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Original Investigations

The Stimulus Properties of Morphine and Ethanol

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Abstract. The present investigation sought (a) to establish the efficacy of morphine and ethanol as discriminative stimuli when each is paired with the administration of saline and (b) to compare, in a qualitative sense, the stimulus properties of the two drugs. Additional experiments examined the effects of treatment with naloxone or *l*-propranolol upon morphine and ethanol-mediated discriminated responding. Finally, the stereospecificity of the stimuli produced by morphine was determined by a comparison, in morphine-trained rats, of levorphanol and dextrorphan. Discriminated responding developed rapidly in both the morphine and ethanol groups. In tests in which ethanol was administered to morphine-trained animals and vice versa, no similarity to stimulus properties was apparent. Antagonism of discriminated responding induced by morphine and ethanol was attempted using naloxone and *l*-propranolol. Naloxone blocked the actions of morphine but was without effect upon ethanol. No evidence of antagonism of either drug by propranolol was found. When a range of doses of levorphanol (0.1–3 mg/kg) and dextrorphan (3–100 mg/kg) was tested in morphine trained animals, only levorphanol was able to substitute for morphine. The present results suggest that the stimulus properties of morphine represent typical opiate effects.

Key words: Ethanol – Morphine – Drug discrimination – Naloxone – Propanolol – Levorphanol – Dextrorphan.

Operant behavior which is reinforced only in the presence of a specified stimulus may come to occur with greater frequency in the presence of the stimulus than in its absence. In such a situation, the behavior is said to be under the control of the stimulus which is then termed a discriminative stimulus (Kelleher and Morse, 1968; Reynolds, 1968). In addition to the usual sensory stimuli, it is now well established that the effects of drugs may function as discriminative stimuli (see review by Barry, 1974) and, more than 20 years ago, Conger (1951) trained rats to respond differentially following the injection of ethanol and water, respectively. Subsequent investigators compared the effects, in ethanol-trained subjects, of a variety of drugs including barbiturates, meprobamate, chlordiazepoxide, chloral hydrate, and chlorpromazine (Overton, 1966; Kubena and Barry, 1969a; Krimmer and Barry, 1973). In 1964, Belleville demonstrated that morphine could produce state-dependent learning. The efficacy of morphine as a discriminative stimulus was first observed by Hill *et al.* (1971). Attempts to characterize the stimuli produced by morphine have been few in number. It has been reported that (a) morphine will not substitute for Δ^1-THC in rats trained with the latter drug (Barry and Kubena, 1972), (b) lysergic acid diethylamide will not substitute for morphine in morphine-trained rats or vice versa (Hirschhorn and Rosecrans, 1974), and (c) naloxone, a narcotic antagonist, blocks the stimuli produced by morphine Rosecrans *et al.*, 1973). Antagonism of the stimulus properties of both ethanol and morphine has been observed following treatment with *p*-chlorophenylalanine, a depletor of 5-hydroxytryptamine (Rosecrans *et al.*, 1973; Schechter, 1973).

A general method for the comparison of the stimulus properties of drugs was described previously (Winter, 1973; 1974a, b). With minor modifications, this method has been employed in the present investigation to (a) establish the efficacy of morphine and ethanol as discriminative stimuli when each is paired with saline and (b) compare, in a qualitative sense, the stimulus properties of morphine and ethanol. In an attempt to more clearly delineate the pharmacologic basis for morphine and ethanol-induced discriminated responding, the effects of naloxone and propranolol upon such responding were examined. Finally, the stereospecificity of the stimuli produced by morphine was determined by a comparison, in morphine-trained rats, of levorphanol, a morphine-

like narcotic analgesic, and dextrorphan, the dextro isomer of levorphanol, which is devoid of activity as a narcotic agonist (Jaffe, 1972).

Methods

Subjects. Female CFN strain rats (Carworth Farms, New City, N.Y.) were housed in individual cages and maintained at 70–80% of the expected free-feeding weight by adjusted feedings after each experimental session. Water was freely available in the home cage. Prior to these experiments, the rats had received neither drugs nor behavioral training.

Apparatus and Procedures. The apparatus employed in these experiments and the procedures for initial training of drug discriminations have been described previously (Winter, 1973, 1974a). In the present experiments, the total number of responses in all test sessions was recorded as was the latency to the first response. Preliminary analysis suggested that although latencies were indeed shorter in S^D as compared with S^Δ sessions, initial response rates provided a more reliable indication of discriminated responding. Consequently, only the latter measure is reported here.

To determine the degree of similarity of the stimulus properties of other drugs to those of morphine, tests were conducted in which ethanol, levorphanol, and dextrorphan were administered to morphine-trained animals. Similar tests were conducted with morphine in ethanol-trained subjects. The general procedure for the conduct of cross-tests has been discussed previously (Winter, 1974a). In brief, the agent to be cross tested (Y) is administered in increasing doses to subjects trained with a second drug (X) as S^Δ. A dose of Y is found which mimics the action of X, *i.e.*, a low rate of responding appropriate for the S^Δ condition. This dose of Y is then cross-tested in subjects with X as S^D.

Sessions in which the ability of one drug to antagonize the stimulus properties of a second are similar to cross tests in that (a) sessions are terminated 2 min after emission of the first response (b) a minimum of one S^D and one S^Δ test-session precedes each test of antagonism and (c) responses have no programmed consequence. However, because the maximum dose of a purported antagonist which can be tested is that which itself does not suppress responding, the order of tests for antagonism is reversed as compared with cross-tests, *i.e.*, the antagonist (Z) is first administered to subjects trained with a second drug (X) as S^D. A dose of Z is found which, in combination with the training dose of X, yields a response rate appropriate for the saline (S^Δ) condition. To determine whether this result reflects antagonism of the discriminative properties of X by Z or is the consequence of non-specific suppression of responding, the same dose of antagonist is tested in subjects trained with X as S^Δ.

Statistical Analysis. Two groups of 6 rats each were trained with morphine and saline (group I-1: S^D = saline, S^Δ = morphine; group I-2: S^D = morphine, S^Δ = saline). Two additional groups of 4 rats each were trained with ethanol (group II-1: S^D = saline, S^Δ = ethanol; group II-2: S^D = ethanol, S^Δ = saline). The effect of the preceding training session upon a subsequent test was determined by obtaining, for each subject, the difference between the rate of responding in S^D tests following S^D training sessions and S^D tests following S^Δ training sessions as well as a similar difference score for the tests under S^Δ. The resultant values were tested for statistical significance by Wilcoxon's signed-ranks test for paired observations (Goldstein, 1964). Next, the data from each group were subjected to analysis of variance according to a two-factor design with repeated measures on one factor (Winer, 1971). A preliminary *F*-test of the data obtained from group I indicated non-homogeneity of variation and, for this reason, the data were subjected to a square root transformation prior to analysis of variance. Differences were considered to be significant if the probability of their having arisen by random sampling alone was < 0.05.

Drugs. Morphine sulfate (Mallinkrodt Chemical Works, St. Louis, Mo.), naloxone hydrochloride (Endo Laboratories, Inc.), levorphanol tartrate (Hoffman-LaRoche Inc.), and dextrorphan tartrate (Hoffman-LaRoche Inc.) were dissolved in a 0.9% saline and injected in a constant volume of 1 ml/kg b.wt. Ethanol was administered as a 10% volume/volume solution in saline. *Levo*-propranolol (Ayerst Laboratories, Montreal, Canada) was injected in a concentration of 10 mg/ml saline. All injections were i.p.

Results

Morphine and Ethanol as Discriminative Stimuli. The initial step in the comparison of the stimulus properties of morphine and ethanol was to establish that each could function as a discriminative stimulus. Gross differences in response rate under S^D and S^Δ stimulus conditions were consistently observed in all subjects. Mean rates (responses/minute $\pm$ S.E.) in sub-group I-1 were 40 $\pm$ 4 and 5 $\pm$ 2 for the S^D (saline) and S^Δ (morphine) conditions, respectively. In sub-group I-2 (S^D = morphine; S^Δ = saline), the corresponding rates were 44 $\pm$ 5 and 6 $\pm$ 2. Mean rates in sub-group II-1 were 41 $\pm$ 8 and 8 $\pm$ 4 for the saline (S^D) and ethanol (S^Δ) conditions, respectively. The corresponding values for sub-group II-2 (S^D = ethanol; S^Δ = saline) were 44 $\pm$ 6 and 7 $\pm$ 2. Analysis of variance revealed that, of the two possible main effects, only the S^D and S^Δ stimulus conditions had a significant influence upon the rate of responding (morphine: $df = 1, 10$; $F = 153$; $P < 0.001$; ethanol: $df = 1, 6$; $F = 73$; $P < 0.001$). In neither group did the *F* ratio for the interaction term reach the level of statistical significance. Prior to the analyses of variance for the ethanol and morphine groups, it was determined that the nature of the training session preceding a test session had no significant effect upon the outcome of the latter.

After the demonstration that the effects of morphine and ethanol could, when paired with saline, serve as discriminative stimuli, cross-tests were conducted, *i.e.*, morphine trained animals were tested with ethanol and vice versa. The general procedure for such cross-tests has been described above. The initial dose of ethanol and of morphine which was tested was that which had been established as effective when paired with saline. These doses (ethanol: 630 mg/kg; morphine: 6 mg/kg) were followed by intermediate rates of responding (50 $\pm$ 11% and 79 $\pm$ 16% of S^D-rate, respectively) in subjects trained with morphine

Table 1. Effects of naloxone upon the discriminative properties of morphine and ethanol

Subgroup	N[a]	S^D		S^Δ		Test of antagonism[d]	
		Stimulus[b]	Response[c] rate (S.E.)	Stimulus[b]	Response rate (S.E.)	Stimulus	Response rate (S.E.)
I-1	6	Saline	53 (4)	Morphine	2 (1)	Morphine + naloxone	43 (11)
I-2	6	Morphine	62 (7)	Saline	6 (2)	Morphine + naloxone	9 (3)
II-1	4	Saline	58 (12)	Ethanol	3 (1)	Ethanol + naloxone	1 (1)
II-2	4	Ethanol	73 (6)	Saline	5 (3)	Ethanol + naloxone	74 (6)

[a] N, number of subjects.
[b] Morphine · SO_4 (6 mg/kg) injected i.p. 60 min before testing. Ethanol (630 mg/kg) injected i.p. 20 min before testing.
[c] Measured as responses per minute during the initial 2 min of test sessions.
[d] Naloxone · HCl (0.4 mg/kg) injected i.p. 15 min before test sessions.

and ethanol as the S^Δ condition. However, a doubling of the test doses of ethanol and morphine yielded rates ($3 \pm 2\%$ and $7 \pm 1\%$ respectively) similar to those seen under S^Δ ($2 \pm 3\%$ and $2 \pm 1\%$, respectively). However, when the same test doses of ethanol and morphine were examined in subjects trained with morphine and ethanol, respectively, as the S^D condition, no similarity in stimulus properties was apparent, *i.e.*, response rates did not significantly exceed that observed in the saline condition (S^Δ).

Interaction of Naloxone with Morphine and Ethanol. The general method for the testing of antagonism of discriminative properties of drugs has been described above. The results obtained from animals treated with naloxone (0.4 mg/kg) and either morphine or ethanol are presented in Table 1. Antagonism was also attempted in all subjects with a lower dose of naloxone (0.1 mg/kg) but it was uniformly without effect. In Table 1, it is seen that animals for whom morphine was either S^D or S^Δ responded in a fashion appropriate for the saline condition when treated with morphine plus naloxone. In contrast, response rates in ethanol-trained subjects were unaffected by pretreatment with naloxone.

Interaction of Propranolol with Morphine and Ethanol. The combination of progressively higher doses of propranolol (3, 10, and 30 mg/kg) with either morphine or ethanol in rats trained with the latter drugs as the S^D condition led to a decline in response rate until, at the highest dose, the rate was indistinguishable from that observed in the saline (S^Δ) condition. However, when the same doses of propranolol were administered to rats in which morphine and ethanol were trained as S^Δ, response rates remained appropriate for the S^Δ condition. Thus, the apparent antagonism of morphine and ethanol by propranolol seen in groups I-2 and II-2 is, in fact, a non-specific, rate-depressant effect.

Stereospecificity of the Stimulus Properties of Morphine. Data obtained in sub-group I-1 are shown in Fig. 1. Significant discrimination between the effects of saline and morphine is indicated by the clear separation of the points for sessions after saline (S^D, ●) and morphine (S^Δ, ▲). Intermediate doses of morphine (0.3 – 3 mg/kg, ○) yielded a dose-effect curve with a midpoint (50% of S^D-rate) at 0.7 mg/kg (estimated by eye). Similar dose-effect curves were obtained with levorphanol (0.1 – 1 mg/kg) and dextrorphan (3 – 10 mg/kg). The midpoints of these curves were at 0.25 mg/kg and 42 mg/kg, respectively. The highest doses of both drugs are followed by a rate of responding appropriate for the training dose of morphine (6 mg/kg). However, this suppression of responding could be due to (a) the similarity of the stimulus properties of levorphanol and dextrorphan to those of morphine or (b) a non-specific rate-depressant effect of the two drugs. The data of Fig. 2 suggest that the former explanation is applicable to levorphanol while the latter is appropriate for the results with dextrorphan. The same range of doses of morphine, levorphanol, and dextrorphan was tested in rats trained with saline as S^Δ (▲) and morphine (6 mg/kg, ●) as S^D. The midpoints for the morphine and levorphanol curves occurred at 1.7 mg/kg and 0.44 mg/kg respectively. Dextrorphan, over the range of doses tested, did not produce a dose-related increase in response rate nor was responding appropriate for the S^D (morphine) condition observed following any dose.

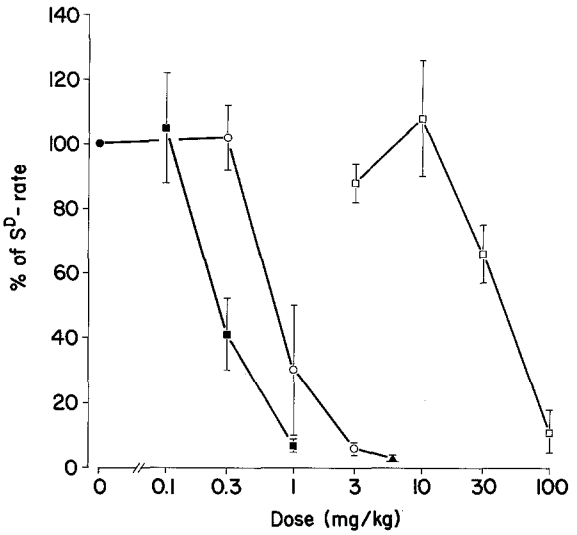

Fig. 1. Dose effect relationship for morphine (○), levorphanol (■), and dextrorphan (□) in rats trained to discriminate the effects of saline (S^D; ●) and morphine (S^{Δ}, ▲). All drugs injected i.p. 60 min before testing. Ordinate: mean rate of responding (± S.E.) expressed as a percentage of the S^D-rate. Abscissa: Doses of the respective salts plotted on a log scale

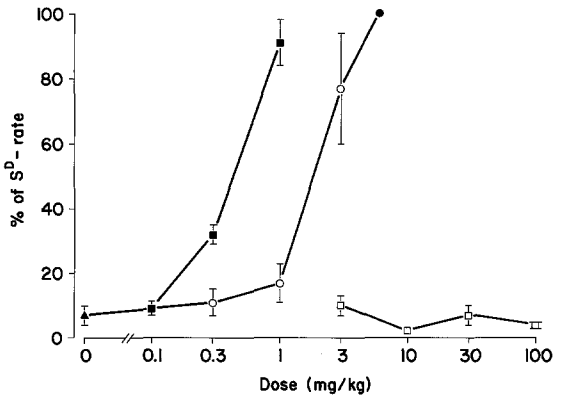

Fig. 2. Dose effect relationship for morphine (○), levorphanol (■), and dextrorphan (□) in rats trained to discriminate the effects of saline (S^{Δ}, ▲) and morphine (S^D, ●). All other details as in Fig. 1

Discussion

The rationale which underlies cross-tests such as those conducted in morphine and ethanol-trained subjects and illustrated in Figs. 1 and 2 is that if the stimulus properties of two drugs, X and Y, are similar then Y should substitute for X in X-trained subjects and vice versa. Examples of apparent equivalency of stimuli produced by two or more drugs are not uncommon (Barry, 1974) and are often predictable, *e.g.*, the effects in man of mescaline and lysergic acid diethylamide are quite similar (Hollister, 1968) and their stimulus properties appear to be indistinguishable in the rat (Hirschhorn and Winter, 1971). Although both morphine and ethanol may appropriately be classified as depressants of the central nervous system, the conclusion drawn from the present data that they are non-equivalent in terms of their stimulus properties is compatible with a vast body of information derived from studies of a variety of other pharmacologic effects in man as well as in animals. Furthermore, these data argue against the suggestion by Overton (1974) that "when rats learn a drug versus non-drug discrimination they (may) actually learn a rather generalized 'normal versus abnormal' discrimination...". Indeed, the present data indicate that the saline-appropriate response continues to be emitted by morphine and ethanol-trained rats even when cross-tested with doses of ethanol and morphine, respectively, which equal or exceed those required to establish stimulus control when paired with saline.

Interpretation of the data summarized in Table 1 appears unambiguous. Naloxone is an antagonist of many morphine-induced effects including analgesia, respiratory depression and, in man, euphoria (Martin, 1967). In contrast, no interactions between naloxone and ethanol have been reported. It is seen in Table 1 that the administration of naloxone (0.4 mg/kg) causes morphine-treated subjects to respond in a manner appropriate for the saline condition whether morphine had functioned as S^D or as S^{Δ}. In contrast, the same dose of naloxone was without effect upon discriminated responding mediated by ethanol. The present results are in agreement with the report by Rosecrans *et al.* (1973) that naloxone blocks the stimulus effects of morphine in a shock-escape task.

The literature with respect to interactions between propranolol and either morphine or ethanol is inconsistent. Propranolol has been reported to antagonize the effects of ethanol in animals (Smith *et al.*, 1970) and in man (Mendelson *et al.*, 1972) but a subsequent investigation by Mendelson and his colleagues (1974) found no evidence of blockade by propranolol of the acute effects of ethanol in chronic alcoholics. It has been suggested by Grosz and his associates that propranolol is an antagonist of certain of the effects of heroin (Grosz, 1972a, b) and morphine (DeFeudis and Grosz, 1972; Black and Grosz, 1974). The present results provide no evidence that propranolol antagonizes the stimulus properties of either morphine or ethanol. Schechter (1974) recently reported a similar inability of propranolol (1 – 20 mg/kg) to antagonize ethanol (1200 mg/kg) in a shock motivated discrimination. It was noted in the course of the present experiments that rats treated with propranolol in combination with morphine or ethanol seemed ataxic, a condition not observed in the absence of propranolol. A separate study (Winter, 1974c) was then conducted and it was found that propranolol potentiated the lethal effects of morphine.

The present results with propranolol provide illustrative material for the discussion of a general problem in the determination of the efficacy of purported antagonists of the stimulus properties of drugs. The maximum dose of an antagonist which can be employed is that which, in combination with the drug trained as a stimulus, is on the threshold of incapacitation of the subject, in the present instance that dose which suppresses food-motivated behavior. In the absence of demonstrable antagonism at doses below the incapacitating dose, it may be argued that antagonism would have been manifest had suppression of responding not intervened. It is apparent that this dilemma is of the same nature as that encountered in the evaluation of a drug of unknown efficacy as a discriminative stimulus in animals trained with a second drug, *i.e.*, the drug being cross-tested may suppress responding at doses below those required to demonstrate its stimulus properties. No general solution to these difficulties is at hand.

The antagonism of morphine by naloxone (Table 1; Rosecrans *et al.*, 1973) is reassuring in the sense that the actions of morphine as a stimulus are thus shown to be related to the classical effects of the drug. Further evidence that we are dealing with a typical opiate effect is provided by the data of Figs. 1 and 2. Not only are the stimulus effects of morphine shown to be stereospecific but also the apparent potency relationship between morphine and levorphanol is in reasonable agreement with that observed for analgesia in man. Following subcutaneous administration to human subjects, levorphanol's analgesic potency is reported to be 3.3 to 5 times that of morphine (Jaffe, 1972). The potency ratios for levorphanol estimated from Figs. 1 and 2 are 2.8 (0.7/0.25) and 3.9 (1.7/0.44), respectively. It seems reasonable to suggest that assessment of the stimulus properties of narcotic analgesics may provide a useful alternative or supplement to the determination of the analgesic, soporific, or reinforcing properties of these agents.

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