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Importance of noradrenaline synthesis for the interaction between desipramine and reserpine

SIR,—We have previously reported that the hyperthermic effect induced by desipramine in rats given reserpine may be inhibited by peripheral adrenergic blocking agents (Jori, Paglialunga & Garattini, 1966) and by α-methyl-*m*-tyrosine (Garattini & Valzelli, 1961), an agent which depletes brain noradrenaline stores (Hess, Connmacher, Ozaki & Udenfriend 1961; Gessa, Costa, Kuntzman & Brodie, 1962).

These results suggested that imipramine-like drugs might antagonise the reserpine hypothermia by interacting with the adrenergic system. In fact, an increase of the concentration of noradrenaline at the receptor sites might be expected as a consequence of the inhibitory action of desipramine on the catecholamine re-uptake at the nerve endings (Iversen, 1965).

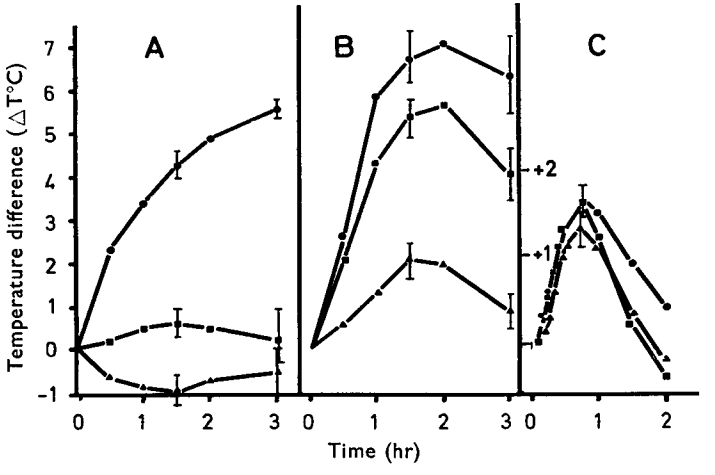

FIG. 1. Hyperthermic agents (desipramine, dopa and noradrenaline) were given at zero time, 18 hr after reserpine and 2 hr after the enzymatic inhibitors (α-methyl-*p*-tyrosine and diethyldithiocarbamate). Each point represents the average of 8 rats. The vertical bars indicate the standard errors. A. ●——● desipramine (7·5 mg/kg i.p.). ■——■ α-Methyl-*p*-tyrosine (80 mg/kg i.p.) + desipramine. ▲——▲ Diethyldithiocarbamate (300 mg/kg i.p.) + desipramine. B. ●——● Dopa (150 mg/kg i.p.). ■——■ α-Methyl-*p*-tyrosine + dopa. ▲——▲ Diethyldithiocarbamate + dopa. C. ●——● Noradrenaline (300 μg/kg i.v. in 15 min.). ■——■ α-Methyl-*p*-tyrosine + noradrenaline. ▲——▲ Diethyldithiocarbamate + noradrenaline.

In an attempt to adduce further evidence in support of this hypothesis, some experiments were made to establish if the inhibition of noradrenaline biosynthesis effected a decrease in desipramine-induced hyperthermia in reserpinized rats. Noradrenaline synthesis was blocked with either α-methyl-*p*-tyrosine —an inhibitor of tyrosine hydroxylase (Spector, Sjoerdsma & Udenfriend, 1965; Torchiana, Stone & Porter, 1965)—or diethyldithiocarbamate—an inhibitor of dopamine-β-hydroxylase (Collins, 1965; Carlsson, Lindqvist, Fuxe & Hökfelt, 1966).

Female Sprague-Dawley rats were given reserpine (5 mg/kg i.v.) and 16 hr after either α-methyl-*p*-tyrosine (80 mg/kg) or diethyldithiocarbamate (300 mg/kg) was injected intraperitoneally. Desipramine (7·5 mg/kg i.p.) was given 2 hr after the inhibitors. In other experiments dopa (150 mg/kg i.p.) or noradrenaline (45 μg/rat infused in 15 min) was given instead of desipramine.

When the hyperthermic agents were injected, rats were placed in individual cages and temperatures recorded with an automatic device (Jori & Paglialunga, 1966).

All the experiments were made at an environmental temperature of 20° with a relative humidity of 56%.

Fig. 1 shows that desipramine, dopa and noradrenaline increase, although to a different extent, the body temperature in fully reserpinized rats. The hyperthermia induced by desipramine, but not that induced by noradrenaline, is blocked by α-methyl-*p*-tyrosine and by diethyldithiocarbamate. Dopa-induced hyperthermia is blocked by diethyldithiocarbamate but not by α-methyl-*p*-tyrosine. These findings are consistent with the results that should be expected considering the postulated site of enzymatic inhibition exerted by α-methyl-*p*-tyrosine and by diethyldithiocarbamate. We therefore conclude that the presence of noradrenaline itself is essential for the achievement of desipramine-induced hyperthermia in reserpinized animals.

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