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Changes of thirst threshold produced by chlorpromazine

The effect of chlorpromazine on the activity of the hypothalamohypophyseal antidiuretic system has been described by Kovacs, Kovacs & others (1957), Moses (1964) and Boris & Stevenson (1967). As this system is morphologically and functionally close to the hypothalamic thirst centre it could be supposed that chlorpromazine might also effect the mechanism of thirst.

We have investigated the effect of chlorpromazine on the osmotic reactivity of thirst mechanism. The experiments were made with 10 mongrel dogs, 13–22 kg, fasted for 18 h but with free access to water. The osmotic reactivity of the thirst mechanism was examined under control conditions and after intravenous infusion of chlorpromazine, and was measured as the thirst threshold in relation to osmotic stimuli (Wolf, 1950). A solution of saline (5%) was infused (6·4 ml/min) into the saphenous vein of a dog having free access to water and with freedom of movement. When the dog began to drink, the infusion was stopped, and it was assumed that the osmotic load induced by the infusion had reached the thirst threshold. Measurements of the volume of water ingested, the volume of urine produced, and quantity of sodium excreted during the infusion were taken.

The level of thirst threshold was expressed by the magnitude of the sodium load (i.e. the number of m-equiv of Na^+ in the infusion less the number of m-equiv of Na^+ excreted in urine) necessary to induce the drinking response. The cellular dehydration produced at the point of thirst threshold by infusion of hypertonic NaCl was also calculated. The total body water and the extracellular water were measured in each dog. The plasma Na^+ concentration was also measured and the total amount of Na^+ calculated. The amount of Na^+ and water in the infusion are known, hence the shift of water caused by hypertonic infusion and cellular dehydration inducing the drinking reaction could be calculated (threshold cellular dehydration). In each dog, control measurements of thirst threshold were checked 4–6 times.

Chlorpromazine, (Specia-Largactil) 0·22 mg/kg, dissolved in 1·4 ml of 0·9% saline, was given by intravenous infusion 1 h before the thirst threshold measurement. Total body water was measured using tritiated water (Chwalinski, Mikulski & Kossakowska, 1965), and extracellular water by using sodium thiocyanate. The sodium concentration was measured by the Zeiss III flame photometer.

In 9 dogs, chlorpromazine, 0·22 mg/kg, lowered the osmotic reactivity of the thirst mechanism. One dog treated with 0·44 mg/kg showed a higher thirst threshold. The difference between cellular threshold dehydration (%) in controls ($4 \pm 0{\cdot}5$) and after chlorpromazine infusion ($6{\cdot}7 + 0{\cdot}7$) was statistically significant ($P < 0{\cdot}1$).

The volume of water drunk under the threshold stimulus did not differ significantly from the controls. Diuresis increased in 8 dogs during chlorpromazine infusion in a range from 14–204% with an average of 10%. It remained unchanged in one dog and in another decreased by 13%.

The lowering of osmotic reactivity of the thirst mechanism by chlorpromazine may be connected with its direct action upon the central nervous system. A secondary effect of this drug on the thirst mechanism, which might well be due to

its peripheral action in inhibiting vasomotor reflexes, would be expected to produce a rise not a fall of osmotic reactivity of thirst mechanism.

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The effect of chloral hydrate on the metabolism of ethanol in mice

The enhancement of the hypnotic effect of ethanol by chloral hydrate is well documented (Maynert, 1965). Bardodej (1965) described an disulfiram-like reaction in man after this drug combination and suggested increased acetaldehyde as the cause. However, Kaplan, Forney & others (1967) were unable to show any alteration in ethanol metabolism in man after chloral hydrate and attributed the additive effect to the formation of trichloroethanol. Gessner & Cabana (1967) showed significant differences in the rate of disappearance of chloral hydrate and of the formation of trichloroethanol and trichloroacetic acid in mice when chloral hydrate was given with ethanol. We have now measured ethanol and acetaldehyde in the blood after intravenous injection of ethanol into mice pretreated with chloral hydrate.

Adult male DBA/2 mice, 25 g, received chloral hydrate 200, 400, or 600 mg/kg intraperitoneally. Thirty min later they were injected with ethanol 1·33 g/kg as an 8·33% solution in isotonic saline into the tail vein. The duration of the injection was 1 min and blood samples were withdrawn at 5, 20, 35 and 50 min after the injection was complete. Samples were taken from the retro-orbital sinus directly into a 50 μl disposable micropipette and the acetaldehyde and ethanol concentrations determined by the method previously described (Roach & Creaven, 1968).

With 200 mg/kg of chloral hydrate, increases in blood acetaldehyde of 131% ($P < 0{\cdot}005$), 60% ($P = 0{\cdot}01$), 42% ($P = 0{\cdot}05$), and 27% (N.S.) are seen at 5, 20, 35, and 50 min after ethanol injection. With 400 mg/kg the increases are 318, 341 and 121% ($P < 0{\cdot}001$ for each) and 55% ($P = 0{\cdot}01$) at the same four time intervals; with 600 mg/kg, they are 270, 342, 171 and 93% ($P < 0{\cdot}001$ for each). With 200 mg/kg of chloral hydrate, but twice the dose of ethanol (2·67 mg/kg), acetaldehyde is significantly greater than control values only at 5 min (207%, $P < 0{\cdot}005$). At all four times the values are lower than those found with the same dose of chloral hydrate and the smaller dose of ethanol, and at 35 and 50 min they are significantly lower ($P = 0{\cdot}02$). (For treated groups $n = 6$; for the control group $n = 13$.)

The effect on blood ethanol levels are less dramatic. In control animals the decline in the level of blood ethanol is nearly linear with time, in agreement with previous findings in this laboratory for the dose of ethanol (1·33 g/kg) used. Chloral hydrate, 200 mg/kg, causes a 10% increase in the blood ethanol level at 5 min but the rate of decrease is the same as for the controls (Fig. 1). At doses of 400 and 600 mg/kg of chloral hydrate, the 5 min blood ethanol levels are somewhat higher than the control values (16 and 22% respectively; $n = 6$ for each experiment) but the rate of decrease is no longer constant, being greatest in the first 15 min and