Inhibition by propranolol of ethanol-induced narcosis

Large doses of propranolol increase the sleeping time of mice or rats injected with barbiturates (Leszkovsky & Tardos, 1965) or chloral hydrate (Laverty & Taylor, 1968). This action is attributed to the central depressant property, rather than the β-blocking effect of propranolol. Ethanol also depresses the central nervous system. When biogenic amines are given with ethanol the sleeping time of mice is prolonged (Rosenfeld, 1960) and the lethal effect of large doses of amine is potentiated. We now report on the influence of propranolol on the depressant effect of ethanol.

Female, Swiss-Webster mice, 20–30 g in groups of 5, were tested for each dose; controls numbered 10 or more. Only 5 mice were observed at each time and observation was continuous. The drugs propranolol, 1 mg/kg, given 15 min before ethanol or ethanol as a 25% solution, w/v in normal saline, or sodium pentobarbitone, 60 mg/kg, were injected intraperitoneally.

As shown in Fig. 1, the time for the return of righting reflex after pentobarbitone injection was increased by propranolol. However the return of the righting reflex after ethanol was shortened by low doses of propranolol but increasing the dose caused the righting reflex time to rise, roughly paralleling the slope for the barbiturate curve.

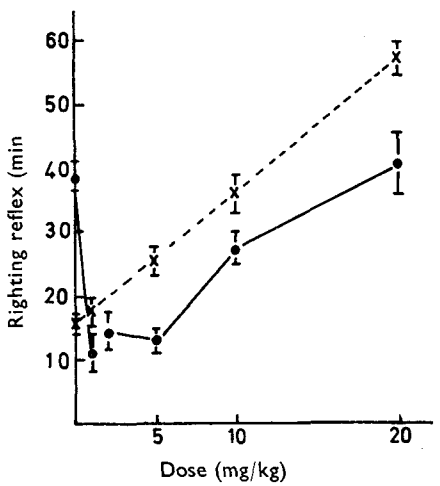

FIG. 1. The effect of propranolol on the time of return of righting reflexes after injection of —— ethanol, 4 g/kg or - - - pentobarbitone, 60 mg/kg. Vertical lines indicate s.e.

The finding that a β-adrenergic blocking agent can inhibit the central depressant actions of ethanol, but not pentobarbitone, suggests that perhaps brain noradrenaline modulates the depressive response to ethanol but not to pentobarbitone. A similar modulating effect of noradrenaline is suggested by the fact that reserpine inhibits the analgesic effect of morphine (Sigg, Caprio & Schneider, 1958) whereas it is enhanced by adrenaline. On the other hand, the respiratory depression produced by morphine was not inhibited by propranolol pretreatment (Smith & Hayashida, 1970).

The specificity of propranolol for ethanol depression was tested using several other alcohols. Methanol, isopropanol or propanol were injected intraperitoneally in doses of 6, 3 or 2 g/kg so as to produce loss of righting reflex for 27 to 54 min. Pretreatment with propranolol increased the depressant effect of methanol and propanol by 33 and 42% whereas propranolol shortened by 35% the righting reflex time for isopropanol. A control study using ethanol, 4 g/kg, showed that propranolol blocked the depressant effect of ethanol by 54%. In each instance the change in

righting reflex time, compared with control, was significant at P, 0·05. Evidently propranolol was more effective against the depression induced by 2 carbon alcohols.

This study was supported by a grant from the New York Medical College.

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May 4, 1970

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Insulin tolerance in thiamine-deficient rats

In studies on thiamine-deficiency, we reported that the tissue concentration of catecholamine was significantly elevated in thiamine-deficient rats (Iwata, Fujimoto & others, 1968) and that monoamine-oxidase is involved in accumulation of endogenously formed catecholamine in tissues in thiamine-deficiency (Iwata, Nishikawa & Fujimoto, 1969a). Further, we recognized that a sedative effect was rarely seen in deficient animals given reserpine, but that when present, sedation was possibly due, at least in part, to slow depletion of the elevated catecholamine level caused by thiamine-deficiency (Iwata, Watanabe & Nishikawa, 1969b). Wien (1936) found that rats deprived of all the vitamin B complex exhibited a greater hypoglycaemic reaction to insulin than animals on a normal diet. On the other hand, Burke & McIntyre (1938) showed that thiamine added to the diet of rats, increased their hypoglycaemic response to insulin.

On the basis of these results, we examined the differences in behaviour and changes in blood sugar in control and thiamine-deficient rats caused by toxic or lethal doses of insulin. Thiamine-deficient rats were obtained as described by Iwata & others (1969a).

When control animals, on diet supplemented with thiamine, and pair-fed animals, showing a loss of body weight similar to that of the thiamine-deficient group, received 100 i.u./kg insulin intraperitoneally, they generally showed reduction in spontaneous motor activity about 1·5 h later and then developed tremor followed by clonic convulsions. They invariably showed symptoms of severe collapse after about 2·5 h and died after about 3·2 h. However, in the thiamine-deficient group only a very slight decrease in spontaneous motor activity was observed and neither convulsions nor prostration were seen within 12 h after administration of insulin. Moreover, as shown in Table 1, no animals in the deficient group died. When thiamine-deficient animals had been injected with 4 mg/kg thiamine hydrochloride 5 h previously, they developed the same symptoms as the control and pair-fed rats after injection of insulin, and four of the five animals died within about 7 h after administration of insulin.

Insulin shock is thought to be due to the hypoglycaemic effect of the hormone, because patients usually recover from insulin coma on infusion of glucose. The effect on the blood sugar level of a large dose of the hormone (100 i.u./kg, i.p.) was examined in deficient, control and pair-fed animals to see whether deficient rats showed a hypoglycaemic response to insulin. As seen in the Fig. 1, after this dose of insulin, the blood sugar level of control animals decreased by about 50% after 1 h,