Hypotensive action of tyramine in cats

SIR,—During experiments on the interaction between cheese and monoamine-oxidase inhibitors in cats (Maj & Langwiński, 1966) we noticed that repeated administration of tyramine decreased the blood pressure. We now report on investigation of this depressor action.

The experiments were made on 38 cats anaesthetised with chloralose (80 mg/kg, i.p.), most of them pretreated with nialamide (20 mg/kg, i.p.). Blood pressures were recorded from the carotid artery by a mercury manometer and all the substances were injected into a femoral or jugular vein.

Repeated doses of tyramine were given until complete tachyphylaxis to its pressor effect was obtained, the total dose being 4–8 mg/kg. After this, the subsequent injection produced only a depressor response. The minimal hypotensive dose of tyramine was 1–3 mg/kg. Higher doses (10–50 mg/kg) caused a 30–70 mm Hg fall in blood pressure. The onset of the depressor response was delayed for 15–30 sec, and the minimal level was seen 1–2 min after injection and then the blood pressure increased gradually to reach the initial value within 5–15 min. In some cats, after the large doses, the blood pressure did not return at all. The hypotensive effect was observed also in cats not treated with nialamide, but under these conditions the total dose of tyramine needed to induce the blood pressure decrease was 3–5 times greater. After reserpine (3 mg/kg, i.p.) injected one day before, the depressor response to tyramine appeared more rapidly than in untreated animals.

The hypotensive action of tyramine was not influenced by bilateral cervical vagotomy, pretreatment with atropine sulphate (0·5 mg/kg) blockade of the α-adrenergic receptors with dihydroergotamine (0·3 mg/kg) or of the β-adrenergic receptors with dichloroisoprenaline (5–10 mg/kg). It was antagonised only by the antihistamine drugs, antazoline hydrochloride (10–30 mg/kg) and cyclizine hydrochloride (2 mg/kg).

The depressor response to tyramine has also been observed after repeated doses in rats anaesthetised with urethane (1 g/kg), especially in those previously treated with nialamide. The doses of 2–8 mg/kg produced a 20–70 mm Hg blood pressure fall. Atropine had no influence on this action, but antazoline abolished it.

Tyramine (5×10^{-4}) contracted the isolated guinea-pig ileum, an effect partially antagonised by atropine (10^{-6}). Antazoline ($10^{-6} - 10^{-5}$) protected the atropinised ileum completely against the contractive action of tyramine.

The results of our experiments on the depressor response to tyramine, especially the delayed onset and the antagonistic effect of antihistamine drugs seem to indicate that this action of tyramine is mediated through the release of histamine. The fact that the response was more pronounced in cats pretreated with monoamine oxidase inhibitor may be a consequence of a simultaneous diamine oxidase blockade, well known from the literature. In fact we have observed a stronger hypotensive action of exogenous histamine in these cats.

The hypotensive action of tyramine in some species has been reported by several authors. Dresse & Cession-Fossion (1961) observed it in rats pretreated with guanethidine. Maxwell & others (1959) observed it in reserpinised dogs, but they did not analyse it. Vanderipe & Kahn (1964) reported a number of facts indicating that the depressor response to tyramine in dogs depends on the histamine liberation. According to Chandra, Dhawan & Gupta (1965) this response in dogs may be induced by the release of acetylcholine. Only Paton (1957) suggested the histamine releasing properties of tyramine in cats from the skin preparation.

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References

Chandra, O., Dhawan, K. & Gupta, G. (1965). *Archs int. Pharmacodyn. Thér.*, **157**, 141–147.
Dresse, A. & Cession-Fossion, A. (1961). *C. r. Séanc. Soc. Biol.*, **155**, 2212–2214.
Maj, J. & Langwiński, R. (1966). *Polski Tygod. lek.* **21**, 562–564.
Maxwell, R., Powalski, H. & Plummer, A. (1959). *J. Pharmac. exp. Ther.*, **125**, 178–183.
Paton, W. D. M. (1957). *Pharmac. Rev.*, **9**, 269–314.
Vanderipe, D. & Kahn, J. (1964). *J. Pharmac. exp. Ther.*, **145**, 292–298.

The effect of ethanol on the activity of central catecholamine neurones in rat brain

SIR,—There are no apparent changes in the dopamine, noradrenaline or 5-hydroxytryptamine levels in rabbit and rat brain after administration of ethanol (Häggendal & Lindqvist, 1961; Efron & Gessa, 1963). But although the amine levels are unaffected, this does not exclude the possibility that the activity of the central monoamine neurones may be influenced by ethanol. As a result of the development of inhibitors of the rate-limiting step in catecholamine synthesis it has now become possible to examine the activity of the central catecholamine neurones directly at cellular level by the histochemical fluorescence technique (Hillarp, Fuxe & Dahlström, 1966). These experiments showed that the release and synthesis of amine is dependent on neuronal activity (Fuxe & Gunne, 1964; Dahlström, Fuxe, Kernell & Sedvall, 1965; Andén, Corrodi, Dahlström, Fuxe & Hökfelt, 1966; Corrodi & Malmfors, 1966). H 44/68 (DL-α-methyl-tyrosine-methylester) used in this and previous studies (Corrodi, Fuxe & Hökfelt, 1966a) inhibits the biosynthesis of noradrenaline and dopamine without affecting the uptake-storage mechanism of the amine granules (Andén & others, 1966; Corrodi, Fuxe & Hökfelt 1996b; Corrodi & Hanson, 1966).

The present communication affords evidence that changes do occur in the central catecholamine neurones during treatment with ethanol as revealed by both histochemical and biochemical techniques.

Male, Sprague-Dawley rats (150–250 g) were treated with ethanol (2 g/kg as a 5% solution i.p. and H 44/68 (250 mg/kg i.p.). Some animals were given one injection of ethanol and this was followed by H 44/68 15 min later. The rats were then killed 2, 4 or 6 hr later. Other animals were given two doses of ethanol, H 44/68 was administered to these 15 min after the first dose and 4 hr before death; the second dose of ethanol was given 1½ hr before death by which time the animals were asleep without a righting reflex. The whole brains were dissected and analysed separately for dopamine and noradrenaline (Bertler, Carlsson & Rosengren, 1958; Carlsson & Waldeck, 1958; Carlsson & Lindqvist, 1962). Control rats were given either ethanol or H 44/68. The rectal temperature in all animals was found to be normal. After the ethanol the animals showed no signs of peritoneal pain nor did the peritoneal cavity show inflammation.

In the histochemical study the effect of two different doses of ethanol (1 and 2 g/kg) was investigated. Ethanol was administered intraperitoneally once or twice as described above. The animals were killed 4 hr after the i.p. injection of H 44/68 (250 mg/kg) which was given 15 min after the ethanol. Other rats were given ethanol (2 g/kg) by mouth and after H 44/68 treatment as described they