Effect of amphetamine and amphetamine-like drugs on homovanillic acid concentration in the brain

It is generally assumed that amphetamine excitatory behaviour (hypermotility and stereotyped activity) and hyperthermia are related to an interaction with the brain catecholamines. Monoamine oxidase inhibition, release of intra- or extra-granular stored catecholamines (Hanson, 1967; Stein & Wise, 1967), blockade of the amine pump at the cell membrane (Carlsson, Lindqvist & others, 1965; Carlsson, Fuxe & others, 1966), modifications of noradrenaline and dopamine turnover (Javoy, Thierry & others, 1968) have been alternatively implicated.

We report here the effect of amphetamine on homovanillic acid (HVA) concentration in the neostriatum. In an attempt to correlate the modifications of HVA with the hyperthermic response we have compared amphetamine with two amphetamine-like drugs lacking hyperthermic activity, fenfluramine (Le Douarec, Schmitt & Laubie, 1966; Jespersen, Bonaccorsi & Garattini, 1969) and S 992 compound [trifluoromethylphenyl(benzoyloxy)ethylamino-2-propane; Laboratoires Servier, Paris, France]. As all the agents show anorexic properties, the anorexigenic activity was also measured in relation to the reported biochemical modification.

Sprague-Dawley female rats (150 $\pm$ 10 g) and female Swiss mice (20–22 g) were used. HVA was measured on pooled neostriata of 4 animals for each sample (Anden, Roos & Werdinius, 1963).

Increase in striatum HVA after (+)-amphetamine sulphate administration appears in mice and rats at relatively high dosages. These results confirm the evidence obtained by Laverty & Sharman (1965) in cats and by Pletscher (1969) in rats and are compatible with the reported increase in synthesis (Javoy & others, 1968) and turnover (Javoy & others, 1968; Costa & Groppetti, 1969) of dopamine into striatum after amphetamine, but they would not support the possibility that high doses of amphetamine may significantly block the monoamine oxidase *in vivo* (Carlsson, 1969; Glowinski, 1969).

Fig. 1 shows a correlation of neostriatum HVA concentration and hyperthermia in rats. But as it appears in Table 1, this correlation is only casual, because amphetamine elicits the usual effect on neostriatum HVA also in particular experimental conditions such as the isolation of animals and the lowering of room temperature when the hyperthermic effect was reduced. Furthermore fenfluramine and S 992 increased neostriatum HVA without affecting body temperature.

However, in the case of fenfluramine this lack of correlation of pharmacological and biochemical responses may be attributed to a possible central adrenolytic property of the compound (Gomulka & Bonaccorsi, unpublished data) masking the typical hyperthermic activity of amphetamine-like drugs. It is interesting in this respect that fenfluramine is able to elicit, in given experimental conditions, an anti-amphetamine activity (Bizzi, Bonaccorsi & others, 1969).

Other adrenolytic drugs such as chlorpromazine (Da Prada & Pletscher, 1966a,b) or haloperidol (Pletscher & Da Prada, 1967), showing hypothermic activity, also induce an important increase in HVA brain concentration following an increased turnover of dopamine. This effect was suggested to be related to a feed-back mechanism that enhances the dopamine synthesis as a result of a block of dopaminergic receptors evoked by chlorpromazine (Nybäck, Sedvall & Kopin, 1967; Gey & Pletscher, 1968; Da Prada & Pletscher, 1966a,b). A similar effect might explain the increase in neostriatum HVA induced by fenfluramine. However, an effect of fenfluramine on the removal of HVA from brain cannot be excluded.

As far as correlations of anorexic activity and HVA are concerned, the observation that the anorexic effect of amphetamine and fenfluramine occurs at doses which do

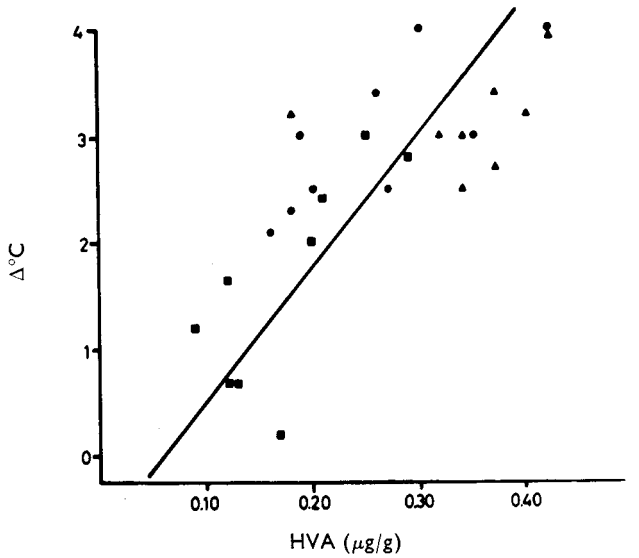

FIG. 1. Correlation between increase of body temperature and neostriatum HVA 1 h after 7·5 (■), 15 (●) or 30 (▲) mg/kg, i.p. of (+)-amphetamine sulphate to rats. Each point represents a pool of 4 animals.

not elicit an increase in neostriatum HVA is relevant (Bizzi, Bonaccorsi & others, 1969). Accordingly data reported in Table 2 indicate that after repeated treatments with fenfluramine, tolerance to anorexia develops without a corresponding modification of the effect on HVA in the neostriatum. On the contrary, repeated treatments with amphetamine, do not modify the effect on food intake, at least in the 2 h after the last injection, but completely remove the effect on HVA.

Table 1. *Effect of (+)-amphetamine sulphate and amphetamine-like drugs on body temperature and brain HVA concentration in rats and mice*

Determinations	Species	Treatment (mg/kg, i.p.)		Body temperature (° C ± s.e.)	Striatum HVA (μg/g ± s.e.)
11	Mouse	Saline		37·0 ± 0·2	0·13 ± 0·01
14	,,	Amphetamine	7·5	38·9 ± 0·4*	0·26 ± 0·01*
6	,,	Fenfluramine	15	36·7 ± 0·2	0·26 ± 0·04*
5	,,	S 992	15	37·0 ± 0·2	0·20 ± 0·03*
13	Rat	Saline		36·7 ± 0·1	0·14 ± 0·01
9	,,	Amphetamine	7·5	38·1 ± 0·3*	0·18 ± 0·02
9	,,	,,	15	39·6 ± 0·3*	0·26 ± 0·03*
8	,,	,,	30	41·0 ± 0·2*	0·36 ± 0·01*
4	,,	,, †	15	38·1 ± 0·6	0·26 ± 0·01*
4	,,	,, ‡	15	37·2 ± 0·5	0·30 ± 0·04*
7	,,	Fenfluramine	15	38·0 ± 0·1	0·28 ± 0·01*
6	,,	,,	30	37·2 ± 0·5	0·34 ± 0·03*
9	,,	S 992	15	36·9 ± 0·1	0·28 ± 0·01*
5	,,	,,	30	36·7 ± 0·3	0·36 ± 0·03*

Drugs were given 1 h before determinations.
Experiments were usually made at a room temperature of 22°.
Animals were grouped (4 rats and 6 mice per cage).
Each determination is the mean of 4 animals.
* $P < 0{\cdot}01$ versus saline.
† Animals were isolated.
‡ Room temperature 18°.

Table 2. *Effect of (+)-amphetamine sulphate and (±)-fenfluramine chloride on food intake and neostriatum HVA concentration*

Determinations	Treatment (mg/kg i.p.)		Food intake g/2 h per rat ± s.e.	Neostriatum HVA (μg/g ± s.e.)
7	Saline		16·8 ± 0·9	0·15 ± 0·01
2	Amphetamine	15	0·5	0·37
2	Fenfluramine	15	1	0·32
7	*Amphetamine	15	0	0·09 ± 0·02‡
4	*Fenfluramine	15	10·2 ± 1·4†	0·38 ± 0·02†

* Rats receiving (±)-fenfluramine chloride or (+)-amphetamine sulphate (5 mg/kg, i.p.) daily for 4 days.

24 h after the last treatment, animals were injected with 15 mg/kg of drugs.

Experiments were made with 40 h fasted rats.

Food intake and HVA concentration were measured 2 h after the last treatment.

Each determination is the mean of 4 animals.

† $P < 0.01$ versus saline.

‡ $P < 0.05$ versus saline.

In conclusion these experiments suggest that hyperthermic and anorexic activity of amphetamine as well as the anorexigenic effect of fenfluramine are not related to the alterations of dopamine metabolism in neostriatum or, at least, that HVA neostriatum concentration is not a suitable parameter to evaluate central biochemical mechanisms responsible for these pharmacological actions.

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The effects of α- and β-sympathicomimetics on rumen motility and heart rate frequency in conscious goats

In the ruminal smooth muscle preparation *in vitro* there exist α-stimulatory and β-inhibitory adrenergic receptors. The effect of adrenaline, either contraction or relaxation, is the result of interactions with both types of receptors (van Miert & Huisman, 1968). It is of interest to note that Titchen & Newhook (1968), who made their experiments with anaesthetized vagotomized sheep and lambs or with vagotomized decerebrate preparations of lambs, reported similar adrenergic mechanisms near the reticulo-omasal orifice.

Adrenaline is known to cause a single slow contraction of reticulum, rumen and abomasum in unanaesthetized vagotomized sheep (Habel, 1956). This is also the case in the anaesthetized goat with intact vagi. However, normal cyclical movements of the reticulo-rumen cease after the vagus nerves have been cut or after induction of anaesthesia. An intravenous injection of adrenaline in the conscious ruminant always gives an inhibition of the regular contractions of the rumen, although it is not known whether α- or β-adrenergic receptors, or both, are involved in this phenomenon. I now report the effects of sympathicomimetics activating α- or β-adrenergic receptors.

Materials and methods. An open-ended water filled polyethylene tube was passed into the rumen intra-nasally, and the other end connected to a pressure transducer. An electrically driven slow-infusion pump was also connected to prevent occlusion of the tube with food particles. The volume of fluid administered was 1 ml/min. Pressure records made in this way show the well-known regular contractions of the rumen occurring with a frequency of about 1/min. The frequency and the amplitude

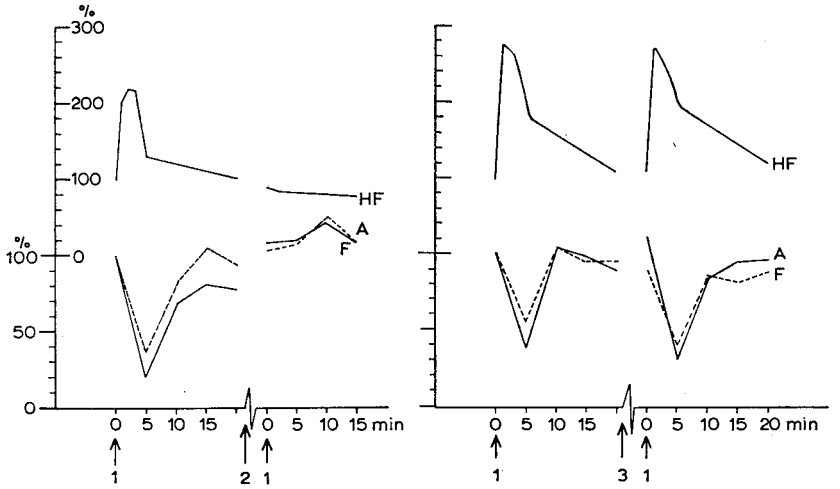

FIG. 1. Mean change in rumen motility for 3 goats to isoprenaline 2·5 μg/kg i.v. (= 1) before and after propranolol 0·5 mg/kg i.v. (= 2) or dibenamine 2·5 mg/kg i.v. (= 3) respectively. A—Summation during 5 min intervals of amplitude, expressed as percentage of the initial value. F—Frequency/5 min expressed as percentage of the initial value. HF—Change in heart rate.