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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REFERENCES

LESZKOVSKY, G. & TARDOS, L. (1965). *J. Pharm. Pharmac.*, **17**, 518–519.
LAVERTY, R. & TAYLOR, K. M. (1968). *Ibid.*, **20**, 605–609.
ROSENFELD, G. (1960). *Q. J. Stud. Alc.*, **21**, 584–596.
SMITH, A. & HAYASHIDA, K. (1970). *Fedn Proc. Fedn Am. Socs exp. Biol.*, **28**, 261.
SIGG, E. B., CAPRIO, G. & SCHNEIDER (1958). *Proc. Soc. exp. Biol. Med.*, **97**, 97–100.

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,

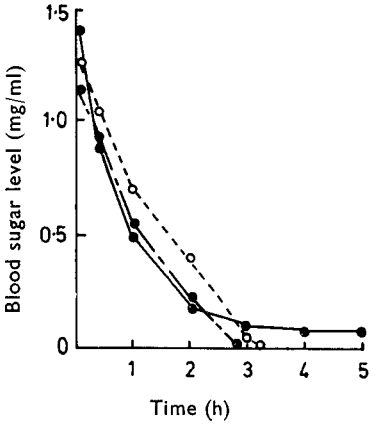

FIG. 1. Effect of insulin (100 i.u./kg, i.p.) on the blood sugar level of rats. Each point represents the mean of values of 3 to 5 animals. ●—● Thiamine deficient; ○--○ control; ●--● pair fed.

Table 1. *Effect of thiamine-deficiency on the lethal effect of insulin.* Insulin (100 i.u./kg) was injected intraperitoneally. Thiamine hydrochloride (4 mg/kg) was injected subcutaneously 5 h before insulin.

	No. of animals	Mortality (%)
Control	28	100
Thiamine-deficient	26	0
Pair-fed	8	100
Thiamine-deficient + thiamine	5	80

and by 70% after 2 h and was undetectable after 3·2 h. The blood sugar of thiamine-deficient animals decreased more rapidly than that of control animals for the first 2 h after insulin administration, but then decreased only slightly and was 0·07–0·08 mg/ml after 5 h.

This is the first report of the unexpected phenomenon that thiamine-deficient rats, unlike control and pair-fed animals show, no toxic reactions, such as convulsions and collapse, after a large dose of insulin. Based on our previous findings (Iwata & others, 1968) it seems possible that increased endogenous catecholamines in the brain or in other tissues caused by thiamine-deficiency may be responsible for this resistance to insulin toxicity. Furthermore, though the sustained low level of anthrone positive substance in the thiamine-deficient group after insulin is unknown, it seems possible that utilization of amino-acids or carbohydrates other than glucose in brain metabolism is enhanced in thiamine-deficiency.

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April 28, 1970

REFERENCES

BURKE, J. C. & MCINTYRE, A. R. (1938). *J. Pharmac. exp. Ther.*, **64**, 465–477.
IWATA, H., FUJIMOTO, S., NISHIKAWA, T. & HANO, K. (1968). *Experentia*, **24**, 378–380.
IWATA, H., NISHIKAWA, T. & FUJIMOTO, S. (1969a). *J. Pharm. Pharmac.*, **21**, 237–240.
IWATA, H., WATANABE, K., NISHIKAWA, T. & OHASHI, M. (1969b). *Europ. J. Pharmac.*, **6**, 83–89.
WIEN, R. (1936). *Q. Jl Pharm. Pharmac.*, **9**, 268–297.