Morphine and Its Potentiated Form: Effects on Pain Sensitivity in Rats

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We studied the effects of morphine and its potentiated form on nociceptive thresholds in rats with the morphine withdrawal syndrome. Repeated combination (bipathic) treatment with morphine and its potentiated form increased nociceptive threshold and, therefore, activated the nociceptive system in the brain.

Key Words: *morphine withdrawal syndrome; pain sensitivity; potentiated morphine; bipathic treatment*

Here we studied the effects of morphine and its potentiated form (PM) synthesized at the "Materia Medica Holding" Research-and-Production Company on pain sensitivity in chronically morphinized rats.

MATERIALS AND METHODS

Experiments were performed on 22 adult outbred male rats weighing 200-250 g. Seven rats of group 1 perorally received PM for 10 days (1 drop in 0.5 ml distilled water). Narcotic dependence in group 2 rats (n=7) was produced by intraperitoneal injections of 1% morphine hydrochloride in a dose of 1 mg/kg for 10 days. After morphinization these animals received PM for 10 days. Eight non-morphinized rats of group 3 received PM and 1% morphine hydrochloride for 10 days. The dose of morphine hydrochloride increased daily from 1 to 10 mg/kg.

Pain sensitivity was evaluated by thresholds of the nociceptive reaction to electrical stimulation of the limbs. The measurements were performed before and 90 min after administration of preparations at 10-min intervals.

The results were analyzed by Student's t test.

RESULTS

The nociceptive threshold decreased in group 1 rats 30 min after administration of PM. These changes were progressive and persisted for 80 min (Table 1). Pretreatment with PM had no effect on pain sensitivity. Before the 10th treatment nociceptive threshold surpassed the baseline level. Nociceptive threshold increased after the 5th treatment. Nociceptive threshold decreased 30 min after the 10th treatment, increased by the 90th minute, but did not reach the baseline level.

In group 2 rats nociceptive thresholds increased 20-30 min after single treatment with morphine. Nociceptive threshold underwent a further increase in animals receiving morphine for 10 days (Table 2). In rats withdrawn from morphine for 3 days nociceptive thresholds were lower than in chronically morphinized animals. Administration of PM more significantly decreased nociceptive threshold, which approached the baseline level. Nociceptive thresholds were similar in animals receiving PM for 10 days and subjected to chronic morphinization (Table 2).

These data show that administration of PM to narcotized rats with the withdrawal syndrome activates the antinociceptive system in the brain and produces the analgetic effect, which is similar to the influence of morphine.

In group 3 rats nociceptive thresholds decreased 30 min after the first administration of morphine and PM (Table 3). Repeated treatment increased nociceptive threshold. Therefore, morphine and PM produced the analgetic effect. Immediately before the 5th treatment with morphine and PM nociceptive threshold surpassed the baseline level. Then we revealed a further increase in nociceptive threshold (Table 3).

Our results indicate that single administration of morphine and PM does not produce the analgetic effect in intact rats, but increases nociceptive threshold in morphinized animal. Repeated combination (bipathic) treatment with morphine and PM activates the nociceptive system in the brain.

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TABLE 1. Nociceptive Thresholds in Non-morphinized Rats Receiving PM (V, $\bar{X}\pm m$)

Period		PM administration		
		1	5	10
Before treatment, min		30.7±2.5	30.7±2.7	35.3±3.2
After treatment, min	5	25.0±2.1	27.1±2.9	33.5±3.6
	10	25.0±2.2	26.7±2.3	31.4±2.9
	20	21.7±2.2	28.2±2.3	31.4±2.9
	30	19.2±1.7	28.5±2.5	27.1±2.4
	40	16.0±1.5	27.1±2.6	24.2±2.3
	50	15.3±1.3	27.8±2.2	21.4±1.8
	60	13.8±1.1	24.6±2.0	24.2±1.9
	70	18.5±1.5	29.2±2.2	26.4±2.1
	80	21.0±1.8	26.4±3.1	21.0±2.2
	90	26.4±2.4	30.0±3.1	32.1±1.9

TABLE 2. Nociceptive Thresholds in Rats Consecutively Treated with Morphine (10 Days) and PM (10 Days, V, $\bar{X}\pm m$)

Period		Morphine administration			PM administration		
		1	5	10	1	5	10
Before treatment, min		21.4±1.8	62.1±5.4	50.0±5.1	27.1±2.3	43.9±3.8	67.1±5.8
After treatment, min	5	22.8±2.1	40.7±3.4	52.9±4.6	28.5±2.1	40.7±3.6	50.5±4.3
	10	25.0±2.2	36.4±3.3	52.2±5.1	26.0±1.8	37.1±3.2	44.1±3.8
	20	28.9±2.7	35.7±3.1	61.5±5.7	23.2±1.9	47.8±3.8	50.0±4.8
	30	27.5±2.9	47.9±3.7	51.2±4.3	22.8±1.8	30.7±2.5	56.6±4.9
	40	21.1±1.7	44.2±3.8	57.5±4.8	21.8±1.6	35.0±2.8	45.8±4.3
	50	21.1±2.2	50.0±4.8	59.9±5.1	22.8±1.8	28.4±2.2	43.6±4.6
	60	15.0±1.6	43.6±4.1	52.9±4.7	20.3±1.6	36.8±3.3	36.0±4.1
	70	30.6±3.2	41.1±3.8	45.4±4.6	22.1±1.5	29.2±2.5	41.6±3.9
	80	28.7±3.1	40.0±3.2	47.0±4.6	19.2±1.3	31.6±3.6	40.8±3.9
	90	21.3±2.7	37.1±3.1	47.0±4.5	26.7±1.9	28.3±2.6	40.9±3.8

TABLE 3. Nociceptive Thresholds in Rats after Combination Treatment with Morphine and PM (V, $\bar{X}\pm m$)

Period		Administration of morphine and PM		
		1	5	10
Before treatment, min		22.9±1.8	30.7±2.8	34.6±2.9
After treatment, min	5	21.4±1.9	29.3±2.6	38.6±3.5
	10	21.8±2.1	24.3±2.2	39.3±3.4
	20	18.6±2.6	25.7±2.3	37.9±3.5
	30	17.1±1.5	22.9±1.9	41.4±3.8
	40	15.7±1.6	25.4±2.3	39.6±3.9
	50	17.5±1.6	26.8±2.8	45.7±4.3
	60	17.5±1.7	23.4±2.6	44.3±4.4
	70	17.5±1.5	27.5±2.5	44.2±4.1
	80	20.0±1.8	29.6±2.6	42.9±4.1
	90	20.9±2.2	26.9±2.5	36.0±3.5

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