Inhibition of noradrenaline synthesis and the pressor response to tyramine

SIR,—The hypothesis of Burn & Rand (1958), that tyramine affects the liberation of noradrenaline from sympathetic nerve endings, has received experimental confirmation from a number of laboratories. Reduction of noradrenaline stores may not parallel the reduction in response to tyramine (Bhagat, Kopin, Gordon & Booker, 1964; Bhagat, Gordon & Kopin, 1965) and the concept of an "available" or a "tyramine releasable" store of noradrenaline has been presented by a number of investigators (Trendelenburg, 1961; Kopin & Gordon, 1962; Bhagat, 1964). In atria from reserpinised guinea-pigs only 1% of the noradrenaline in the stores is required to restore about 70% of the response to tyramine (Crout, Muskus & Trendelenburg, 1962).

This letter reports the effect of an inhibition of synthesis by a tyrosine hydroxylase inhibitor on the pressor response to tyramine.

Experiments were made on mongrel dogs weighing 8–12 kg which were either anaesthetised with chloralose (80–100 mg/kg i.v.) or were spinalised. Blood pressure was recorded from the femoral artery by a mercury manometer. All drugs were injected into a cannula inserted into the femoral vein and were flushed in with 1 ml of 0·9% saline; α-methyltyrosine (60 mg/kg i.v.), a potent inhibitor of tyrosine hydroxylase (Spector, Sjoerdsma & Udenfriend, 1964), was used to block the synthesis of noradrenaline. Catecholamines were determined by the trihydroxyindole fluorometric assay of Shore & Olin (1958).

It was found that α-methyltyrosine reduced the vasopressor response to occlusion of the carotid arteries as well as to tyramine. If the inhibition of the pressor response to tyramine produced by acute administration of α-methyltyrosine were due to this compound's depleting effect on tissue stores of noradrenaline, myocardial catecholamine should be reduced. But, in a separate group of animals treated with α-methyltyrosine alone, the catecholamine concentrations in ventricles were not altered significantly. The mean value (±s.e.) for these hearts was 1·12 (0·04) μg/g. The comparable value obtained for a group of 3 untreated control dogs was 1·07 (0·05) μg/g.

Since there were no alterations in the catecholamine levels, sensitivity of the receptors to exogenous noradrenaline was tested in 4 spinalised dogs before and after the administration of α-methyltyrosine. It was observed that there was a shift of the dose-response to the right. Perhaps reduced sensitivity to noradrenaline may explain the inhibition of the response to tyramine. Tyramine may be releasing the same amount of noradrenaline from its storage site(s) in the postganglionic sympathetic nerve endings, but the amount released would be acting on the affector cells at the sites involved, the sensitivity of which to noradrenaline is reduced.

Whether the reduced sensitivity to noradrenaline is a result of blockade in synthesis or is caused by a direct action of α-methyltyrosine on the adrenergic receptors has yet to be shown.

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Effect of γ-aminobutyric acid upon brucine convulsions

SIR,—γ-aminobutyric acid (GABA) when applied to the surface of the cerebral cortex of certain mammalian species has been shown to protect the animals from electrically or chemically induced seizures (Purpura & Grundfest, 1956; Purpura, Girado & Grundfest, 1957). Furthermore it has been shown by several investigators that acute parenteral administration of GABA protects animals from electrically or chemically induced seizures (Hawkins & Sarett, 1957; McLennan, 1957; 1958). During the course of our experiments we found that, shortly after parenteral administration of GABA (3·0 g/kg) to rats, no protection from electrically induced seizures and strychnine seizures was observed. Pylkkö & Woodbury (1959) showed that the CD50 of strychnine was increased in rats pretreated with GABA 72 hr before treatment with the convulsant.

Since brucine differs from strychnine by having two methoxyl groups attached to the aromatic ring, it was of interest to study the possible protective properties of GABA against brucine seizures and to study the time course of any protective properties found.

Mature male albino Holtzman rats were pretreated with 3·0 g/kg GABA intraperitoneally and brucine alkaloid was administered after 3, 8, 15, and 30 days. The CD50 values for these animals were calculated ($CD50_1$) according to the method of Litchfield & Wilcoxon (1949). The CD50 values for brucine alkaloid ($CD50_2$) were calculated at the same time intervals for rats without GABA pretreatment. The potency ratio (P.R. = $CD50_1/CD50_2$ and the $f_{P.R.}$ were calculated by the method of Litchfield & Wilcoxon (1949).

TABLE 1. EFFECT OF GABA ON CD50 OF BRUCINE ON GROUPS OF 36 RATS

Weight of rats g	Days after GABA	$CD50_1$ with GABA	$CD50_2$ without GABA	Potency ratio	$f_{P.R.}$
83–132	3	117·0 (92·1–148·6)	71·8 (61·0–83·3)	1·63 (1·20–2·20)	1·35
112–170	8	91·0 (70–118·3)	69·8 (61·2–79·6)	1·30 (0·96–1·75)	1·35
112–218	15	88·0 (69·3°111·7)	72·0 (61·5–84·2)	1·22 (0·9–1·65)	1·35
93–220	30	82·0 (74·6–90·2)	82·0 (73·2–91·0)	1·0 (0·83–1·20)	1·2

It is evident from Table 1 that three days after GABA administration, the CD50 of brucine was elevated significantly. Thus the present observations seem to indicate that the anticonvulsant activity of GABA is not seen until three days after its parenteral administration.

Since Eccles (1956) has established that strychnine selectively blocks the inhibitory synapses in the central nervous system, it is possible that its dimethoxyl derivative, brucine, acts similarly. It is therefore of interest that the convulsant