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RAPID COMMUNICATION

The Reinforcing Properties of the Mixed Agonist-Antagonist Buprenorphine as Assessed by Brain-Stimulation Reward

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HUBNER, C. B. AND C. KORNETSKY. *The reinforcing properties of the mixed agonist-antagonist buprenorphine as assessed by brain-stimulation reward.* PHARMACOL BIOCHEM BEHAV 30(1) 195–197, 1988.—The effect of buprenorphine on the threshold for rewarding brain stimulation to the medial forebrain bundle-lateral hypothalamus was determined in rats using a rate-independent psychophysical method. Increased sensitivity to rewarding brain stimulation (i.e., lowering of the reward threshold) was used as the measure of a drug's reinforcing action. Buprenorphine (SC) produced a significant dose-dependent lowering of the reward threshold, with effective doses varying from 0.004–0.06 mg/kg. These results are consistent with buprenorphine's euphoria producing effects in humans and its ability to sustain self-administration in animals and suggest that buprenorphine may have abuse potential.

Brain-stimulation reward Buprenorphine hydrochloride Reward threshold Drug abuse

BUPRENORPHINE hydrochloride is a mixed agonist-antagonist opioid that causes only minimal, if any, physical dependence in animals [1,18] and in man [8,12]. It has antinociceptive activity [1, 2, 6]. Subjects with histories of narcotic abuse report feelings of euphoria similar to those experienced with morphine [8]. It decreases heroin self-administration in heroin addicts [12,14] as well as opiate self-administration in the monkey [13].

Using the drug substitution model of self-administration in animals, Woods [17] reported that buprenorphine had lower reinforcing efficacy than codeine, heroin or morphine. Lukas *et al.* [10], using a similar procedure, reported that buprenorphine caused lower response rates when compared to codeine, butorphanol, nalbuphine or pentazocine.

In order to further characterize the reinforcing effects of buprenorphine the present study examined its effects on the sensitivity of the rat to rewarding brain stimulation. We have found that a variety of abused substances, e.g., morphine [11], cocaine [4], and d-amphetamine [5], lower the threshold for such stimulation.

METHOD

Four male F-344 albino rats (Charles River Laboratories, Inc., Wilmington, MA) weighing approximately 300 g were anesthetized with Chloropent® (0.3 ml/100 g body weight) and bipolar stainless steel electrodes (0.13 mm in diameter) (Plastic Products, Roanoke, VA) were stereotaxically implanted with tips of the electrodes aimed at lateral hypothalamic region of the medial forebrain bundle (MFB-LH coordinates: 4.0 mm posterior to bregma, 1.4 mm lateral from the midline suture, and 8.5 mm ventral to the skull surface). The electrodes were placed through small burr holes in the skull and attached permanently to the surface with an acrylic platform. After surgery, animals received 60,000 units of penicillin (Bicillin®) IM and were given at least one week for post-operative recovery before behavioral testing was begun. Animals were maintained on a 12-hour light/dark cycle, housed individually in stainless steel cages, and had ad lib access to food and water.

Animals were trained and tested in an acrylic chamber

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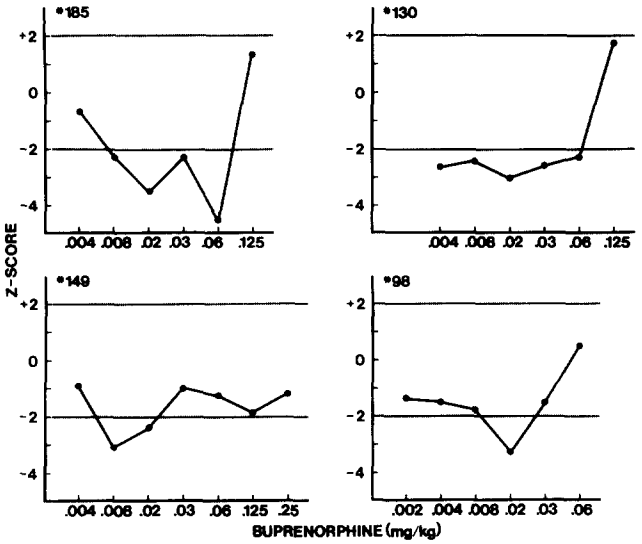

FIG. 1. The effect of buprenorphine on the threshold for rewarding brain stimulation in each of four animals. The dose-response curves represent the standard score (z-score) changes in the reward threshold value from pre- to post-drug as a function of dose of buprenorphine for each of 4 animals. A z-score of ±2.0 indicates the 95% confidence limits based on the mean and standard deviation for all saline days.

(20×20×35 cm) on a rate-independent threshold procedure previously described [3]. A cylindrical manipulandum (15 cm in length and 7.5 cm in diameter) was mounted within one wall of the test chamber. Four equally spaced cams on one endplate of the manipulandum operated a microswitch which resulted in immediate delivery of a stimulation when the manipulandum was rotated one-quarter of a turn. A constant current stimulator (Sunrise Systems, Pembroke, MA) was used to deliver the 500 msec stimulation which consisted of biphasic symmetrical rectangular pulses occurring at a frequency of 160 Hz, with a pulse width of 0.2 msec, and an intervening delay of 0.2 msec between the positive and negative pulses. Stimulus intensities were varied using a modification of the classical psychophysical method of limits. Thresholds were determined by a procedure involving the use of discrete trials systematically presented over a range of stimulus intensities. A trial began with the delivery of a non-contingent intracranial stimulus. A response of one-quarter wheel turn within 7.5 sec of this stimulus resulted in the delivery of a contingent stimulus, identical in all parameters to the non-contingent stimulus, and terminated the trial. Failure to respond had no scheduled consequences and the trial was terminated after 7.5 sec. The interval between trials varied around an average of 15 sec and responses made during the intertrial interval (error responses) resulted in a 15 sec delay before the start of the next trial. Stimuli were presented in an alternating descending and ascending series with a step size of 3, 5 or 10 μA, depending on the sensitivity of the individual animal.

Animals required approximately four one-hour training sessions to learn the task and approximately four additional sessions for the establishment of a stable threshold level whereupon subcutaneous vehicle (saline) injections were begun. Animals were tested with vehicle injections for at least 5 days before drug administration was initiated. Buprenorphine hydrochloride was dissolved in isotonic saline and administered subcutaneously. All injections were made in volumes of 1 ml/kg body weight and the sequence of doses was counter balanced between animals. Vehicle days were interspersed between each day of drug treatment so that animals received drug only twice weekly.

Threshold values were calculated for both the pre-injection and the post-injection of each session, with the difference between the two scores taken as the dependent measure. The threshold difference scores for drug days were transformed to standard scores (z-scores) based on the mean and standard deviation of the threshold difference scores for all vehicle control days. A z-score that exceeded 2.0 (greater than the 95% confidence limits) was preselected as the level of significance. Dose-effect curves based on z-scores, were generated for each of the four animals.

RESULTS

Figure 1 depicts the effect of buprenorphine on the threshold for rewarding brain stimulation. Individual dose-response curves, based on z-scores which reflect changes in threshold difference scores for drug days compared to mean difference score changes obtained on vehicle control days, are shown for each of the four animals tested. The mean post- minus pre-change in threshold ± the standard deviation after the saline treatment was 11.8±8.4, 2.1±1.9, 2.1±2.1, and 8.1±6 μA for animal 185, 130, 149 and 98, respectively. Significant lowering of the reward threshold was obtained in all animals, with the effective doses being between 0.004–0.06 mg/kg. A significant decrease in the threshold was obtained at doses of 0.008–0.6 mg/kg for No. 185, 0.004–0.06 mg/kg for No. 130, 0.008–0.02 mg/kg for No. 149 and 0.02 mg/kg for No. 98. The U-shape of the dose-response curve is characteristic of all drugs that lower the threshold. The upward turn of the curve is probably the result of competing actions of the drug that occur at higher doses.

DISCUSSION

Buprenorphine clearly increased the sensitivity of all four animals to rewarding brain stimulation as indicated by the significantly lowered stimulation thresholds. This effect on brain-stimulation reward is not different from that seen with other abuse substances and specifically not different from other abuse opiate drugs.

The threshold lowering effect of buprenorphine also is not different from other mixed agonist-antagonists that we have tested, pentazocine [15] and nalbuphine [16]. Pentazocine had been abused, primarily in combination with tripelennamine, commonly referred to as T's and Blues. In the case of nalbuphine, Jasinski and Mansky [7] concluded from studies in opiate users that nalbuphine possesses some properties that could lead to its abuse.

Although self-administration studies in animals suggest that the abuse liability seems less than that seen with many other opiate drugs, studies in human subjects do suggest abuse potential. The effect of single doses [8] and direct addiction [8,12] in subjects with a history of narcotic abuse indicate that buprenorphine is primarily classified by these subjects as an opiate with euphoric effects typical of morphine. This is supported by reports of buprenorphine abuse by opiate users when their preferred drug is unavailable [9].

In summary, buprenorphine lowers the threshold for rewarding brain stimulation, an action that is consistent with its euphoria producing effects in humans and its ability to sustain self-administration in animals.

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