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BRIEF COMMUNICATION

Taming Effect of Nonnarcotic Analgesics on the Septal Syndrome in Rats

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LOIZZO, A. AND M. MASSOTTI. *Taming effect of nonnarcotic analgesics on the septal syndrome in rats.* PHARMAC. BIOCHEM. BEHAV. 1(3) 367–370, 1973.–A series of nonnarcotic analgesics (aspirin, mefenamic acid, phenylbutazone, aminopyrine and methampyrone) as well as chlordiazepoxide and trazodone were administered to septal rats to examine the effects of these drugs on the hyperreactivity and viciousness characteristic of this syndrome. All the nonnarcotic analgesics tested showed taming effects, as did chlordiazepoxide and trazodone. To examine whether this effect was due to an antiinflammatory action of the nonnarcotic analgesics, acute and chronically prepared septal rats were treated with these drugs at different time periods following lesioning. No noticeable difference of the effect of these drugs existed between acute and chronic groups. The nonnarcotic analgesic drugs have a taming action on septal rats which appears to be independent of an antiinflammatory component.

Nonnarcotic analgesics Septal syndrome

NONNARCOTIC analgesics consist of a large group of miscellaneous compounds that have analgesic action but do not produce euphoria, tolerance or addiction. The majority of these drugs also have antipyretic and antiinflammatory properties. Although the effects of nonnarcotic analgesics on temperature control and pain centers have been postulated to act *via* a central mechanism, there are very few results which could be accepted as conclusive evidence of a central mechanism and site of action of these drugs. Wit and Wang [10,11] demonstrated that aspirin affects the thermosensitive neuronal activity of single cells in the anterior hypothalamus, and that the most effective antipyresis resulted from a direct application of the drug into the third ventricle.

Apart from these effects, other central actions have seldom been considered. In effect, neurophysiological and psychopharmacological techniques have rarely been applied to the study of these agents. Charpentier [2] described four components in the reaction of rats to a painful stimulus applied to the tail: startle, flight, squeak, and a coordinated reaction (a reaction orienting the animal response directly to the source of the pain, i.e., biting the electrodes applied to the tail). In considering the effects of a certain number of drugs on these reactions he described different properties for the nonnarcotic analgesics. Aspirin, for instance, inhibited the flight and the coordinated reaction while leaving the other components unaffected. On the basis of these results Charpentier [2] postulated an influence of aspirin and other similar substances on the level of vigilance. Napolitano and Longo [4] demonstrated that antipyrine, aminopyrine and aspirin attenuated the flight reaction which follows the electrical stimulation of the anterior hypothalamus in rabbits. According to Monnier and Nosal [3] aminopyrine, acetopheneditin and aspirin influenced the somatomotor reaction to tooth pulp stimulation, but did not significantly alter the electroencephalogram of the rabbit.

The present investigation was prompted by a serendipitous finding that methampyrone had a taming effect in septal rats. Following this observation, a search of the literature indicated that an attenuation of the hyperactivity in septal rats upon administration of aminopyrine had been reported by Beattie *et al.* [1]. Taming of the septal syndrome has also been described for drugs with antianxiety properties [6] – this might indicate that some nonnarcotic analgesics have tranquilizing effects. We have therefore undertaken a study of several nonnarcotic analgesics in order to assess their effectiveness in blocking the septal syndrome.

METHOD

A total of 100 female albino rats of the Wistar strain bred at our Institute, weighing 200 ± 20 g, were used. In the anesthetized animal (sodium pentobarbital, 35 mg/kg), a bilateral electrolytic lesion was stereotaxically placed in the septum. The animals were then housed in individual cages with free access to food and water; sodium penicillin,

50,000 units per day, was given for 3 days after the operation. At the end of the experiments the brains were fixed in Formalin and sectioned to check the placement of the lesions.

A modification of the methods described by Stark and Henderson [9] and Beattie *et al.* [1] was used for behavioral scoring. Six reactions to various kinds of stimuli were considered: (1) startle reaction to a hand clap; (2) startle reaction to a puff of air; (3) biting of an object in contact with the nose; (4) biting of an object in contact with the back; (5) attacking an object approaching the animal; (6) vocalization during handling. A score of (0), no reaction; (1), weak reaction; (2), marked reaction, was assigned to each of the six challenges; thus, a combined score of 12 represented the maximal rating. For the study, only rats which were clearly hyperreactive, with a score of 8 or higher, were used.

The calming action of any drug on a septal rat could be simply due to motor impairment induced by the compound, hence the presence of a motor deficit was assessed using a modified rating scale reported by Beattie *et al.* [1]. Motor performance was monitored by following: (1) ataxia; (2) grasp reflex (climbing an inclined screen at 60°); (3) righting reflex. When the animal was normally active and alert, the motor deficit was scored (0); a score of (4) was given when ataxia was observable and the animal moved slowly; a score of (8) indicated marked ataxia and loss of the grasping reflex; a score of (12) was given to rats prostrate or asleep, without any grasping or righting reflex.

The animals were scored at 30 min intervals, three times before drug treatment, after the treatment they were scored at the same time interval for 6 hr. After 6 hr, ratings were made at longer intervals (1–2 hr). When the drug effect was of long duration, the observations were countinued into the following days. At least 3 animals were used for each drug dosage; the overall effect was evaluated by totaling the individual scores at the various time intervals, and calculating the mean and standard error.

The nonnarcotic analgesics used in this study were acetylsalicylic acid (aspirin), methampyrone, aminopyrine, mefenamic acid and phenylbutazone. In addition, the influence of chlordiazepoxide and trazodone, a drug with tranquillizing and painkilling effects [8], were also tested.

The commercially available injection preparations of chlordiazepoxide, phenylbutazone and methampyrone were employed; the other drugs were dissolved in distilled water. All drugs were administered intraperitoneally. Control experiments were carried out administering 0,5 ml of saline.

RESULTS

A marked hyperirritability was present in the rats soon after recovery from the operation: the animals were aggressive and could not be touched or picked up, without gloves. If they were touched with a rod, they attacked and bit it. When left undisturbed, they did not demonstrate any particular signs of excitation and crouched quietly in their cage. This hyperirritability remained constant for about 10 days; after this period, this syndrome began to decrease in intensity and three weeks after the operation was no longer detectable in the majority of the animals. However, about 20% of the operated rats remained intractable for much longer periods (up to one year). Histological evaluation of all rat brains was performed to check the extent and location of the electrolytic lesion. This confirmed that in all cases of hyperirritability the septal nuclei had been destroyed. However, there was no clear evidence of a direct relationship between the magnitude and location of the lesion and the duration and severity of the septal syndrome.

Injections of saline did not appreciably alter the viciousness of the animals, while all the nonnarcotic analgesics tested showed some taming effect, which in general was short lasting, since the animal viciousness and hyperirritability returned within 6 hr. The effects of the seven drugs considered are presented in Fig. 1. The most effective drug was methampyrone, which had a noticeable effect at 12,5 mg/kg. The others rank in order of potency as follows: aminopyrine, aspirin, mephenamic acid, phenylbutazone. The taming action of chlordiazepoxide was confirmed; trazodone also demonstrated some calming effect. Noticeable motor impairment appeared after 20 mg/kg of chlordiazepoxide; a slight deficit was also present, although short lasting, following the highest doses of mefenamic acid and trazodone (Fig. 2).

In some animals the effect lasted up to 24 hr. This prolonged action modified the average curves and enhanced the standard error (see for instance the curves relevant to the effects of aminopyrine 50 mg/kg or methampyrone 50 mg/kg). This diminution in hyperirritability may rely upon a composite action of these compounds: a taming effect and a general antiinflammatory property. Possibly, those animals whose hyperirritability was attenuated for longer periods of time had more local inflammatory-edematous reaction to the lesioning, which contributed to the septal syndrome.

For these reasons, the effects of these drugs were examined on animals who retained the hyperirritability syndrome for longer than one month. Allegedly, in these animals, the inflammatory reactive components should have been reduced. For this investigation the operated animals were divided into two groups, acute and chronic, then submitted to pharmacological testing under separate schedules. The acute animals were challenged with the drugs from 3 to 7 days after the operation, whereas chronic animals were challenged at least 4 weeks after the operation.

The effect of a selected dose of all drugs, except aspirin, on the hyperreactivity of acute and chronic animals is summarized in Fig. 3. Acute and chronic animals showed essentially the same taming following treatment with all the compounds tested.

DISCUSSION

These results show that some nonnarcotic analgesics are able to attenuate hyperreactivity and aggressiveness in septal rats. In order to determine whether the observed taming effect was due to an antiinflammatory action on the lesioned brain or to a tranquilizing effect of these compounds, experiments involving acute and chronic animals were undertaken. The results of these experiments produced evidence that the nonnarcotic analgesics are equally able to attenuate the syndrome in chronic septal rats, when the swelling in the tissues probably no longer plays a significant role in causing hyperreactivity. It should be mentioned that animals challenged at random from three months up to one year following lesioning showed an equivalent taming reaction to these drugs. It seems therefore that the nonnarcotic analgesic drugs tested have a taming component which appears to be separate from the

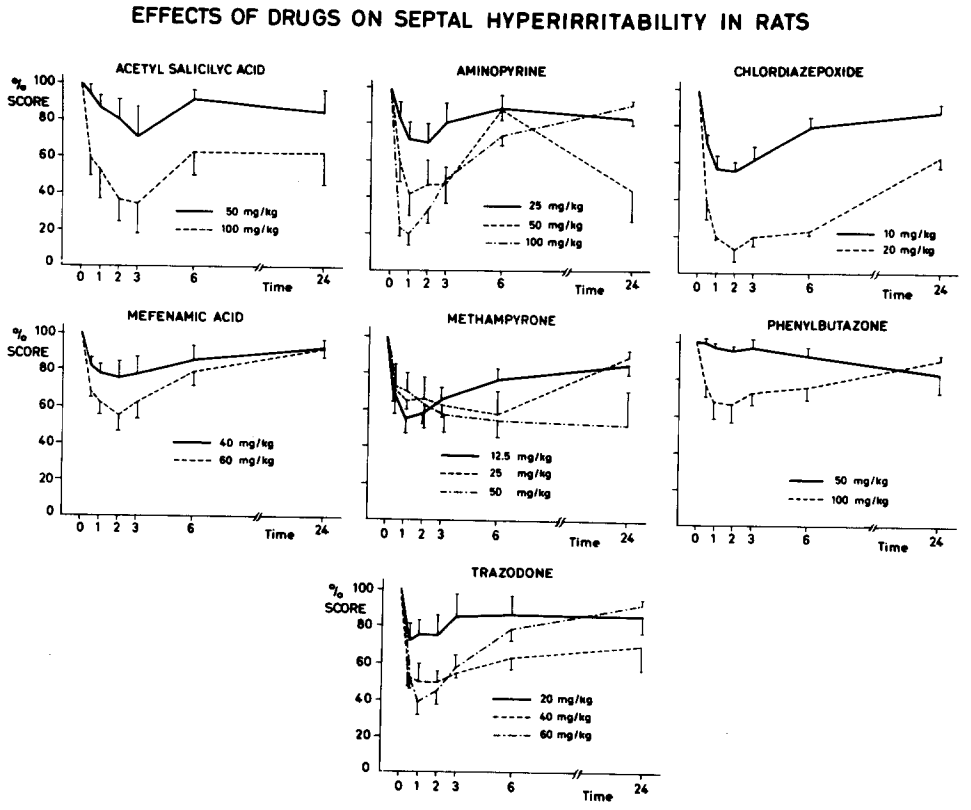

FIG. 1. Effect of drugs on septal hyperirritability in rats. Ordinates: irritability scores expressed as per cent on the control score before drug. Abscissa: time in hr (injection at time 0). Each curve represents the mean ± SE of at least 3 animals treated with the indicated dose of the drugs.

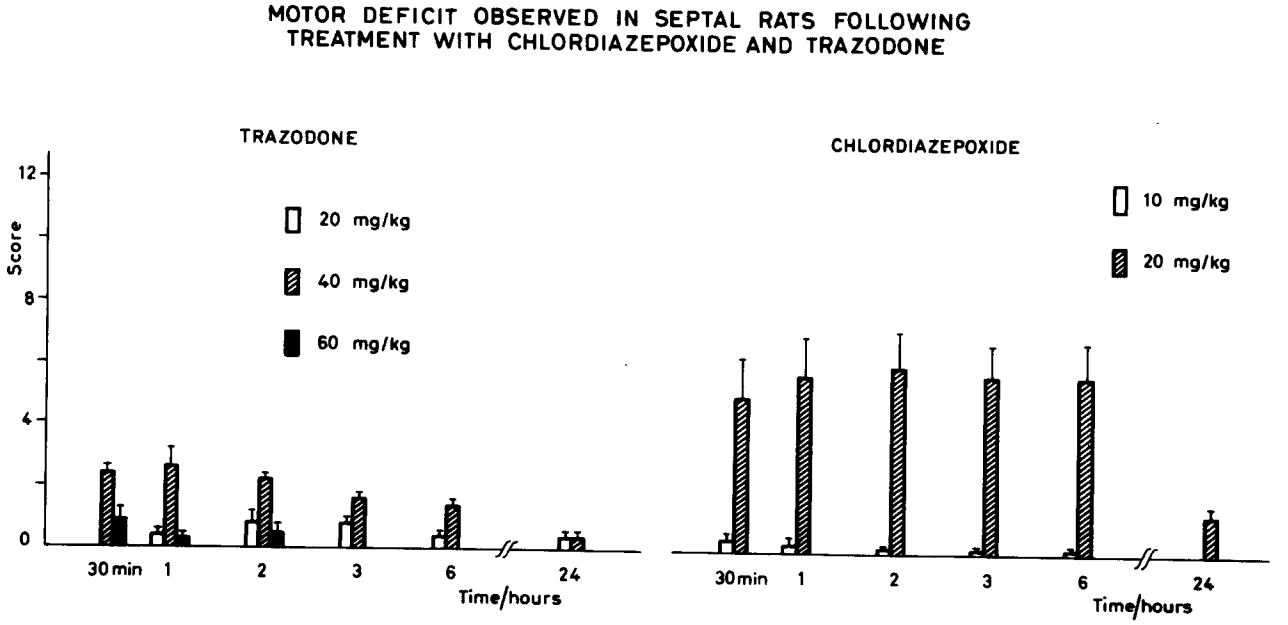

FIG. 2. Motor deficit observed in septal rats following treatment with chlordiazepoxide and trazodone.

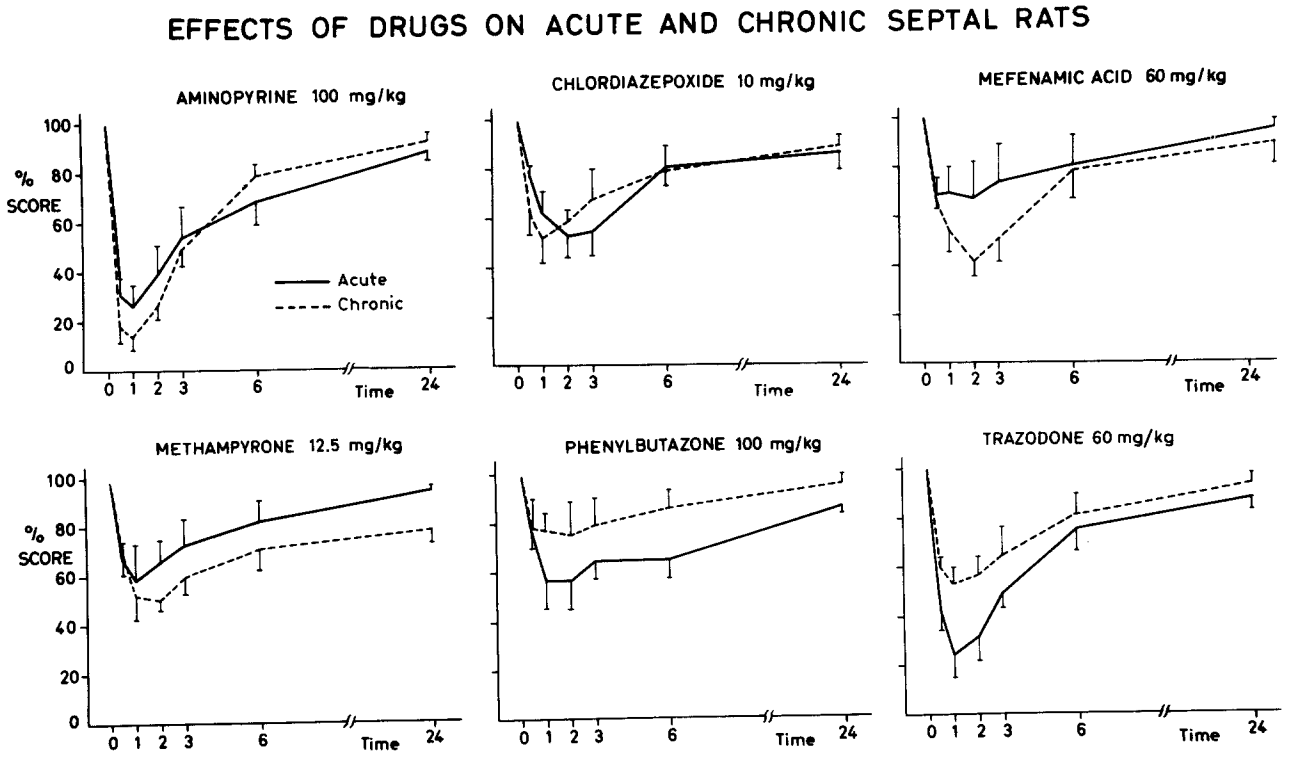

FIG. 3. Effect of drugs on hyperirritability of acute and chronic septal rats. A selected dose of each drug was administered to two groups of four animals, operated respectively 3–7 days (acute) and four weeks (chronic) before drug treatment.

various pharmacological effects described in the literature. In this connection, Pfeiffer *et al.* [5], using a quantitative appraisal of the variability and mean energy content of brain electrical activity in man, described a spectrum of activity for aspirin similar to the antianxiety agents, namely a reduction of mean energy content and an increase of the variability of the EEG.

Both chlordiazepoxide and trazodone were active in reducing septal aggressiveness. While this effect has already been described for chlordiazepoxide, this is the first report of a taming effect for trazodone in septal rats. These latter results are in accord with the observed calming effect of trazodone in man [7].

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