Hyperthermic response to (—)-cathinone, an alkaloid of *Catha edulis* (khat)

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Recently, a new khat alkaloid of the phenylethylamine type has been identified and the name (—)-cathinone has been proposed (UN document 1975; Schorno & Steinegger 1979). Most of the symptoms associated with the chewing of khat have been recognized as similar to those induced by amphetamine (Halbach 1972) and some recent findings suggest that the pharmacological characteristics of cathinone and amphetamine are similar (J. Knoll, unpublished experiments). Since hyperthermia is a well known effect of amphetamine, the present study was undertaken to determine whether (—)-cathinone also would induce hyperthermia.

The effect of (—)-cathinone on body temperature was tested in rabbits kept at 18–21 °C with free access to water and food pellets. The animals were given intraperitoneal injections of either solvent alone (1 ml kg^{-1} tartaric acid, solvent A) or haloperidol or pimozide. About 15 min after the injection, the animals were restrained by a leather mat attached to a wooden frame with their legs protruding through holes, 45 min later rectal temperatures were measured and immediately afterwards (—)-cathinone HCl, or its solvent (1 ml kg^{-1} NaCl 0·9%, solvent B), was injected into the ear vein, and temperatures were recorded at 20 min intervals for 2 h.

In three preliminary experiments, injection of 24 mg kg^{-1} (—)-cathinone caused a high degree of excitation the principal symptoms of which were hypermotility, stereotyped oral activity such as gnawing and licking (in two of three animals), and mydriasis. The animals developed pronounced hyperthermia and two out of three died with convulsions at body temperatures of 42·7 ° and 43·9 °C, respectively. When the dose was reduced to 16 mg kg^{-1}, the behavioural symptoms were less pronounced, with no signs of oral hyperactivity. At this dose, the maximal hyperthermic response was 1·89 ± 0·31 °C above the initial temperature and was reached 120 min after the (—)-cathinone injection (Fig. 1). Pre-experiment temperature levels were re-established after approximately 5 h.

The dopamine antagonist, haloperidol, has been reported to inhibit the hyperthermic response to amphetamine (Morpurgo & Theobald 1967). Similarly, pimozide has been shown to prevent amphetamine-induced hyperthermia in rabbits (Hill & Horita 1971) and rats (Yehuda & Wurtman 1972). In the present study, rabbits, pretreated with either haloperidol or pimozide, were injected with 24 mg kg^{-1} (—)-cathinone. Although symptoms of excitation, such as hyperreactivity to audiogenic stimulation, jerking head movements and attempts to escape their restraints were noted, these were limited to the 10–20 min following the injection and they were less pronounced than those observed in animals receiving 16 mg kg^{-1} (—)-cathinone without prior administration of an antagonist. More pertinently, however, the hyperthermic response to (—)-cathinone was strongly inhibited in animals that had been given pimozide and blocked in those having received haloperidol (Fig. 1).

Thus, (—)-cathinone induces in rabbits an increase in body temperature that is comparable to that reported for (+)-amphetamine (Hill & Horita 1971) and pretreatment with haloperidol or pimozide inhibits the hyperthermic response. Since both antagonists also affect (+)-amphetamine hyperthermia, it is probable that the mechanism mediating the effect on body temperature is identical for (—)-cathinone and (+)-amphetamine. (—)-Cathinone also induces in rabbits, as well as in rats (Kalix 1980), symptoms of excitation similar to those known to be characteristic for (+)-amphetamine.

That (—)-cathinone induces a rise in body

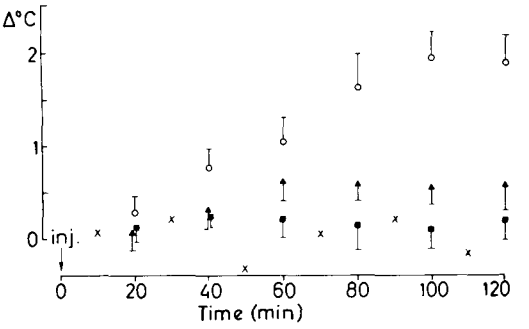

FIG. 1. The effect of haloperidol and pimozide on the hyperthermia induced by (—)-cathinone. Rabbits were pretreated with either haloperidol, pimozide or solvent A and 60 min later they were given an injection of either (—)-cathinone HCl or solvent B (see Methods). The symbols correspond to: solvent A followed by (—)-cathinone (16 mg base kg^{-1}) (○), haloperidol (2 mg kg^{-1}) followed by (—)-cathinone (24 mg base kg^{-1}) (■), pimozide (4 mg kg^{-1}) followed by (—)-cathinone (24 mg base kg^{-1}) (▲), and solvent A followed by solvent B (X). Each point with vertical bars (s.e.) indicates the mean increase of rectal temperature above pre-experiment levels as observed in 4 rabbits. Crosses represent the mean of temperature changes observed in two rabbits given blank injections; in these control experiments, the measurements began 10 min after the last injection.

temperature which can be antagonized by substances known to prevent amphetamine hyperthermia favours the classification of the khat alkaloid as a substance with amphetamine-like effects.

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Evidence to suggest that dopamine-induced increase in GABA concentrations in chick brain is mediated through cyclic AMP

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We have previously reported (Di Giorgio et al 1979) that, in chicks an oral subacute treatment with L-dopa produces a significant increase in glutamate-decarboxylase (GAD) activity and in the GABA content in the nucleus basalis (the homologue of the mammalian striatum) (Juorio & Vogt 1967; Nisticò & Stephenson 1979).

The present experiments were aimed at substantiating the idea that the functional link between dopaminergic and GABA-ergic mechanisms in the brain (see Pycock et al 1978) has a biochemical basis. Thus the effects of apomorphine, a dopamine receptor agonist, and of (—)-dopa, the precursor of dopamine, given into the IIIrd cerebral ventricle were studied on GABA-ergic mechanisms in the diencephalon.

In addition, we planned to ascertain if the effects of (—)-dopa and apomorphine on GABA-ergic mechanisms are mediated through an increase in 3′,5′-cyclic adenosine monophosphate (cAMP). Therefore, an increase in intracellular cAMP was achieved by giving adenosine, the precursor of cAMP, to chicks pretreated with a phosphodiesterase inhibitor (Mc Ilwain 1971), or by giving the dibutyryl-derivative of cAMP directly as this crosses biological membranes and is more stable to enzymatic degradation (Gessa et al 1970).

Rhode Island Red chicks, 7 days old were kept in a cage maintained at thermoneutral ambient temperature for young chicks (Marley & Stephenson 1970). Cannulae were chronically implanted into the IIIrd cerebral ventricle by means of a 10 μl Hamilton syringe; the infusion rate was 1 μl min^{-1} and the maximum infusate volume was 2 μl. Control infusions of 1–2 μl of the vehicle (pyrogen free dist. H_2O) were without effects on behaviour and body temperature. The diencephalon was quickly dissected out and frozen in liquid nitrogen. GAD activity was assayed by measurement of the $^{14}CO_2$ formed from L-[1-^{14}C]glutamic acid in a liquid scintillator according to Nisticò et al (1979a,b). Preliminary experiments have shown that in our conditions $^{14}CO_2$ loss was approximately 1·5–2%. To avoid non GAD-dependent decarboxylation of glutamate, Triton X-100 (final concn 0·5%) was added to the reaction mixture. GABA content was determined by the enzymatic fluorimetric procedure of Graham & Aprison (1966), as modified by Balcom et al (1975). GABA-transaminase (GABA-T) activity was determined by a radiometric assay (Less & Weiner 1975).

(—)-Dopa and adenosine were from Fluka, apomorphine hydrochloride from Macfarlan Smith Ltd., aminophylline from Macarthys Ltd. Essex, dibutyryl-cAMP from Sigma Chemical Co.), L-[1-^{14}C]glutamic acid and U-[-^{14}C]-γ-aminobutyric acid from Amersham, U.K. GABAase was from Sigma Chemical Co., St. Louis, USA; α-ketoglutaric acid, NADP and NADPH, from Boehringer Mannheim Gmbh, Germany. Other compounds used were the highest purity commercial products available.

Both (—)-dopa and apomorphine given into the IIIrd cerebral ventricle significantly stimulated GABA synthesis. In particular, (—)-dopa given for four consecutive days (0·25 μmol each day, last administration 30 min before) produced, in comparison with control chicks receiving the same volume of the vehicle, a significant increase in GAD-activity and in GABA content in the diencephalon (Table 1). An increase in GAD activity and in GABA was also observed after apomorphine given intraventricularly for four consecutive days (0·5 μmol each day) (Table 1). No changes were observed in GABA-transaminase activity. A single intraventricular injection of dibutyryl-cAMP (0·2 μmol), or of adenosine (0·2 μmol), in chicks pretreated with aminophylline (100 μmol kg^{-1} i.m. 30 min before) increased GAD activity and GABA content in the diencephalon 15 min later (Table 2).

Previous experiments have shown that in rat striatum (Lloyd & Hornykiewicz 1973) and substantia nigra (Kim & Hassler 1975; Lloyd et al 1977) long-term

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