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Inhibition of (+)-amphetamine hyperthermia by blockade of dopamine receptors in rabbits

The hyperthermia produced in rabbits by (+)-amphetamine is apparently due to an action of the drug on the CNS (Hill, 1971). Indications for this central action include the findings that (+)-amphetamine hyperthermia in this species is markedly reduced by prior curarization (Belenky & Vitolina, 1962) or spinal section (Hill & Horita, 1970) but is not diminished by blockade of β- or peripheral α-adrenergic receptors (Hill & Horita, 1970). Other evidence suggests that (+)-amphetamine might produce hyperthermia by influencing a central dopaminergic system. For example, several of the neuroleptic drugs antagonize (+)-amphetamine hyperthermia in rats (Morpurgo & Theobald, 1967). These and other neuroleptics were later found to be potent inhibitors of central dopaminergic function (Andén, Butcher & others, 1970). That low doses of (+)-amphetamine can elevate both body temperature and the turnover rate of brain dopamine without altering the turnover rate of brain noradrenaline in the rat further implicates dopamine as the neurochemical concerned in (+)-amphetamine-induced hyperthermia (Costa & Groppetti, 1970).

However, it is difficult to determine from such information whether dopamine receptor activation is necessary for production of hyperthermia by (+)-amphetamine. The neuroleptics employed by Morpurgo & Theobald (1967) are known to also block central and peripheral α-adrenergic receptors (Janssen, Niemegeers & others, 1968; Andén & others, 1970). Further, an increased turnover rate of dopamine does not necessarily imply increased dopamine receptor activation. A more direct means of evaluating the possible involvement of central dopamine receptors in the production of hyperthermia by (+)-amphetamine is to assess the effect of specific dopamine antagonists on this response. Since pimozide* had been shown to selectively inactivate dopamine receptors in the CNS (Andén & others, 1970), the ability of this drug to antagonize (+)-amphetamine hyperthermia was investigated.

Male New Zealand rabbits (1·8–2·0 kg) received an injection of either pimozide or the pimozide solvent (dilute tartaric acid) intraperitoneally 3 h before intravenous injection of (+)-amphetamine or saline. Sedation and catalepsy were evident 30 min after pimozide administration, reached maximal intensity at about 2 h and persisted for more than 12 h in rabbits receiving no (+)-amphetamine. In addition, these animals exhibited marked and continuous miosis. Administration of (+)-amphetamine 3 h after pimozide resulted in a transient increase in pupillary size and motor activity. Sedation, catalepsy, and miosis were again evident 15 min later and persisted for more than 12 h.

* 1-{1-[4,4-bis(*p*-fluorophenyl)butyl]-4-piperidyl}-2-benzimidazolinone.

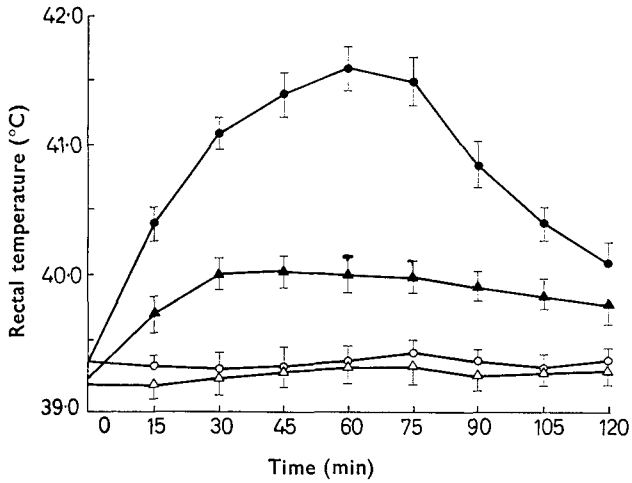

FIG. 1. The effect of pimozide on the time course of (+)-amphetamine-induced hyperthermia. Rabbits were pretreated with pimozide solvent (dilute tartaric acid) or pimozide solution (4 mg/kg pimozide i.p.) 3 h before to injection of (+)-amphetamine (5 mg/kg, i.v.) or saline. Each curve represents the mean rectal temperatures of 6 rabbits receiving: solvent before saline (○), pimozide before saline (△), solvent before (+)-amphetamine (●), and pimozide before (+)-amphetamine (▲). The vertical lines indicate s.e.

The effect of (+)-amphetamine on rectal temperature was examined in rabbits treated 3 h previously with pimozide (Fig. 1). (+)-Amphetamine produced significantly less elevation of rectal temperature ($P < 0{\cdot}01$) in pimozide-treated compared to solvent-treated rabbits at all but the last observation time (120 min). Peak hyperthermia was reduced by about 70% by pimozide pretreatment ($P < 0{\cdot}005$). Although the time required to reach maximal temperature after (+)-amphetamine injection was not significantly different in pimozide- or solvent-treated rabbits, the *rate* of temperature increase was decreased by pimozide. Saline injection had no effect on rectal temperature of rabbits with either pretreatment. These observations suggest that pimozide inhibits (+)-amphetamine hyperthermia by preventing activation of heat-generating mechanisms and not by enhancing heat-dissipation.

Pimozide has been shown to be a persistent antagonist of many apparently central dopaminergic functions (Janssen & others, 1968; Andén & others, 1970; Janssen, 1970; Fuxe, 1970). Whether the antagonism by pimozide of (+)-amphetamine hyperthermia was similarly persistent, was investigated in rabbits pretreated with saline or pimozide and then injected with (+)-amphetamine (5 mg/kg) at three 4 hourly intervals. The results indicate that a single injection of pimozide can inhibit (+)-amphetamine hyperthermia for at least 16 h. Cns excitatory effects of (+)-amphetamine (increased motor activity and chewing) were also inhibited throughout the experiment. No tolerance to (+)-amphetamine hyperthermia developed with the dosage regimen employed. This observation contrasts with the results of Gessa, Clay & Brodie (1968) which showed marked tolerance development in the rat with similar doses (5 mg/kg at 6 h intervals). Since development of tolerance to (+)-amphetamine appears to be related to neuronal accumulation of a *para*-hydroxylated "catabolite" in the rat (Brodie, Cho & Gessa, 1970), the fact that the rabbit produces very little *p*-hydroxyamphetamine from a given dose of (+)-amphetamine (Axelrod, 1954; Dring, Smith & Williams, 1966) might be the basis for this species difference in tolerance development.

Throughout these experiments, we noted that pimozide produced miosis which was only transiently reversed by (+)-amphetamine. This raised the possibility that pimozide

was acting as a competitive antagonist at peripheral α-receptors. Although we had previously reported that such receptors were probably not involved in the hyperthermic response to (+)-amphetamine, it was desirable to determine whether pimozide possessed α-adrenergic blocking activity in this species. Rabbits were anaesthetized with pentobarbitone and mechanically ventilated through a tracheal cannula. Blood pressure was monitored via a cannula in the left femoral artery. Solvent or pimozide (4 mg/kg, i.p.) was administered 2 h before intravenous injection of 5 μg adrenaline. Drug effects on blood pressure and the pressor response were as follows: saline, 82 and 33 mmHg; pimozide, 77 and 35 mmHg; phentolamine, 5 mg/kg, 65 and 8 mmHg. Pimozide was found to have perhaps a slight hypotensive effect. However, this drug did not inhibit the pressor response to noradrenaline. As usual, phentolamine inhibited the pressor response. Therefore, it appears that blockade of peripheral α-receptors is not the basis of the antagonism of (+)-amphetamine hyperthermia by pimozide.

These preliminary observations indicate that pimozide, a potent and selective inhibitor of central dopaminergic functions, is a potent antagonist of (+)-amphetamine hyperthermia in rabbits. Since pimozide is believed to exert its inhibitory effect at the receptor level (Andén & others, 1970), our results suggest that operational dopamine receptors are necessary for the production of hyperthermia by (+)-amphetamine.

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