REFERENCES

BERDE, B. & CERLETTI, A. (1958). Quantitative comparison of substances related to oxytocin: a new test. *Acta endocr., Copenh.*, **27**, 314–324.

HORTON, E. W. (1968). The prostaglandins. In *Recent Advances in Pharmacology*, 4th ed., ed. Robson, J. M. & Stacey, R. S., pp. 185–212. London: Churchill.

Changes in drug sensitivity in hyperthyroidism

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Some of the clinical effects of hyperthyroidism resemble those of increased sympathetic activity, and there is evidence that in hyperthyroidism the pharmacological effects of catecholamines are potentiated (Harrison, 1964). Coville & Telford (1968) found that treatment of rats or guinea-pigs with thyroxine increases the sensitivity of the isolated heart and uterus not only to catecholamines but also to acetylcholine, histamine, 5-hydroxytryptamine and calcium. In contrast, thyroxine depresses the sensitivity of the isolated aorta and intestine. Thyroid hormones are known to influence calcium metabolism, and these opposing and non-specific changes in sensitivity may be related to opposing influences on availability of Ca^{2+} ions.

Rats or guinea-pigs were pretreated with L-thyroxine sodium (1–5 mg/kg, subcutaneously, daily, 8–15 days). The influence of both raised and lowered calcium concentration in the bathing fluid was then determined on the 50% maximal responses of the isolated uterus and aorta of the rat and the isolated ileum of the guinea-pig to acetylcholine, histamine or 5-hydroxytryptamine. On the uterus, sensitivity to change in calcium concentration was increased by thyroxine administration, whereas on the intestine and aorta it was depressed.

The ability of uteri from hyperthyroid rats to bind Ca^{2+} was measured by a modification of the method of Knifton (1966). Isolated uteri were driven by optimal field stimulation (usually 80 V, pulse width 5 msec, 20 pulses/sec, for 5 sec every min). The Krebs solution was then replaced by a Ca^{2+}-free solution, stimulation continued, and the time taken for tension to decrease to half the original plateau height. It was found that pretreatment with thyroxine increases the rate of loss of tension in both oestrus and dioestrus uteri. This suggests that binding of Ca^{2+} is reduced so that increased availability of free Ca^{2+} in the uterus could explain the increased sensitivity of this tissue to drugs.

Further experiments showed that on the central nervous system, as on cardiac and smooth muscle, thyroxine in similar dosage likewise induces non-specific changes in sensitivity to drugs. Locomotor activity in grouped rats induced by a single dose (0·5 or 1·0 mg/kg, intraperitoneally) of dexamphetamine is approximately doubled, whilst the LD50 of dexamphetamine is reduced 25 times. Spontaneous locomotor activity is not modified by thyroxine alone, but is reduced by thyroidectomy which also affords partial protection against doses of dexamphetamine (50 mg/kg, intraperitoneally) lethal to control rats. In hyperthyroid rats toxicity to caffeine is increased, a dose of 160 mg/kg producing 100% mortality but no deaths in control rats. Hexobarbitone sleeping time in hyperthyroid mice (thyroxine, 20 mg/kg) is increased by up to 300%. Doses of hexobarbitone (50 mg/kg, intraperitoneally) which in control mice produce slight sedation induce narcosis after thyroxine treatment.

The mode of action of the hormone in raising sensitivity to these centrally acting drugs is not clear, but the results point to possible difficulties in drug therapy in hyperthyroid patients.

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REFERENCES

COVILLE, P. F. & TELFORD, J. M. (1968). Influence of thyroid hormones on the responses of smooth muscle to drugs. *Naunyn-Schmeidebergs Arch. exp. Path. Pharmak.*, **259**, 161–162.

HARRISON, T. S. (1964). Adrenal medullary and thyroid relationships. *Physiol. Rev.*, **44**, 161–185.

KNIFTON, A. (1966). The influence of the female sex hormones on the response of the pig uterus to electrical stimulation. *J. Pharm. Pharmac.*, **18**, 151*S*–159*S*.

Diuretics and carbohydrate metabolism in the mouse

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Numerous reports appear in the literature concerning the so-called diabetogenic effect of benzothiadiazine diuretics (for example, Goldner, Zarowitz & Akgun, 1960). Recent reports suggest that frusemide (Toivonen & Mustala, 1966) and ethacrynic acid (Lebacq & Marcq, 1967) may also produce impairment of glucose tolerance in some patients. It is not yet clear whether or not these compounds can produce these abnormalities in subjects exhibiting no predisposition towards diabetes mellitus. Attempts to induce abnormal carbohydrate metabolism in normal animals with benzothiadiazine compounds have yielded conflicting results.

In this communication results are presented to show the effects of short-term (14 days) treatment with hydrochlorothiazide, ethacrynic acid and frusemide on fasting blood glucose levels, oral glucose tolerance, fasting plasma levels of immuno-reactive insulin, and insulin sensitivity.

Fasting blood glucose determinations were carried out on 0·05 ml. blood samples using a micro-colorimetric copper reduction method. The results indicate a small but significant fasting hyperglycaemia compared with controls, in animals treated with large daily doses (100 mg/kg) of frusemide or ethacrynic acid but not with hydrochlorothiazide. Low doses of the diuretics produced no effect.

Fasting plasma levels of immuno-reactive insulin were determined by the method of Hales & Randle (1963). Elevation in the levels was seen in animals treated with ethacrynic acid and frusemide, statistical significance being shown in the latter case.

Oral glucose tolerance was assessed by measuring blood glucose in groups of mice sampled 30, 60, 90, 120 and 180 min after an oral glucose load (5 g/kg). Significant elevations of blood glucose compared with control animals were seen at 30 and 60 min in the ethacrynic acid treated animals and at 60 and 90 min in the frusemide-treated animals. No change was observed with hydrochlorothiazide or with low doses of the other diuretics.

The insulin sensitivity of the animals was assessed by measuring blood glucose before and 30 min after insulin (0·5 u./kg), administered intravenously. No diuretic-induced change was observed.