mice, indicating that a phase shift induced by meal-feeding had occurred. These results are consistent with those of Scheving & others (1968) in that high concentrations of amphetamine are correlated in time with high susceptibility to the drug. Since Radzialowski & Bousquet (1969) reported the activities of several oxidative drug-metabolizing enzymes in mice to be highest at night, the rate at which amphetamine is metabolized may not cause the rhythm. It remains to be determined that the rhythm represents a rhythm of metabolism rather than of uptake by the liver.

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Preliminary evidence that syrosingopine produces a selective depletion of central stores of sympathomimetic amines

The convulsive effects of leptazol are markedly facilitated by pretreating laboratory animals with reserpine (Jenney, 1954; Chen & Bohner, 1956; Kobinger, 1958; Lessin & Parkes, 1959; Pfeifer & Galambos, 1967). Reserpine is reported to produce non-selective depletion of both central and peripheral amine stores (Carlsson, 1964). These results have been confirmed in our laboratories.

Syrosingopine is a synthetic analogue of reserpine reported to produce a selective depletion of peripheral stores of sympathomimetic amines (Plummer, Barrett & others, 1959; Brodie, 1960; Orlans, Finger & Brodie, 1960).

Sixty male Porton Wistar albino rats, 200–250 g, were divided into groups of five. After pretreatment with syrosingopine at 0·4, 0·8 and 2·0 mg/kg (administered in 1 ml/kg dissolved in a mixture of 4% w/v propylene glycol, 4% ethanol and 2% lactic acid in distilled water into the penile vein of rats lightly anaesthetized with halothane), leptazol (65 mg/kg) was administered subcutaneously to the animals 4 h later and the number of clonic phases in the following 30 min period recorded, and expressed as a percentage maximum clonic convulsions (Spencer & Turner, 1969). Control animals received the vehicle intravenously under the same conditions. The mean and standard error of not less than three determinations was calculated. The results are shown in Fig. 1 (a). At 0·4 and 0·8 mg/kg there was no significant decrease of the leptazol threshold but at 2 mg/kg the number of clonic convulsive phases increased 100%. It seemed likely that at 0·8 mg/kg only peripheral amines were depleted and at 2 mg/kg there was a depletion of central amines which produced the marked decrease in leptazol threshold. Therefore, the effect of these two doses of syrosingopine on brain and cardiac amine concentrations was determined.

Thirty male Porton Wistar albino rats, 200–250 g, were divided into three groups of ten. Two groups received the syrosingopine at 0·8 or 2 mg/kg administered as before and the third group received the vehicle under identical conditions. Four h later the animals were killed and the brains and hearts removed for determination of

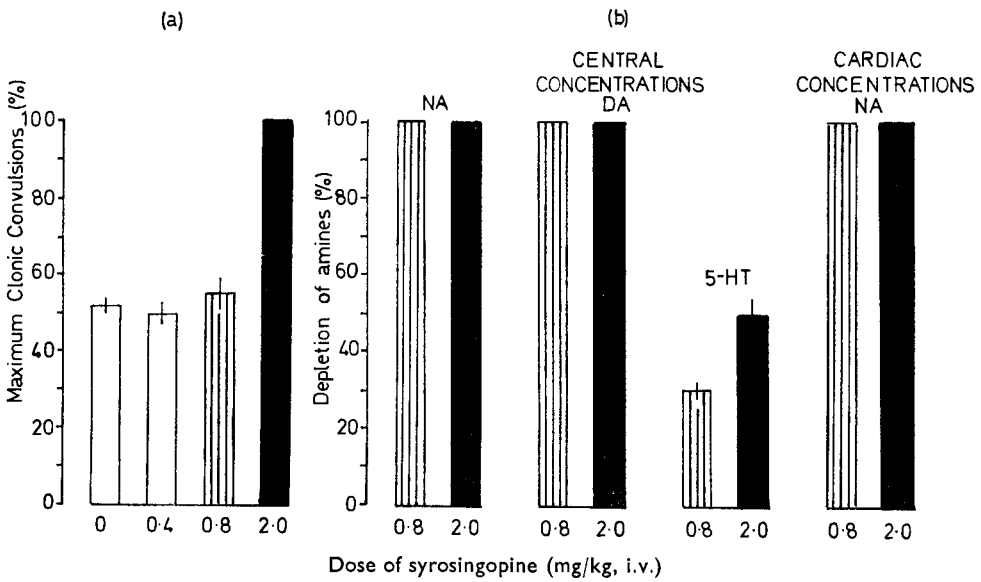

FIG. 1. Effect of 4 h pre-treatment with syrosingopine on (a) the incidence of leptazol-induced clonic convulsions and (b) the whole brain noradrenaline (NA), dopamine (DA) and 5-hydroxytryptamine (5-HT) concentrations and cardiac noradrenaline concentrations in the rat. Vertical bars indicate the standard error of the mean of not less than three determinations.

central noradrenaline, dopamine and 5-HT and cardiac noradrenaline concentrations (Spencer & Turner, 1969). The results are expressed as a percentage depletion of control concentrations. Each result is the mean of five determinations at each dose (Fig. 1 b). Both doses of syrosingopine produced total depletion of central noradrenaline and dopamine, and also cardiac noradrenaline. However, there was a less marked depletion of central 5-HT concentrations which appeared to be dose related.

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