Biochemical Pharmacology, 1967, Vol. 16, pp. 237–238. Pergamon Press Ltd., Printed in Great Britain.

PRELIMINARY COMMUNICATION

Monoamine oxidase inhibition in the adrenergic neuron by bretylium, debrisoquin, and other adrenergic neuronal blocking agents

(*Received* 18 *August* 1966; *accepted* 28 *September* 1966)

THE MECHANISM whereby those antihypertensive drugs known as adrenergic neuronal blocking agents (TM 10, bretylium, debrisoquin, bethanidine, etc.) exert their hypotensive action is not understood, although it is realized that these agents somehow interfere with the physiological release of norepinephrine.[1] The clinical hypotensive action of classical monoamine oxidase (MAO) inhibitors, such as iproniazid, is also poorly understood, although several hypotheses have been presented, as described in a recent review.[2] We have uncovered evidence that some adrenergic neuronal blocking agents inhibit MAO in the adrenergic neuron, suggesting the possibility that a part, at least, of the antihypertensive action of these drugs may be manifested by a mechanism similar to that of the classical MAO inhibitors.

Slices of rabbit heart were incubated with low concentrations of *l-m*-octopamine or *l*-metaraminol, and accumulation of these amines in the slices was measured, as described previously.[3] Addition of bretylium (Darenthin) (2×10^{-6} M) or debrisoquin (Declinax) (10^{-6} M) markedly increased the accumulation of *l-m*-octopamine, a MAO substrate, but did not enhance, in fact decreased, accumulation of *l*-metaraminol, a non-MAO substrate (Table 1). No enhancement of *l-m*-octopamine accumulation was seen when the concentration of bretylium or debrisoquin was increased to 10^{-4} M, while uptake of *l*-metaraminol was largely blocked at the higher concentration (Table 1). Since metaraminol

TABLE 1. EFFECT OF BRETYLIUM AND DEBRISOQUIN ON AMINE ACCUMULATION BY RABBIT HEART SLICES

Drug	Net amine uptake (μg/ml slice water $\pm$ S.E.)	
	l-m-Octopamine	*l*-Metaraminol
None	0·18 $\pm$ 0·01	0·34 $\pm$ 0·02
Bretylium, 2×10^{-6} M	0·58 $\pm$ 0·04	0·35 $\pm$ 0·05
Bretylium, 10^{-4} M	0·26 $\pm$ 0·02	0·10 $\pm$ 0·01
Debrisoquin, 10^{-6} M	0·97 $\pm$ 0·04	0·26 $\pm$ 0·02
Debrisoquin, 10^{-4} M	0·09 $\pm$ 0·02	0·04 $\pm$ 0·02

Slices were prepared and incubated with *l-m*-octopamine (0·2 μg/ml) or *l*-metaraminol (0·025 μg/ml) as described previously.[3] Incubation time was 60 min. Bretylium and debrisoquin were added at the start of the 15-min preincubation period. Net uptake denotes accumulation/ml slice water minus concentration in the medium.

accumulates in the heart slice by the action of an amine pump in the adrenergic neuronal membrane,[3] bretylium and debrisoquin at the higher concentrations must have inhibited the membrane amine pump in a manner similar to that of cocaine or imipramine.[3, 4] The enhanced accumulation of *l-m*-octopamine brought about by the lower drug concentrations, and the absence of an enhanced effect on *l*-metaraminol accumulation is similar to the effects seen with the classical MAO inhibitors iproniazid and pheniprazine.[3]

It is known that bretylium is concentrated in the adrenergic neuron,[1] and we have observed that debrisoquin is also highly concentrated in organs with a high degree of adrenergic innervation. We have also found that, like bretylium,[5] debrisoquin is a MAO inhibitor. It thus appears that these adrenergic neuronal blocking agents are contained within the adrenergic neuron in concentrations

sufficiently high to inhibit intraneuronal MAO. We have observed similar effects of other adrenergic neuronal blocking agents, bethanidine and BW 392C60, both of which are weak MAO inhibitors.[5]

Additional evidence supporting this hypothesis comes by taking advantage of the optical specificity of MAO. Thus, *l-m*-octopamine is a better MAO substrate than is *d-m*-octopamine, and, consequently the initial rate of accumulation of the dextro isomer in the heart slice proceeds more rapidly.[6] This difference in initial accumulation is abolished by pheniprazine or by low concentrations of bretylium or debrisoquin. Added to this evidence is the recent report[7] that bretylium, like classical MAO inhibitors, promotes the retention of norepinephrine by reserpinized guinea pig atria, thus leading to a similar conclusion.

Although guanethidine is also concentrated in the adrenergic neurone,[8] it has no MAO inhibitory action, even at a high concentration,[5] and thus does not share the action of bretylium and debrisoquin in promoting amine accumulation in the heart slice; in fact, it is an amine depleter and blocks accumulation of *l-m*-octopamine.[9]

Blockade of neuronal MAO by low concentrations of adrenergic neuronal blocking agents thus might be of importance in the antihypertensive response in man after oral administration of relatively small doses. This phenomenon also probably explains the action of bretylium in inhibiting reserpine or guanethidine-induced norepinephrine depletion.[10] This action of bretylium is again similar to that of classical MAO inhibitors.

Department of Pharmacology,
University of Texas Southwestern Medical School,
Dallas, Texas, U.S.A.

A. GIACHETTI
P. A. SHORE

REFERENCES

1. A. F. GREEN, *Adv. Pharmac.* **1**, 161 (1962).
2. A. PLETSCHER, *Pharmac. Rev.* **18**, 121 (1966).
3. A. GIACHETTI and P. A. SHORE, *Biochem. Pharmac.* **15**, 607 (1966).
4. A. CARLSSON, *Pharmac. Rev.* **18**, 541 (1966).
5. R. KUNTZMAN and M. M. JACOBSON, *Ann. N.Y. Acad. Sci.* **107**, 945 (1963).
6. A. GIACHETTI and P. A. SHORE, *Life Sci.* **5**, 1373 (1966).
7. R. F. FURCHGOTT and P. SANCHEZ-GARCIA, *Pharmacologist*, **8**, 176 (1966).
8. L. S. SCHANKER and A. S. MORRISON, *Int. J. Neuropharmac.* **4**, 27 (1965).
9. P. A. SHORE and A. GIACHETTI, *Biochem. Pharmac.* **15**, 899 (1966).
10. B. A. CALLINGHAM and R. CASS, *J. Pharm. Pharmac.* **14**, 385 (1962).