The effect of 6-hydroxydopamine on the tolerance development to the hyperthermic effect of (+)-amphetamine in the rat

The site of action, peripheral or central, of the hyperthermic effect of amphetamine has yet to be established. Brodie, Cho & others (1969) suggested that the hyperthermia would depend on a peripheral mechanism involving release of free fatty acids from adipose tissue. However, the effect of amphetamine on the plasma free fatty acid concentration was found not to be essential for the development of hyperthermia by Matsumato & Shaw (1971). Furthermore, there is other evidence on the central origin of hyperthermia (see Matsumato & Griffin 1971; Hill & Horita 1971).

We have investigated the effect of intraventricularly injected 6-hydroxydopamine (6-OH-DA) on the hyperthermic effect of (+)-amphetamine, and the tolerance development to this effect in rats. Intracisternal or intraventricular injection of 6-OH-DA has been reported to cause prolonged depletion of brain catecholamines, presumably because of the selective destruction of central catecholaminergic neurons, without affecting peripheral stores (Uretsky & Iversen, 1970; Breese & Traylor, 1970).

Male albino rats (200–280 g) were given 250 μg of 6-OH-DA hydrobromide intraventricularly according to Noble, Wurtman & Axelrod, (1967) under light ether anaesthesia. The compound was dissolved in saline containing 0·5% ascorbic acid to prevent oxidation; total volume administered was 10 μl. Control animals received the same volume of vehicle. All rats were pretreated with tranylcypromine sulphate, (5 mg kg^{-1}, i.p.) 30 min before 6-OH-DA or vehicle injection, to increase the dopamine depletion (Fibiger, Fibiger & Zis, 1973).

Two months later these animals were divided into two groups. The first group of rats were killed, and brain dopamine and noradrenaline were analysed according to Weil-Malherbe (1972), and Anton & Sayre (1962) respectively. The second group of rats received 5 mg kg^{-1} (+)-amphetamine sulphate (as a base) daily for 20 days. The rectal temperatures were measured with an electric thermometer (Ellab, Copenhagen, accuracy: 0·1°) just before and 60 min after the administration of (+)-amphetamine sulphate. Experiments were at room temperature (21° to 23°).

The increase in body temperature of 6-OH-DA-pretreated rats was significantly lower ($P<0·01$) than the increase in temperature control rats on the first day of (+)-amphetamine administration. With time, the increase in body temperature gradually decreased in the 6-OH-DA-pretreated animals until there was no difference between the rectal temperature of saline controls and of (+)-amphetamine treated rats on the 20th day. In the vehicle-injected rats no difference was observed in the

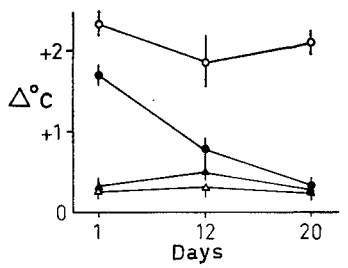

FIG. 1. Changes in body temperature induced by chronic administration of (+)-amphetamine and saline in 6-OH-DA-pretreated and sham operated rats. ○——○ 5 mg kg^{-1} (+)-amphetamine in sham operated rats. ●——● 5 mg kg^{-1} (+)-amphetamine in 6-OH-DA-pretreated rats. ▲——▲ saline in 6-OH-DA-pretreated rats. △——△ saline in sham operated rats. Each point represents the mean body temperature change (± s.e.m.) of group of 10 rats.

temperature responses to (+)-amphetamine injection on the 1st, 12th and 20th days (Fig. 1). Brain noradrenaline and dopamine concentrations were 27 and 19% of control values in the 6-OH-DA-treated rats, the control values being 627 ± 53 and 960 ± 36 ng g^{-1} respectively.

According to these results it would appear that (+)-amphetamine-induced hyperthermia may be due to some central catecholaminergic mechanisms rather than peripheral mechanisms, because, as is clearly shown in Fig. 1, the selective elimination of central catecholamines by intraventricular 6-OH-DA facilitated the tolerance development to the hyperthermic effect of (+)-amphetamine. However, we do not know which of these amines, noradrenaline or dopamine, plays a predominant role in the development of hyperthermia. Some workers have attributed the amphetamine-induced hyperthermia to stimulation of dopaminergic receptors in the central nervous system in rats (Matsumato & Griffin, 1971) and rabbits (Hill & Horita, 1971).

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REFERENCES

ANTON, A. H. & SAYRE, D. F. (1962). *J. Pharmac. exp. Ther.*, **138**, 360–375.

BRESSE, G. R. & TRAYLOR, T. D. (1970). *Ibid.*, **174**, 413–420.

BRODIE, B. B., CHO, A. K., STEFANO, F. J. E. & GESSA, G. L. (1969). In: *Advances in Biochemcial Psychopharmacology*, Vol. 1 pp. 219–238. Editors: Costa, E. and Greengard, P. New York.

FIBIGER, H. C., FIBIGER, H. P. & ZIS, A. P. (1973). *Br. J. Pharmac.*, **47**, 683–692.

HILL, H. F. & HORITA, A. (1971). *J. Pharm. Pharmac.*, **23**, 715–717.

MATSUMATO, C. & GRIFFIN, W. (1971). *Ibid.*, **23**, 710.

MATSUMATO, C. & SHAW, W. N. (1971). *Ibid.*, **23**, 387–388.

NOBLE, E. P., WURTMAN, R. J. & AXELROD, J. (1967). *Life Sci.*, **6**, 281–191.

URETSKY, N. J. & IVERSEN, L. L. (1970). *J. Neurochem.*, **17**, 269–278.

WEIL-MALHERBE H. (1972). In: *Methods of Biochemical Analysis, Suppl: Analysis of Biogenic Amines and Their Related Enzymes*, p. 133. Editor, Glick, D. New York. Wiley-Interscience.

The influence of desipramine and amitriptyline on the accumulation of [^{3}H]noradrenaline and its two major metabolites formed from [^{3}H]tyrosine in the rat brain

The tricyclic antidepressant drug desipramine, in contrast to amitriptyline, is a potent inhibitor of the neuronal uptake of noradrenaline into central noradrenergic neurons (Glowinski, Axelrod & Iversen, 1966; Giese, Rüther & Matussck, 1967; Carlsson, Corrodi & others, 1969; Schildkraut, Schanberg & others, 1967; Schildkraut, Draskoczy & others, 1971; Squires, 1974). It has also been shown, that desipramine produces a decreased accumulation of labelled noradrenaline synthesized from tyrosine without affecting the endogenous noradrenaline level (Nybäck, Borzecki & Sedvall, 1968; Schubert, Nybäck & Sedvall, 1970; Nielsen, Eplov & Scheel-Krüger, 1974). Amitriptyline produces only a weak or no effect on noradrenaline accumulation from labelled tyrosine (Schubert & others, 1970). The present investigation was made to clarify the influence of desipramine and amitriptyline on the metabolism of brain [^{3}H]noradrenaline (^{3}H-NA) synthesized from intravenously or intraventricularly injected [^{3}H]tyrosine.