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INDIVIDUAL DIFFERENCES IN PAIN SENSITIVITY AND THE ANALGESIC EFFECT OF MORPHINE IN NONINBRED MICE

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Clinical observations show that during the relief of pain by neuroleptanalgesia, the analgesic properties of the narcotic analgesics are manifested only weakly in 10% of patients [2]. This state of affairs is evidence that patients differ in their sensitivity to substances of this group.

The aim of the investigation described below was accordingly to study individual differences in levels of sensitivity to pain and in the analgesic effect of opiates (with morphine as the example) in a population of noninbred mice, during nociceptive stimulation of varied modality (thermal, mechanical, electrical), in order to discover individual predictors of the degree of the pain-relieving action of narcotic analgesics.

EXPERIMENTAL METHOD

Experiments were carried out on 197 noninbred male mice weighing 21-26 g. The animals were divided into three groups (for thermal, mechanical, and electrical stimulation respectively) and were kept during the testing period in individual transparent plastic cages measuring 2.5 × 2.5 × 8 cm.

For thermal stimulation the animal's tail was immersed in a glass of hot water (55°C) [4]. The latent period of tail withdrawal in response to thermal stimulation was determined in each mouse before and after administration of morphine. Mechanical stimulation was effected by means of an analgesimeter (No. 21025, Ugo Basile Biological Research Apparatus, Italy). The animal's tail was subjected, at a distance of 1 cm from its base, to gradually increasing mechanical compression by means of a weight of 350 g moving along a lever. The threshold of pain sensation was recorded in conventional units in accordance with the reading on the analgesimeter scale when the animal gave a motor response. Electrical pain stimulation was applied through two needle electrodes 0.3 mm in diameter, made of stainless steel and arranged parallel to each other at a distance of 20 mm apart. The electrode nearest to the animal's trunk was located 7 mm from the base of the tail. Stimulation was given by

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TABLE 1. Thresholds of Nociceptive Response and Level of Analgesia Induced by Morphine during First and Repeated Testing in Association with Thermal, Mechanical, and Electrical Stimulation (M ± m)

Type of stimulation	Background		Morphine		Coefficient of correlation (r) between		
	first test (A)	retesting (B)	first test (C)	retesting (D)	A and C	B and D	C and D
Mechanical, conventional units (77)	6,37±0,16	6,56±0,25	19,9±0,7	15,9±0,7**	+0,1	−0,04	+0,27
Thermal, sec (55)	1,06±0,04	1,63±0,06***	5,08±0,35	5,06±0,52	+0,0081	+0,04	+0,02
Electrical, μA (65)	0,3±0,02	0,26±0,015*	5,03±0,79	3,21±0,6*	+0,39	−0,02	+0,34

Legend. *p < 0.05, **p < 0.01, ***p < 0.001. Number of experiments given in parentheses.

square pulses (1 msec, 25 pulses per volley) by means of an ÉSU-1 electrostimulator, with current stabilization at the output. Stimulation was applied three times with an interval of 3 sec on each occasion. The strength of the current was gradually increased from zero to 20 μA, and stimulation was again applied. The threshold of response was taken to be the minimal strength of current at which the animal vocalized to every successive stimulation (three squeaks in a row).

The doses of morphine were chosen so as to be as close to the maximally effective dose as possible in each test. During thermal and mechanical stimulation the dose of morphine was 12 mg/kg, which is 2-2.5 times higher than ED_{50} [4]; any increase in its strength could cause damage to the tissues in the presence of these types of stimulation, and make adequate retesting impossible. In the electrical stimulation of the tail test the dose of morphine was increased to 70 mg/kg, for with a dose of 60 mg/kg the level of the analgesic action under these conditions is only 67% [4]. Morphine was injected intraperitoneally 15 min before determination of its analgesic activity. Thresholds of pain sensitivity and their response to morphine were tested repeatedly at intervals of 1 week. The data were subjected to statistical analysis by correlation analysis [1] and by Student's test [3].

EXPERIMENTAL RESULTS

In the case of mechanical and thermal nociceptive stimulation of the tail no significant correlation could be found between levels of initial thresholds of the nociceptive response of the mice and thresholds following administration of morphine (Table 1). This applies both to the first and to later (after 1 week) testing of the same animals. During electrical stimulation, it was found in the first test that the higher the background threshold of the nociceptive response, the higher the level of analgesia induced by morphine ($r = -0.39$). This fact is in agreement with clinical data for fentanyl (during surgical operations): according to electrosensometry data in patients with a higher background threshold of sensitivity to pain, the level of analgesia induced by fentanyl is higher [2]. Meanwhile during retesting in animals by electrical stimulation, no such relationship was found.

For the whole mouse population (Table 1) weakening of the analgesic action of morphine could be observed during retesting of mice subjected to mechanical and electrical stimulation; this probably indicates the onset of tolerance to the analgesic effect of morphine. Meanwhile the study of correlation between the levels of the analgesic effect of morphine against these types of stimulation shows that higher levels of morphine analgesia during the first test corresponded to its higher level during retesting ($r = +0.27$ for mechanical and $r = +0.34$ for electrical stimulation). For thermal stimulation this character of the relationship between the first and second tests could not be detected. The data in Table 1 also are evidence that on the whole, allowing for the whole population of mice, changes in the background threshold of the nociceptive response differed in character during retesting: an increase during thermal, a decrease during electrical, and no change during mechanical stimulation. It is still premature to try to explain this fact, for it requires a special study on additional groups of animals in accordance with the types of stimulation examined above.

Thus only under conditions of electrical stimulation of mice is positive correlation found between the background threshold of the nociceptive response and the level of morphine analgesia, and also positive correlation between the level of morphine analgesia during the first test and retesting. This last situation also is characteristic of mechanical stimulation. Incidentally, despite its statistical significance, the degree of correlation revealed is low (Table 1). From the practical point of view, these relationships discovered are only approximate in character.

The parameters of sensitivity to pain which were studied also were examined individually on each animal. It was found that with all types of nociceptive stimulation there were some individuals which were insensitive to the analgesic action of morphine. For instance, the proportion of animals in which morphine did not raise the threshold of nociceptive response at all, in the case of mechanical stimulation, was 3.8% at the first test and 5.2% on retesting; the corresponding fractions for electrical stimulation were 1.5 and 0%, and for thermal stimulation 1.7 and 1.7%. In some cases, moreover, changes both in the background threshold and in the level of the analgesic action of morphine differed in direction on retesting. For a more detailed examination of these changes, therefore, the animals were grouped on the basis of the level of their nociceptive response after and before administration of morphine — the morphine/background index (Table 2*) With all the types of nociceptive stimulation studied the levels of morphine analgesia on retesting were found to be considerably modified in some animals, either reduced or increased (the latter is not in accord with the view that tolerance can develop rapidly). It can be concluded from this fact that even by preliminary testing of the analgesic effect of morphine it is impossible to predict the character of its pain relieving action when readministered. The search for individual predictors of the level of action of narcotic analgesics must therefore be evidently directed toward the period immediately before their administration.

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*Table 2 omitted in Russian original — Publisher.