Inhibition of the dual amine uptake-concentration mechanisms of the adrenergic neurons by ϵ-aminocaproic acid

SIR,—Two different amine uptake-concentration mechanisms of the adrenergic neurons, namely, the amine transport through the nerve cell membrane, the "membrane pump", and subsequent incorporation in the storage granule complex have been demonstrated (Carlsson, Hillarp & Waldeck, 1963; Hillarp & Malmfors, 1964; Malmfors, 1965; Carlsson & Waldeck, 1965). The former mechanism can be selectively blocked with such agents as protriptyline and desipramine while the latter mechanism can be selectively blocked with such agents as reserpine and prenylamine (segontin) (Carlsson & Waldeck, 1965; Malmfors, 1965). Guanethidine inhibits both these mechanisms (Lindmar & Muscholl, 1964; Shore & Giachetti, 1966; Carlsson & Waldeck, 1966).

ϵ-Aminocaproic acid (EACA), a 6-carbon acyclic carboxylamine compound, has been shown to cause almost complete depletion of noradrenaline from the heart of rats (Lippmann & Wishnick, 1965; Andén, Henning & Obianwu, in preparation). This compound has many pharmacological properties similar to those of guanethidine (Andén, Henning & Obianwu, in preparation), though there are important differences. For example, unlike guanethidine, the adrenergic nerve blockade induced by EACA is accompanied by a measurable loss of tissue noradrenaline.

The ability of EACA to inhibit the dual amine uptake-concentration mechanisms of the adrenergic neurons is reported below. For comparison, substances whose actions on these mechanisms have been previously demonstrated are included in the studies.

As an indicator of amine uptake, ^{3}H-metaraminol was used. Metaraminol appears to utilize similar transport and storage mechanisms to noradrenaline (see Carlsson & Waldeck, 1966). Substances such as reserpine and prenylamine which impair the storage mechanism of the amine granules do not significantly affect the uptake of ^{3}H-metaraminol 30 min after its administration whereas substances such as desipramine and guanethidine greatly inhibit its uptake at this time. But both these groups of substances reduce the amount of ^{3}H-metaraminol retained after 3 hr. By estimating the degree of inhibition of ^{3}H-metaraminol 30 min and 3 hr after its administration it is possible to determine which of the two uptake-concentration mechanisms is inhibited by a drug.

Male Sprague-Dawley rats 200–250 g were used. The test substances were administered in the doses indicated in Fig. 1 by intraperitoneal injection and 60 min later, ^{3}H-metaraminol (10 μg/kg) was administered intravenously into the tail; the animals were killed 30 or 180 min after ^{3}H-metaraminol. ^{3}H-Metaraminol was administered 18 hr after in rats given reserpine. In another series of experiments, the jugular veins were cannulated under light ether anaesthesia and the rats were used 2–3 days later. ^{3}H-Metaraminol (10 μg/kg) was administered 15 min after desipramine (0·5 mg/kg) and the rats killed 30 or 180 min later. Both drugs were injected via the cannula. The controls from this series of experiments gave results similar to those from the former series. ^{3}H-Metaraminol in the hearts was estimated by the method previously described by Carlsson & Waldeck (1965). The results are presented in Fig. 1. The initial uptake of ^{3}H-metaraminol (30 min after i.v. injection) was not significantly affected by reserpine and prenylamine but was reduced to about 50% of the control levels by guanethidine, EACA and desipramine. This represents inhibition of the membrane pump mechanism. Three hr after ^{3}H-metaraminol all the substances except desipramine showed clearcut reduction of the amount of ^{3}H-metaraminol retained. This inhibition represents inhibition of the storage

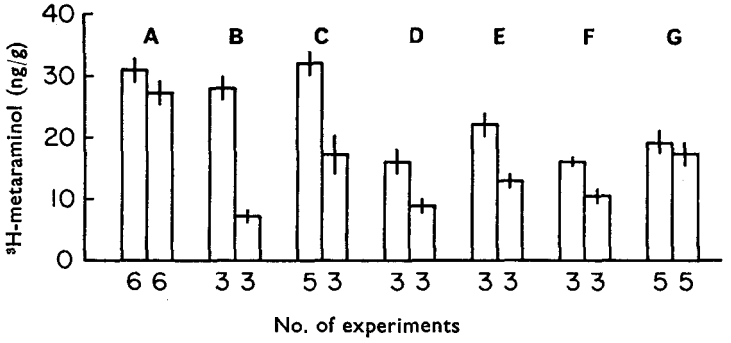

FIG. 1. Effect of various drugs on the uptake of ^{3}H-metaraminol by rat heart. The rats were given guanethidine, EACA or prenylamine 60 min, in the case of reserpine and desipramine 18 hr and 15 min respectively before i.v. administration of ^{3}H-metaraminol (10 μg/kg). The animals were killed 30 or 180 min after ^{3}H-metaraminol. The control rats received saline. The left column of each pair represents the level of ^{3}H-metaraminol 30 min and the right one 180 min after its administration. A, control. B, reserpine, 5 mg/kg. C, prenylamine, 30 mg/kg. D, guanethidine, 15 mg/kg. E, EACA, 500 mg/kg. F, EACA, 1000 mg/kg. G, desipramine, 0·5 mg/kg.

mechanism. The level of ^{3}H-metaraminol 180 min after its administration was not significantly different from that after 30 min in rats treated with desipramine. In fact, the difference (2·5 ng/g) was less than that of the control (3·7 ng/g). This indicates that desipramine, a potent inhibitor of the membrane pumps has no significant effect on the storage mechanism of the amine granules.

EACA in a dose of 500 mg/kg caused only a moderate inhibition of the membrane pump mechanism. This dose also caused only a moderate sympathetic blockade (Andén, Henning & Obianwu, in preparation). However, in a dose of 1000 mg/kg (LD50 = 7·0 g/kg) which had a more pronounced sympathetic blockade, the membrane pump mechanism was inhibited to the same extent as that caused by guanethidine. The present studies demonstrate that EACA inhibits the dual uptake-concentration mechanisms of the adrenergic neurons and provide further evidence in support of the view that reserpine and prenylamine inhibit the storage mechanism while guanethidine inhibits both the membrane pump and the storage mechanisms of the adrenergic neurons.

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