COMPARISON OF THE DISCRIMINATIVE AND ANALGESIC EFFECTS OF MORPHINE

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Many drugs are known to have specific discriminative properties, whereby the ability to discriminate between states induced by drugs and states arising after administration of the solvent only can be formed in animals. Close correlation exists between the discriminative properties of substances and their ability to induce addiction, for both effects are the result of sensations induced by the substance [8]. Discriminative stimuli are characteristic of a class of substances, for example, narcotic analgesics of varied chemical structure [6]. Naloxone, a specific blocker of opiate receptors, antagonizes both the analgesic and the discriminative effect of analgesics. Does this mean that the analgesic and discriminative effects of narcotic analgesics have identical mechanisms?

In this investigation an attempt was made to answer this question by comparing the dynamics of tolerance to pharmacologic effects chosen for study and also by Schild's method [4, 5, 9].

EXPERIMENTAL METHOD

Experiments were carried out on 140 noninbred male albino mice weighing 17-24 g. Since morphine affects both pain sensation and food behavior, standard methods for analysis of discrimination between preparations using food or pain reinforcement [7, 8] were not used. An original method was worked out, using a water T maze. The animals were placed alternately in the starting compartment and the direction of turning was recorded. In experiments with the solvent, the dry platform for avoidance was placed on the left, but after injection of morphine it was on the right. The daily session consisted of 5-10 tests for each animal; only the direction of turning at the first test was counted.

Morphine or isotonic solution was injected in random order intraperitoneally 20 min before the experiment in a volume of 0.1 ml of solution/10 g body weight. For learning, morphine was used in a dose of 4 mg/kg. The criterion of learning was not less than 80% of correct responses in the group in the course of 3-4 days [7]. Naloxone was injected subcutaneously 15 min before the experiment in doses of 0.01-0.2 mg/kg.

The analgesic effect of morphine was estimated from the response of the mice to mechanical nociceptive stimulation of the base of the tail. In a separate series of experiments the tail immersion test with noceptive thermal stimulation was used.

To induce tolerance, morphine was injected into the animals twice a day for 10 days in sessional doses which increased gradually from 10 to 50 mg/kg. The results were subjected to variance analysis, regression analysis, probit analysis, and analysis by Schild's method.

EXPERIMENTAL RESULTS

After 3 weeks of learning morphine discrimination the animals showed stable performance of responses at the 90-100% level (based on the criterion of direction of turning in the first test). When morphine was injected in doses less than the test dose, the results were evidence of some degree of discrimination between drug and solvent. On the basis of these results dose–effect relationships were plotted and values of ED_{50} were calculated. Similar parameters

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TABLE 1. Changes in ED_{50} of Morphine for Analgesic and Discriminative Effects after Course of Subchronic Injections

Parameter	Analgesic effect (mechanical nociceptive stimulation)	Discriminative effect
ED_{50} before course of injections	3,01	1,06
ED_{50} after course of injections	14,62	2,75
ED_{50} after injections/ED_{50} before injections	4,86	2,59

TABLE 2. Comparison of pA_2 of Naloxone for Antagonism with Analgesic and Discriminative Effects of Morphine

Test	ED_{50} of morphine, mg/kg	pA_2	Coefficient of regression ($M \pm m$)
1. Discrimination of morphine (water maze)	1,06	7,03 (6,69—7,37)	—1,0±0,1
2. Response to mechanical nociceptive stimulation	3,01	7,59* (7,30—7,86)	—1,2±0,02
3. Response to thermal nociceptive stimulation	6,60	7,68** (7,20—8,15)	—1,08±0,09

Legend. *P < 0.05 relative to pA_2 for test 1, **P < 0.05 relative to pA_2 for test 2. Confidence limits at 95% level of probability shown in parentheses.

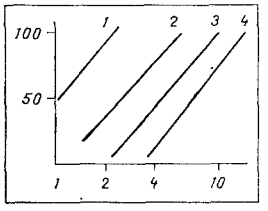

Fig. 1. Regression lines for dose—discriminative effect relationship for morphine alone and together with naloxone. Abscissa, doses of morphine (in mg/kg, logarithmic scale); ordinate, number of correct responses in water T maze (in per cent). 1) Morphine together with isotonic salt solution; 2-4) morphine together with naloxone in doses of 0.05, 0.1, and 0.2 mg/kg, respectively.

were obtained on the same animals for the analgesic effect of morphine (Table 1). The discriminative properties of morphine were discovered even in subanalgesic doses, and ED_{50} for the discriminative effect was almost three times less than ED_{50} for analgesic action. The slope of the regression lines of the dose—effect curves were similar for both effects.

After subchronic administration of increasing doses of morphine, effective doses of the analgesic were again determined in the mice on the basis of the above effects (Table 1). It will be clear from Table 1 that tolerance had developed to both the analgesic and the discriminative effects of morphine, but the degree of tolerance differed. Whereas the discriminative properties required a dose 2.5 times greater for the same effect, ED_{50} for the analgesic effect was increased almost fivefold.

The second method used to study unity or dissociation of the discriminative and analgesic effects of morphine was by experiments with combined administration of the analgesic and its

specific antagonist, naloxone. In this case, dose–effect curves were plotted for morphine together with 3 doses of naloxone after regression analysis of the data. Curves of this kind for the discriminative effect of morphine are given in Fig. 1. Table 2 gives the results of determination of pA_2 for the discriminative and analgesic effects of morphine. The first two parameters were obtained in experiments on the same animals, the last in experiments on a single muscle group. It will be clear from Table 2 that pA_2 for naloxone in different pain tests was identical. These results agree with data in the literature [11]. Meanwhile, a significant difference was found between pA_2 of nalaxone in experiments with discrimination between morphine and solvent in a T maze. Facts of this kind, as we know, lie at the basis of the modern technique of receptor differentiation [10] and, in this particular situation, they suggest that the receptor systems responsible for the above effects of morphine are not identical.

The discriminative properties of morphine are an element of its psychotropic action, but they do not characterize quality of that action. All that can be said is that these properties are exhibited within a range of doses that facilitate the response of self-stimulation of the brain, and maintain the response of intravenous self-injection and are active in the preference test [1, 3], i.e., discriminative properties are manifested most clearly in doses corresponding to the emotionally positive action of morphine. In previous experiments using the response of self-stimulation of the brain it was found that the emotionally positive effect of morphine, unlike the analgesic effect, does not exhibit such marked capacity for habituation [2], in agreement with the results of the present investigation. The possibility of true separation of the analgesic and emotionally positive effects of morphine could create a basis for an oriented search for analgesics free from the risk of drug addiction. The results of this investigation may be regarded as a step in that direction, for differences in the dynamics of development of tolerance to the analgesic and discriminative effects of morphine and the significantly different values for antagonism of naloxone relative to these effects are evidence of differences in the (receptor?) mechanisms of the pain-relieving action of morphine and its discriminative properties.

LITERATURE CITED

1. A. V. Val'dman and É. É. Zvartau, Drug Alcohol Depend., 10, 295 (1982).
2. É. É. Zvartau, Res. Commun. Chem. Pathol. Pharmacol., 16, 707 (1977).
3. É. É. Zvartau, in: Neuropharmacologic Aspects of Pain [in Russian], Leningrad (1982), pp. 19-27.
4. I. V. Komissarov, Elements of a Theory of Receptors in Molecular Pharmacology [in Russian], Moscow (1969).
5. O. Arunlakshana and H. O. Schild, Br. J. Pharmacol., 14, 48 (1959).
6. H. Lal, Psychopharmacol. Commun., 2, 305 (1976).
7. D. A. Overton, Fed. Proc., 33, 1800 (1974).
8. D. A. Overton, in: Drug Discrimination and State-Dependent Learning, New York (1978), pp. 283-318.
9. H. O. Schild, Br. J. Pharmacol., 2, 189 (1947).
10. R. J. Tallarida and L. S. Jacob, Dose–Response Relation in Pharmacology, New York (1979).
11. R. J. Tallarida, A. Cowan, and M. W. Adler, Life Sci., 25, 637 (1979).