (13), serotonin seems involved in the antinociceptive effect of CIM.

In contrast, because adrenalectomy does not affect the antiedema effect of CIM, we can infer that an activation of HPA by serotonin is not involved in the antiedema effect of the drug.

In this study, we administered CIM intraperitoneally; thus, it is reasonable not to exclude a peripheral mechanism for the antiinflammatory effect of the drug. At this purpose, we have recently demonstrated that CIM blocks in a dose-related fashion both spontaneous and stimulated migration of human polymorphonuclear cells in vitro (14). This effect of CIM, certainly not related to the inhibition of biogenic amines uptake, could contribute to its antiedema action.

In conclusion, we have demonstrated that CIM reduces inflammatory edema and inflammatory hyperalgesia by activating different pathways. However, both actions of this antidepressant drug can contribute to reduce acute pain in clinical settings.

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