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Sedation and the Stimulus Properties of Antihistamines

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WINTER, J C *Sedation and the stimulus properties of antihistamines* PHARMACOL BIOCHEM BEHAV 22(1) 15–17, 1985 —A group of six rats was trained to discriminate the effects of diphenhydramine (10 mg/kg, 30 min pretreatment time) and saline in a two-lever choice task using a fixed ratio schedule of water reinforcement. Stimulus control was assumed to be present when 80% or more of the first ten responses were appropriate for the treatment condition on each of five consecutive days. Diphenhydramine established stimulus control in each of the subjects The mean number of sessions prior to the onset of criterion performance was 26 (standard error=7) A second group of six rats was similarly trained with chlorpheniramine (10 mg/kg, 30 min pretreatment time) and saline Four of the group reached criterion performance in a mean of 56 sessions (SE=7) The diphenhydramine stimulus generalized completely to promethazine, azatidine, and chlorpheniramine In rats trained with chlorpheniramine, only promethazine and azatidine substituted completely while diphenhydramine yielded intermediate results, i e , significantly different from both training conditions It is concluded that the relative propensity of antihistamines to induce sedation in humans is not correlated with distinctive stimulus properties in the rat

Stimulus control Diphenhydramine Chlorpheniramine Promethazine Azatidine

RECEPTORS for histamine are conveniently classified as H1 and H2 [2,4]. Antagonists at H1 receptors have been in clinical use for nearly forty years for the treatment of the symptoms of various allergic reactions [5]. Although the sedative properties of the H1 antagonists are of value in their use as anti-anxiety agents, sedation is regarded as an adverse effect in treating allergic disorders. Barnett *et al.* [3] have recently pointed out that the major difficulty in identifying antihistamines for clinical use is the very poor correlation between sedative liability in laboratory animals and in man.

In the present investigation, the properties of representative H1 antagonists as discriminative stimuli have been examined in an attempt to develop a means to predict, in the rat, the sedative liability of antihistamines in human subjects. The only previous study of the stimulus properties of H1 antagonists was by Overton [6] Using a shock-escape T-maze task, he demonstrated the discriminability from saline of diphenhydramine (DPH), pyrilamine, and diminhydrinate in rats. Based on the observation that the H1 antagonists generalized to each other but not to drugs of other classes, Overton suggested that H1 antagonists possess "relatively unique" stimulus properties Although drowsiness may occur following any of the H1 antihistamines in clinical use, it is generally assumed that differences do exist and that the ethanolamines, exemplified by DPH, are most sedative and the alkylamines, of which chlorpheniramine (CPR) is prototypic, are relatively less sedative [5] It is for this reason that DPH and CPR were chosen for initial evaluation in the present study. DPH and CPR-trained subjects were then tested with a range of doses of DPH, CPR, and two other drugs, promethazine, a "sedative" antihistamine [5], and azatidine, a "less sedative" antihistamine [1]

METHOD

Animals

A total of 12 female Wistar strain rats were used in these experiments. They were housed in pairs in quarters exposed to a natural light cycle. Body weights were maintained at about 80% of normal by restriction of water intake. Rat chow was freely available in the home cage. Prior to these experiments, the rats had received neither drugs nor behavioral training

Apparatus

Four standard small animal test chambers (Coulbourn Instruments model E10-10) housed in larger light-proof, sound-insulated boxes were used for all experiments. The chambers contained two levers mounted at opposite ends of one wall. Centered between the levers was a dipper which delivered 0 1 ml of tap water

Procedure

Subjects in Group I (N=6) were trained with DPH (10 mg/kg) and saline in a 2-lever response choice task. After the rats learned to drink from the dipper, they were trained to depress first one and then the other of the two levers. After responding was established on both levers, discrimination training was begun Each 10-minute session was preceded by one of two treatments, following DPH, every tenth response

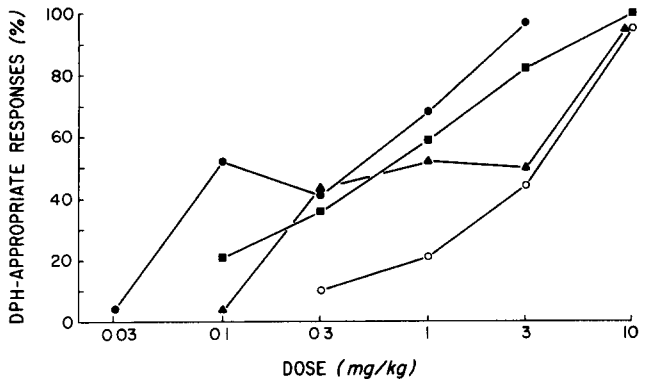

FIG 1 Dose response relationship for DPH (○), CPR (▲), promethazine (●), and azatidine (■) in rats trained with DPH (10 mg/kg) and saline in a 2-lever choice task Each point represents the mean of 2 determinations in each of 6 subjects. *Ordinate* Percentage of the first 10 responses which were emitted on the DPH-appropriate lever *Abscissa* Doses of drugs expressed on a log scale All injections were IP, 30 min before testing

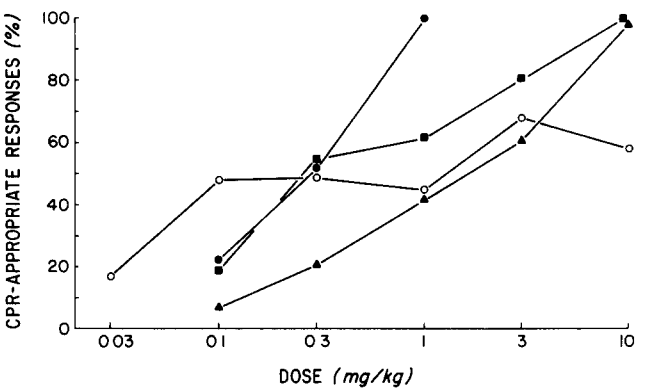

FIG 2 Dose response relationships for CPR (▲), DPH (○), promethazine (●), and azatidine (■), in rats trained with CPR (10 mg/kg) Each point represents the mean of 2 determinations in each of 4 subjects. *Ordinate* Percentage of the first 10 responses emitted on the CPR-appropriate lever *Abscissa* Doses of drugs expressed on a log scale All other details as in Fig 1

on the DPH-appropriate lever was reinforced and, in a similar fashion, responses on the saline-appropriate lever were reinforced following the injection of saline. For 3 subjects, the left lever was designated as DPH-appropriate and, for the remaining subjects, responses on the right lever were reinforced following DPH. During discrimination training, drug and saline were alternated on a daily basis. Drug-induced stimulus control was assumed to be present when, in five consecutive sessions, 8 or more of the initial 10 responses were on the appropriate lever. Subjects in group II (N=6) were trained in a similar fashion using CPR (10 mg/kg) and saline as the drug treatments.

The ability of other drugs or other doses of the training drug to substitute for DPH (Group I) or CPR (Group II) was determined in sessions which were terminated after the emission of 10 responses and in which no responses were reinforced. Such sessions are referred to as cross tests Response distribution between the two levers during cross tests was compared with the distributions in immediately preceding drug (either DPH or CPR) and saline sessions (henceforth referred to as control sessions). All cross test data were compared with control data by means of individual applications of Wilcoxon's signed ranks test (one-tailed). Differences were considered to be significant if they would by expected to arise by random sampling alone with a probability less than 0.025.

Drugs

Diphenhydramine HCl, chlorpheniramine maleate, promethazine HCl, and azatidine maleate were dissolved in 0.9% saline solution and injected in a constant volume of 1 ml/kg body weight

RESULTS

All subjects of Group I exhibited drug-induced stimulus control when trained with DPH (10 mg/kg) and saline The mean rate of responding in training sessions with DPH was not significantly different from that following the administration of saline. The mean number of sessions to criterion performance was 26. Individual values were 10, 14, 16, 39, and 51 sessions Four of the 6 subjects trained with CPR (10 mg/kg) achieved criterion performance after a mean of 56 sessions. Individual values were 38, 56, 60, and 70 sessions The remaining 2 subjects were discarded after 75 sessions CPR caused a modest but statistically significant decrease in response rate to 88% of that observed following the administration of saline Figure 1 shows the results of tests of a range of doses of DPH (○), CPR (▲), promethazine (●), and azatidine (■), in Group I. For each of the drugs, a dose-response function was obtained that ranged from saline-appropriate to complete substitution

In contrast with the effects of CPR in subjects trained with DPH, it is seen in fig. 2 that DPH produces intermediate responses in rats trained with CPR and saline Furthermore, a pattern of responding different from both training conditions extended over a range of two log units. Cross tests with a range of doses of promethazine and azatidine yielded full dose-response functions which ended with complete substitution.

DISCUSSION

The present experiments tested the hypothesis that clinically demonstrable differences in sedative liability of antihistamines are reflected in distinctive discriminative stimuli in the rat Two "sedative" antihistamines, diphenhydramine and promethazine, and two "less sedative" antihistamines, chlorpheniramine and azatidine, were examined. Stimulus control was more readily established by DPH than by CPR and only 4 of 6 subjects reached criterion performance with the latter drug. However, stimulus control by CPR, once established, was quite stable for the duration of the experiments In general, the data did not support the hypothesis in that CPR, azatidine, and promethazine fully substituted for DPH in DPH-trained rats (Fig. 1). Furthermore, promethazine and azatidine substituted completely for CPR in CPR-trained animals (Fig 2) The only exception to these patterns of generalization was the failure of DPH to fully mimic CPR (Fig 2) Taken together, these data indicate that the relative propensity of antihistamines to induce sedation in humans is not correlated with distinctive stimulus properties in the rat.

ACKNOWLEDGEMENTS

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