inhibition curve was produced that gave an IC_{50} of 6×10^{-9} M. With benzylamine and β-phenylethylamine as substrates, the inhibition curves were still sigmoid in shape, but the concetrations of clorgyline needed to inhibit the activity were much greater, with IC_{50} values of about 10^{-5} M. With tyramine a double sigmoid inhibition curve was produced, with a central plateau region separating the two sigmoidal components, which would indicate that this substrate is metabolized by both MAO-A and -B in the human left ventricle. No evidence could be found, with any of the substrates used, for the presence of a clorgyline-resistant amine oxidase.

Both (+)-amphetamine and desipramine were found to be competitive inhibitors of the MAO activity in washed mitochondrial fractions when 5-HT was used as substrate. The K_i values were 3.4×10^{-6} M and 1.0×10^{-4} × for (+)-amphetamine and desipramine respectively. Debrisoquine with 5-HT was a reversible non-competitive inhibitor with a K_i of 2.0×10^{-6} M. With benzylamine and β-phenylethylamine as substrates all three inhibitors were much less potent. This suggests that, in the human heart, these inhibitors are selective for the MAO-A type of activity as they appear to be in other animal tissues.

These results indicate that the MAO activity in the left ventricle of the human heart can be resolved into two components that appear to be MAO-A and -B as defined by Johnston (1968), but the clorgyline-resistant component has not been found.

Supported by a grant from the British Heart Foundation. D.P. is a Vandervell Foundation Scholar. We thank May & Baker, Ltd., for a gift of clorgyline (M&B 9302), and Roche Products, Ltd., for a gift of debrisoquine (Declinax).

References

FOWLER, C.J. & CALLINGHAM, B.A. (1977). The effect of age and thyroid hormones on the ability of the chick heart to deaminate monoamines. *J. Pharm. Pharmac.*, in press.

HALL, D.W.R., LOGAN, B.W. & PARSONS, G.H. (1969). Further studies on the inhibition of monoamine oxidase by M&B 9302 (clorgyline)—I. Substrate specificity in various mammalian species. *Biochem. Pharmac.*, **18**, 1447–1454.

JOHNSTON, J.P. (1968). Some observations upon a new inhibitor of monoamine oxidase in brain tissue. *Biochem. Pharmac.*, **17**, 1285–1297.

LYLES, G.A. & CALLINGHAM, B.A. (1975). Evidence for a clorgyline-resistant monoamine metabolizing activity in the rat heart. *J. Pharm. Pharmac.*, **27**, 682–691.

The effect of some dopamine agonists and antagonists on the rat anococcygeus muscle *in vitro*

A. GIBSON, T. JAMES, N. SHAW & E. TRACY

Department of Pharmacology, Chelsea College, University of London, London SW3 6LX

It is now widely accepted that dopamine (DA) is a neurotransmitter in the CNS. Recently, however, it has been postulated that DA may also function as an important neurotransmitter in the peripheral nervous system, affecting both gastrointestinal and cardiovascular activity (Thorner, 1975; Greenacre, Teychenne, Petrie, Calne, Leigh & Reid, 1976). Such hypotheses rely heavily on the degree of selectivity of the various DA agonists and antagonists employed. It was of interest therefore to observe the effects of some of these drugs on the rat anococcygeus muscle, a recently described smooth muscle preparation, closely associated with the colon, and possessing a dense noradrenergic innervation (Gillespie, 1972).

Pairs of anococcygeus muscles were dissected and set up in organ baths as described previously (Gillespie, 1972). Antagonists were left in contact with the muscle for 30 min, prior to measurement of agonist sensitivity.

The muscle responded to DA with a contraction, the characteristics of which were similar to those produced by noradrenaline (NA). Indeed, the muscle was only slightly less sensitive to DA than to NA. However, cocaine (100 ng/ml) produced a much greater leftward shift of the dose response curve to NA (50-fold) than that to DA (5-fold). The responses to both NA and DA were reduced by haloperidol (1 μg/ml), and by a similar degree.

The DA agonist apomorphine also contracted the muscle. However, a dose-response curve could not be obtained, since apomorphine produced an 'all-or-none' type of contraction, with a threshold of around 1 μg/ml. Unlike NA or DA, apomorphine often resulted in large oscillations in tone which persisted even after washout of the agonist. These appeared to be myogenic since they were not abolished by tetrodotoxin (5 μg/ml).

Bromocriptine, also believed to be a DA agonist,

did not contract the muscle. On the contrary it was found that bromocriptine antagonized the effects of NA and was equipotent in this respect with the α-adrenoceptor blocker phentolamine. Bromocriptine (100 ng/ml) also reduced the responses of the anococcygeus muscle to field stimulation. This effect was not due to a non-specific depression of muscle activity since the responses to carbachol were unaffected.

The dopamine antagonist pimozide also antagonized the actions of NA but was 8 times less effective than bromocriptine or phentolamine.

The above results seem to confirm that DA can act on peripheral α-adrenoceptors. Further, supposedly selective DA agonists can also interact with α-adrenoceptors, and may produce opposing effects. Indeed bromocriptine, rather than possessing only weak α-blocking properties (Thorner, 1975) was equipotent with phentolamine. It would seem therefore that the results of experiments using these drugs to elucidate the role of DA in the peripheral nervous system should be interpreted with caution.

References

GILLESPIE, J.S. (1972). The rat anococcygeus muscle and its response to nerve stimulation and to some drugs. *Br. J. Pharmac.*, **45**, 404–416.

GREENACRE, J.K., TEYCHENNE, P.F., PETRIE, A., CALNE, D.B., LEIGH, P.N. & REID, J.L. (1976). The cardiovascular effects of bromocriptine in parkinsonism. *Br. J. Clin. Pharmac.*, **3**, 571–574.

THORNER, M.O. (1975). Dopamine—an important neurotransmitter in the autonomic nervous system. *Lancet*, **i**, 662–664.

Potentiation of cardiac sympathetic nerve responses *in vivo* by pancuronium bromide

J.R. DOCHERTY & J.C. McGRATH

Institute of Physiology, University of Glasgow, Glasgow G12 8QQ, Scotland

In clinical use pancuronium bromide can produce cardiovascular stimulation (Coleman, Downing, Leary, Moyes & Styles, 1972), part of which has been explained by a vagolytic action (Hughes & Chapple, 1976). Two effects on the cardiac sympathetic innervation have however been postulated; an indirect sympathomimetic action (Domenech, Garcia, Sasiain, Loyola & Oroz, 1976), and blockade of neuronal noradrenaline (NA) uptake (Ivankovitch, Miletich, Albrecht & Zahed, 1975).

We have now found that pancuronium bromide, in doses producing neuromuscular blockade (Clanachan & Muir, 1972), potentiates cardiac sympathetic responses in the pithed rat.

Rats were pithed (Gillespie, MacLaren & Pollock, 1970) and ventilated with 100% oxygen. Heart rate was extracted from carotid arterial pressure using a Devices instantaneous ratemeter. The pithing rod electrode was placed for optimal stimulation of the sympathetic outflow to the heart (C6–T1, 0.05 ms pulses, supramaximal voltage).

In the absence of sympathetic stimulation, pancuronium bromide (2 mg/kg, i.v.) produced a short-lived increase in heart rate (22.7 ± 2.5 bts/min) which returned to baseline within 5–10 minutes. When cardiac sympathetic tone was induced by continuous stimulation at 0.1 Hz, pancuronium bromide (2 mg/kg i.v.) produced an increase in heart rate (52.8 ± 9.3 bts/min) which was significantly larger than in the absence of stimulation ($P < 0.001$), and was maintained until stimulation was terminated. This suggests two effects of pancuronium on heart rate; a short-lived increase following injection and independent of nerve stimulation, and secondly, a longer-lasting potentiation of sympathetic nerve responses.

Pancuronium bromide (2 mg/kg) potentiated the cardiac acceleration produced by single pulses and by trains of up to 5 pulses at 1 Hz. With longer trains of pulses ($\geqslant 10$) no significant potentiation was found. Pancuronium bromide (2 mg/kg) also significantly potentiated the response to 20 pulses at 0.01–0.5 Hz. Potentiation was inversely related to both pulse number and frequency.

The cardio-acceleration response to a single pulse was significantly potentiated in both height and duration by pancuronium bromide (0.1–10 mg/kg). These effects were dose-related. Potentiation of response height was maximal at 2 mg/kg and of duration at 10 mg/kg. The above effects of pancuronium could be reproduced in adrenalectomized rats or during neuromuscular blockade with gallamine (20 mg/kg).

The NA uptake blockers cocaine (0.5 mg/kg) and desipramine (0.05 mg/kg) potentiated and prolonged the cardio-acceleration responses to a single pulse of sympathetic stimulation and to intravenous NA, and inhibited the corresponding response to tyramine.