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Chlorpromazine and Brain-Stimulation Reward: Potentiation of Effects by Naloxone[1]

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ESPOSITO, R. U., W. PERRY AND C. KORNETSKY. *Chlorpromazine and brain-stimulation reward: Potentiation of effects by naloxone*. PHARMAC. BIOCHEM. BEHAV. 15(6)903–905, 1981.—Chlorpromazine (0.25–2.0 mg/kg IP) raised the threshold for brain stimulation reward in a dose-dependent manner in rats. Naloxone (4.0 mg/kg IP) administered alone was without effect on this behavior. However, this dose of naloxone administered concurrently with chlorpromazine produced substantial potentiation of the threshold increases. These results strongly suggest a catecholaminergic-enkephalinergic involvement in the regulation of central reward processes.

Brain-stimulation reward Chlorpromazine Naloxone Enkephalin Schizophrenia

IN early studies of the effects of drugs on self-stimulation behavior Olds reported that chlorpromazine, an antipsychotic phenothiazine, depressed self-stimulation behavior in rats, while promethazine, a non-antipsychotic phenothiazine, augmented this behavior [11,12]. Subsequent research has confirmed that clinically useful antipsychotic drugs uniformly suppress self-stimulation behavior in a dose-related manner [18]. In addition, other experiments, with both rats and monkeys, have shown that chlorpromazine will elevate the self-stimulation threshold, while amphetamine was found to have the opposite effect [15,16]. These opposite effects are believed to be related to their opposing actions on catecholaminergic neurotransmission [7]. Recently, we have reported that the threshold lowering effect of amphetamine can be blocked by the opiate antagonist naloxone [6], suggesting a critical interaction between central catecholamine neurons and endogenous opioids in the mediation of central reward processes. We now report that, conversely, naloxone will potentiate the threshold raising effect of chlorpromazine on brain-stimulation reward.

METHOD

Animals and Apparatus

Four male albino rats, approximately 300 g (CDF strain from Charles River Breeding Laboratories) were stereotaxically implanted with bipolar, insulated (except at tips), stainless steel electrodes (0.15 mm in dia.) aimed at the ventral tegmental area (VTA), or the medial forebrain bundle (MFB). Coordinates for the MFB and VTA placements were respectively: −4.0 mm from bregma, 1.4 mm lateral from the midline suture, and 8.5 mm dorsal from the skull surface; +2 mm from lambda, 1.4 mm from the midline suture and 8.0 mm dorsal from the skull surface. After recovery from surgery, the animals were trained on the threshold determination procedure in a plastic chamber (20×20 cm). Mounted in an opening in one wall of the chamber was a cylindrical manipulandum which was 15 cm long and 7.5 cm in diameter. Turning the manipulandum one-quarter turn resulted in the delivery of a rewarding stimulus to the animal's brain. A constant current stimulator (Sunrise Systems, N. Scituate, MA) was used to deliver the stimuli which consisted of 0.5 sec trains of biphasic symmetrical pulses. Each train occurred at a frequency of 160 Hz, with a pulse width of 0.2 msec and 0.2 msec between the positive and negative pulses. Pulse amplitude was varied according to the procedural requirements for threshold determination.

Thresholds were determined by a modification of the classical method of limits wherein the stimuli were presented in ascending and descending series with a number of trials given at each intensity. This method is described in greater detail in Esposito and Kornetsky [4]. Each test session the reward threshold was determined prior to and immediately after intraperitoneal injections of either saline or drug. The drugs, chlorpromazine hydrochloride (0.25–2.0 mg/kg) and naloxone hydrochloride (4.0 mg/kg) were dissolved in a 0.9%

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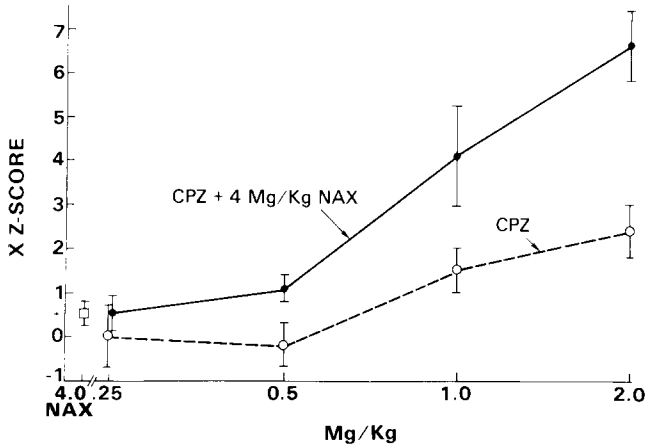

FIG. 1. Mean standard ($\bar{z}$), ± 1 standard error, scores for chlorpromazine (CPZ) alone and in combination with 4 mg/kg of naloxone (NAX). The effects of 4 mg/kg of naloxone alone are shown in the left side of the figure.

saline vehicle and delivered in a volume of 1.0 ml/kg. When the two drugs were given together the naloxone was injected first, followed immediately by the chlorpromazine injection. The doses were randomly administered for each subject. Saline injection days were always interspersed between the drug test sessions. Threshold values were calculated for both the pre-drug and post-drug sessions, with the difference between these two scores taken as the critical dependent measure. These difference scores were transformed to standard scores (z-scores) based on the standard deviation of the difference scores for all saline days. A z-score of 2.00 (95% confidence limit) was selected as the level of significance.

After completion of behavioral testing, the animals were sacrificed with an overdose of Equi-Thesin® and perfused intracardially with saline and then Formalin. The brains were subsequently removed from skull, fixed, embedded, and sectioned at 40 μ. Sections were stained with cresyl violet and Luxol Fast blue, and examined under a light microscope to determine the site of electrode placement.

RESULTS

The results are shown in Fig. 1. Chlorpromazine, by itself, produced dose-related increases in the threshold. This effect was potentiated in all subjects by the co-administration of naloxone (4.0 mg/kg). It is important to note that in most instances the potentiation occurred in the absence of any gross behavioral change. However, in some instances at the higher combination doses, some of the animals exhibited tremors, twitching, head bobbing, gnawing, and chewing behaviors. Only in one instance did an animal fail to resume responding at a current intensity of 255 μA which was the highest intensity that the stimulator would deliver.

Histological analysis revealed that three of the animals had electrode tips in or adjacent to the ventral tegmental nucleus, while the fourth animal's electrode tip was in the MFB at the level of the lateral hypothalamus.

DISCUSSION

It is difficult to characterize the precise nature of the chlorpromazine induced threshold elevations. Not only does chlorpromazine raise the threshold for rewarding brain stimulation, but it has been reported that it will raise the threshold for peripheral nociceptive stimulation and this effect is potentiated by naloxone [9,10]. As we have suggested previously [5], the threshold elevating effect of antipsychotic agents probably does not reflect a simple blunting of the hedonic effect of the stimulation, but, rather seems to represent a more subtle behavioral disruption involving aspects of both reward and attention. Naloxone, which by itself has no effect on brain stimulation reward thresholds [6,13], augmented the chlorpromazine effect by some, as yet, undefined mechanism. These results extend our previous findings with naloxone and amphetamine, rendering further evidence for a functional relationship between the catecholaminergic and enkephalinergic systems, particularly with respect to the brain's reward pathways. These data are in accordance with the growing body of biochemical and anatomical evidence suggesting a neuromodulatory influence of the opioid peptides on central catecholamine neurons [1,14].

Finally, our results may have relevance for the recent clinical studies concerned with the potential use of naloxone in the treatment of schizophrenia. Although the results of these clinical trials are mixed, several studies have demonstrated reductions in hallucinations and bizarre thought content [2, 3, 8, 17]. These latter studies, in contrast to those which have found no therapeutic effects, have generally employed larger doses, involved longer observation periods, and in many instances studied subjects who were concurrently receiving neuroleptic medication. The present results suggest that there may be a population of schizophrenics who will benefit more from the concurrent administration of neuroleptics and naloxone than from the administration of either agent alone.

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