Effect of Chlorpromazine on Antidiuretic Response to Noxious Stimuli.* (24241)

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Exposure of animal or man to noxious stimuli results in an antidiuretic response(1,2,3) with which is associated an increase in the antidiuretic activity of the plasma(3,4,5). Since administration of chlorpromazine reduces the anxiety provoking effect of various environmental stimuli(6,7), it became of interest to examine the effect of such treatment on antidiuretic response to different types of noxious stimuli.

Materials and methods. Male albino rats of the Carworth strain, weighing from 120-200 g, were used after a preliminary fast of approximately 16 hours during which time the animals were permitted access to water. During the experiment the rats were kept in individual metabolic cages. The animals were given 5 ml 0.2% NaCl per 100 g body weight by stomach tube and one hour later the gavage was repeated. At 20 minute intervals after the second gavage, volume of urine excreted was measured. All rates of excretion were expressed as ml/100 g of body weight. The animals were handled and prodded just prior to each measurement of urine volume in order to ensure the emptying of their bladders. The noxious stimulus was applied at 20 minutes after the second gavage.

Three types of noxious stimuli were used in this study. One group of rats was exposed to painful stimuli produced by a 2 minute period of mild electric shocks (50 volts, 60,000 ohms) to the feet *via* a grid which made up the floor of the metabolic cage. A second group of rats was given an intraperitoneal injection of 1 mg histamine dihydrochloride. A third group of rats was given an intraperitoneal injection of 0.1 mg nicotine-tartrate per 100 g body weight. For each experimental group another group of rats was used as controls in that the rats were not exposed to noxious stimuli; those animals which served as controls for the histamine and nicotine treated groups received an injection of an equivalent amount of normal saline. A similar number of groups of rats were treated the same way except that they were given a subcutaneous injection of 0.25 mg chlorpromazine per 100 g body weight 60 minutes before the first gavage.

Results. The rate of secretion of urine by the rats used as controls was fairly constant after the second gavage while the animals exposed to noxious stimuli developed an antidiuretic response (Fig. 1 A). Whereas the group which served as its control excreted 1.54 $\pm$ 0.08 ml urine per 100 g body weight during the second 20 minute interval, the group of rats which was exposed to painful stimuli excreted 0.88 $\pm$ 0.09 ml during the same interval. The difference between the 2 rates was statistically significant ($P<0.001$).

A more intense antidiuretic response followed administration of histamine and nicotine (Fig. 1 A). Thus, the animals treated with histamine excreted 0.48 $\pm$ 0.12 ml while their controls excreted 1.64 $\pm$ 0.11 ml during the 20-minute interval after injection ($P<0.001$). During the 20 to 40 minute interval after injection of histamine the rats excreted 0.39 $\pm$ 0.11 ml while their controls excreted 1.31 $\pm$ 0.10 ml. Likewise, during the same interval the nicotine-injected animals excreted 0.60 $\pm$ 0.13 ml while their controls excreted 1.60 $\pm$ 0.12 ml ($P<0.001$).

Administration of 0.25 mg chlorpromazine per 100 g body weight produced a statistically significant but transient antidiuretic response. Whereas the saline treated groups excreted 1.82 $\pm$ 0.13 ml during the first hour after the first gavage, the chlorpromazine treated rats excreted 1.35 $\pm$ 0.14 ml during the same interval ($P<0.02$). However, during the hour after the second gavage the saline treated rats excreted 4.3 $\pm$ 0.12 ml while the chlorproma-

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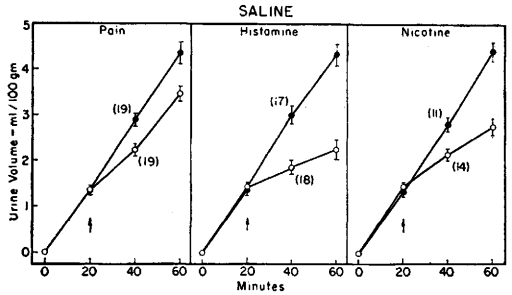

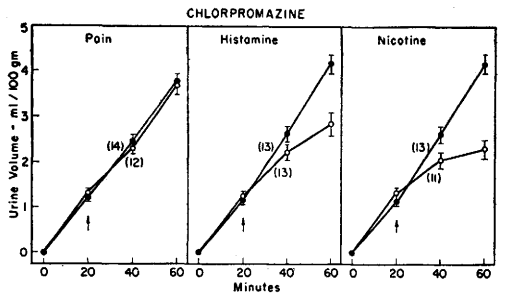

FIG. 1A (top). Antidiuretic response of saline treated rats to noxious stimuli.

FIG. 1B (bottom). Antidiuretic response of chlorpromazine treated rats to noxious stimuli. The mean ± SE ml excreted per 100 g of body wt of the groups that served as controls are designated by closed circles and that of the groups exposed to noxious stimuli by open circles. Numerals refer to No. of animals in each group. Arrows indicate time at which noxious stimulus was applied.

zine treated groups excreted 3.96 ± 0.14 ml. The difference between the two groups was statistically not significant. Accordingly, the antidiuretic effect of chlorpromazine appears to be an evanescent one.

Exposure to painful stimuli did not result in an antidiuretic response in the chlorpromazine treated rats (Fig. 1 B). Administration of histamine, however, produced a significant antidiuretic response which was most apparent during the third 20-minute interval after the gavage. Antidiuretic response to injection of nicotine (Fig. 1 B) was as marked as that observed in the saline-treated controls (Fig. 1 A).

Discussion. The dosage of chlorpromazine used in this study was twice that necessary for complete extinction of a conditioned avoidance response(6). Such dosages, however, have no apparent analgesic properties since the rats appeared to experience the pain as exhibited by their behavioral responses. Yet, pretreatment with chlorpromazine prevents the antidiuretic response which otherwise occurs in rats exposed to painful stimuli. The fact that such pretreatment does not influence significantly the antidiuretic response to injection of histamine or nicotine suggests that whereas the latter agents act directly in the hypothalamus, the effect of painful stimuli is mediated by more centrally placed mechanisms. This hypothesis is in accord with the data which indicate that chlorpromazine acts principally on the reticular system(8,9).

Summary. Administration of chlorpromazine inhibits the antidiuretic response of rats to painful stimuli but has no significant effect on antidiuretic response to injection of either histamine or nicotine.

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