4], respectively. Assumig an indirect action (through the pituitary-adrenal system) of these opioid peptides on hematopoiesis, we selected immobilization for different periods of time as an adequate model. We expected to find that LE would have a suppressive effect on hematopoiesis (normalization of glucocorticoid production), and that ME would have a stimulating action (due to additional activation of glucocorticoid production).

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COMPARISON OF THE EFFECTS OF ANXIOLYTICS AND MORPHINE ON NOCICEPTIVE RESPONSES IN RATS

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There is much evidence, although some is contradictory, that anxiolytics of the benzodiazepine series possess analgesic properties [1]. It has been shown that benzodiazepines can lengthen the latent period of motor responses during exposure to pain [3]. Most workers attribute this elevation of the thresholds of nociceptive motor responses to the ataxic and sedative effect possessed by these preparations [1, 3].

Buspirone, an anxiolytic of the azaspirodecanedione series, which has recently been synthesized, is very similar to the benzodiazepines in its pharmacological properties in behavioral models of anxiety and aggression [4], and also in the clinical treatment of anxiety states [2]. Meanwhile, unlike the benzodiazepines, buspirone has no inhibitory action on muscle tone or movement coordination and does not possess sedative properties [4, 6]. For these reasons it is possible to study whether buspirone gives rise to any antinociceptive effects, and the investigation described below was carried out for this purpose. We also studied the effect of buspirone and diazepam on the depression of nociceptive responses produced by morphine.

EXPERIMENTAL METHOD

Experiments were carried out on 120 noninbred male albino rats weighing 180-220 g, kept eight to 10 to a cage, and receiving water and food ad lib. Nociceptive sensitivity was assessed by the latent period (LP) of the hind limb licking response (LLR) and the tail withdrawal reflex (TWR). To measure LP of LLR the animal was placed in a Plexiglas cage measuring 30 × 30 × 30 cm, the floor of which consisted of a metal plate, kept at a constant temperature of 55°C, and the time interval before the animal licked one of its hind limbs was

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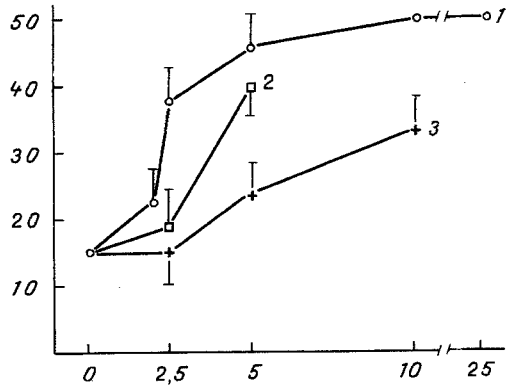

Fig. 1

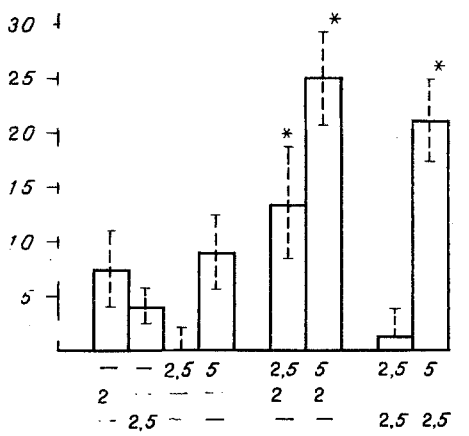

Fig. 2

Fig. 1. Effect of buspirone, diazepam, and morphine on LP of LLR in rats (dependence of effect on dose of drug). Abscissa, dose of drug (in mg/kg); ordinate, LP of LLR 30 min after injection (in sec). 1) Buspirone; 2) diazepam; 3) morphine. No fewer than eight animals were used for each dose of the drug. Short vertical lines indicate mean statistical error.

Fig. 2. Effect of combined injection of morphine and buspirone or diazepam on LP of LLR in rats. Abscissa, doses of drugs (in mg/kg): from top to bottom, morphine, buspirone, diazepam; ordinate, difference between LP measured 30 min after injection of drugs and control value, obtained immediately before injection (in sec). At least eight animals were used for each dose of the drugs. Vertical broken line denotes mean statistical error. *$p < 0.05$ compared with animals receiving morphine in an equal dose.

recorded. After the rat had licked its hind limb, it was not removed immediately from the hot metal plate, but after 5-10 sec, to rule out the possibility of learning. To prevent limb burns, the longest time the animal was allowed to stay on the hot plate did not exceed 50 sec. LP of LLR was measured twice with an interval of 15 sec, and the results were averaged.

LP of TWR was measured as described previously [5], during exposure to heat from a focused light source with a power of 150 W, placed 4 cm away from the tail. For each animal three or four measurements were made and the results were averaged. The longest duration of exposure was 7 sec.

LP of LLR and LP of TWR were determined immediately before injection of the drug (control) and 30 min thereafter. All measurements were made between noon and 3 p.m.

The buspirone was obtained from Bristol-Myers (USA), diazepam, in the form of a solution of Seduxen for injection, was obtained from Richter, Hungary, and morphine chloride also was used. The preparations were diluted in physiological saline immediately before use. All the compounds were injected intraperitoneally in a volume of 10 ml/kg body weight. Control animals received physiological saline. The results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

All the substances used caused a dose-dependent increase in LP of LLR (Fig. 1). Buspirone and morphine had no ataxic or sedative effect. Meanwhile, 30 min after injection of diazepam in a dose of 2.5 mg/kg a moderate reduction of motor activity was observed, whereas a dose of 5 mg/kg had a sedative effect. Consequently, in animals receiving diazepam in a dose of 5 mg/kg, LP of LLR and LP of TWR were determined after 60 min.

Buspirone, in doses of up to 25 mg/kg, and diazepam, in doses of up to 5 mg/kg (the largest doses used) did not change the values of LP of TWR (Table 1). After injection of 2.5 mg/kg of morphine no significant changes were found in LP of TWR, but in doses of 5 and 10 mg/kg it significantly increased this value by 48 ± 5%, respectively (mean ± standard error of the mean, $M = 12$, $p < 0.02$) and 77 ± 9% ($M = 12$, $p < 0.01$).

TABLE 1. Effect of Buspirone, Morphine, and Diazepam on LP of TWR in Rats

Compound and dose (in mg/kg)	LP of TWR		% of change	Student's test
	control	30 min after injection		
Buspirone (2)	2,7±0,2	2,4±0,2	—11	n.s
Buspirone (25)	3,0±0,4	3,2±0,4	7	n.s
Diazepam (2,5)	3,1±0,4	3,3±0,4	7	n.s
Diazepam (5)	2,9±0,5	2,9±0,2*	0	n.s
Morphine (5)	2,7±0,3	4,0±0,5	48	0,02
Morphine (5) + buspirone (2)	2,6±0,3	4,0±0,3	54	0,02
Morphine (5) + diazepam (2.5)	2,9±0,4	4,5±0,5	55	0,01
Buspirone (2) + diazepam (2.5)	2,9±0,6	2,4±0,2	—17	n.s.

Legend. For each animal measurements were done at least three times and the results averaged. From 8 to 15 animals were used in each series. When the two drugs were combined they were injected simultaneously. Asterisk indicates that LP of TWR was measured 60 min after injection. n.s.) Not significantly.

The results indicate that buspirone and diazepam are much more effective inhibitors of LLR than the classical analgesic, morphine. Incidentally, in the case of diazepam this effect may be due to the muscle-relaxing and sedative action of the drug [1, 3]. Unlike diazepam, buspirone, in the doses used, had no ataxic or sedative action, as is confirmed by other workers' observations [4, 6]. Meanwhile buspirone caused a much greater increase in LP of LLR than diazepam (Fig. 1) in all the doses used.

To discover the potentiating action of buspirone and diazepam, the effect of combined administration of morphine with the minimally effective (with respect to their effect on LLR) doses of buspirone (2 mg/kg) and diazepam (2.5 mg/kg) on LP of LLR and LP of TWR was assessed. Buspirone together with morphine caused a significant increase in LP of LLR compared with that observed when morphine was given alone in doses of 2.5 and 5 mg/kg (Fig. 2). If given together with 2.5 mg/kg of morphine, diazepam did not potentiate the analgesic effect in LLR, but if injected together with 5 mg/kg of morphine it increased LP of LLR significantly by 37% compared with the action of morphine alone (Fig. 2). These data show that buspirone and, to a rather lesser degree, diazepam potentiate the analgesic effect of morphine in the LLR test. Meanwhile, neither buspirone nor diazepam caused any change in the effect of morphine in the TWR test (Table 1).

The results obtained by this study of the action of buspirone on LLR in rats suggest that this drug which, unlike diazepam, has neither sedative nor ataxic properties, can cause depression of sensitivity to pain. Meanwhile buspirone does not affect LP of TWR, a test with simpler structure than LLR, and does not potentiate the action of morphine in this test. This observation is evidence that the hypothetical analgesic action of buspirone may be mediated by mechanisms of more complex (emotional, for example) reactions, and it may be closely linked with its basic pharmacological effect, namely anxiolytic.

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