Monoamine oxidase inhibition and bretylium on adrenergic neuronal transmission

Bretylium is known to exert a monoamine oxidase inhibitory action *in vivo* (Malmfors, 1968; Clarke & Leach, 1968); I have now investigated this effect of bretylium upon adrenergic neuronal transmission.

Female Wistar rats were anaesthetized with either sodium pentobarbitone (60 mg/kg) or urethane (1·5 g/kg) both given intraperitoneally. The systemic blood pressure was recorded from the right common carotid artery and drugs were administered into a femoral vein. Intravenous eserine (25–40 μg) was used to stimulate the sympathetic nervous system.

Pretreatment of rats with nialamide (100 mg/kg, i.p.), for 2 or 18 h did not affect the pressor response to eserine, nor did it prevent the ability of bretylium (5 or 10 mg/kg, i.v.) to antagonize the eserine response (Fig. 1a). Under these conditions dexamphetamine (100 μg, i.v.) produced a reversal of the bretylium-induced blockade of eserine.

It seems that the acute adrenergic neuronal blocking activity of bretylium is not linked with any monoamine oxidase inhibitory property of this drug. Under these experimental conditions bretylium exerted a pronounced hypotensive effect showing that it can block not only the excessive and possibly, therefore, atypical sympathetic discharge attributed to eserine, but also the far less intense resting sympathetic discharge contributed by the anaesthesia. This correlates well with the effects of

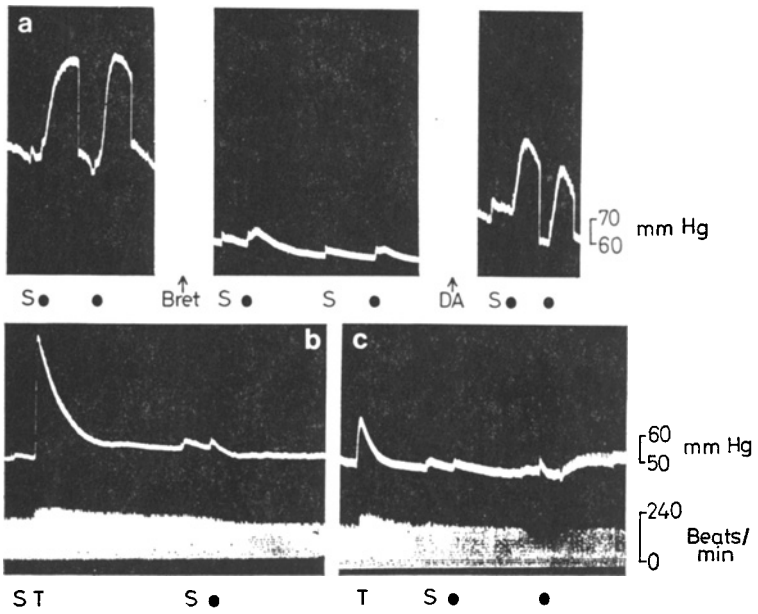

FIG. 1. (a) Rat blood pressure, sodium pentobarbitone anaesthesia, pretreated with nialamide, 100 mg/kg for 2 h. Effect of bretylium (BRET), 5 mg/kg, on the response to eserine (●), 30 μg. Dexamphetamine, 100 μg, was given at (DA). (b) Rat blood pressure (upper record) and heart rate (lower record), sodium pentobarbitone anaesthesia, reserpine-treated, 5 mg/kg for 18 h + nialamide 100 mg/kg for 6 h. Effect of nialamide treatment on the response to tyramine (T), 50 μg and eserine (●), 40 μg. (c) As in (b) except bretylium 5 mg/kg was given for 6 h. S = 0·3 ml normal saline.

bretylium seen under normal conditions in the rat (Cass & Spriggs, 1961), as does the reversal of adrenergic neuronal blockade with dexamphetamine (Spriggs, 1966), and implies that the normal pharmacological mechanism of action of bretylium in sympathetic nerve blockade was in no way altered by monoamine oxidase inhibition.

In rats anaesthetized with sodium pentobarbitone and pretreated with reserpine (5 or 10 mg/kg) for 18 h, the cardiovascular response to tyramine (50 μg) was abolished and repeated doses of eserine failed to give rise to a pressor response. The pretreatment of reserpinized rats with nialamide (100 mg/kg) or bretylium (5 mg/kg) given subcutaneously 6 h before use, restored the cardiovascular response to tyramine but caused little or no restoration of the response to eserine (Fig 1, b and c). In non-reserpinized rats there is an almost complete recovery of the hypertensive effect of eserine, 5 to 6 h after an intravenous injection of bretylium (5 mg/kg). Finally, neither the bretylium or nialamide pretreatment described above, caused a rise in the resting level of the systemic blood pressure or heart rate of reserpinized rats beyond that normally encountered in these preparations.

The restoration of the cardiovascular response to tyramine is consistent with the monoamine oxidase inhibitory actions attributable to bretylium and nialamide under reserpinized conditions and is probably mediated through the accumulation of endogenously formed catecholamines within the postganglionic adrenergic nerves. The specific intraneuronal location of this amine fraction might well account for its inability to be released by sympathetic nerve impulses. However, with bretylium, the assumption has to be made that its noted duration of adrenergic neuronal blockade in non-reserpinized rats is still applicable under reserpinized conditions.

The restoration of adrenergic transmission obtained by Häggendal & Malmfors (1969) with nialamide in reserpinized rats given a subsequent injection of dopamine, appeared to be mediated through the release of newly synthesized noradrenaline. In the experiments here reported, it is highly probable that insufficient endogenously formed amine occurred under the nialamide treatment to overcome the competitive inhibitory effect of reserpine on the intraneuronal granular binding mechanism (Stjärne, 1966) at the site held to be responsible for adrenergic nerve function (Häggendal & Malmfors, 1969). In this respect, Stjärne (1966) has provided evidence that the biosynthesis of noradrenaline is much less sensitive to inhibition by reserpine than is the granular storage mechanism.

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