ated the fall in developed tension produced by hypoxia and significantly reduced the rise in resting tension. At the end of the 30 min reoxygenation period the developed tension in diltiazem-perfused hearts was 65% of the control value, whereas it was only 24% for the verapamil-treated group. The best protection against the rise in resting tension produced by hypoxia was observed in hearts in which pacing was suspended at the moment of the exchange from the oxygenated to the hypoxic perfusate. Under these experimental conditions the recuperation of the developed contractile at the end of the successive 30 min reoxynation period was about 80% of the pre-hypoxic value.

In conclusion, these results confirm that the degree of increase in resting tension produced by hypoxia is dependent upon the myocardial mechanical work. This has been reported, for instance, by Nayler, *et al.* (1978) for the guinea-pig heart paced at different rates. The attenuation of this deleterious effect by verapamil and diltiazem can be accounted for, at least to a substantial extent, by the reduction in contractile force produced by both compounds. Other mechanisms, such as an action on intracellular calcium availability, may contribute to this beneficial action.

References

BING, O.H.L., BROOKS, W.W. & MESSER, J.V. (1973). Heart muscle viability following hypoxia: protective effect of acidosis. *Science*, **180**, 1297–1298.

DURRET, L.R. & ADAMS, H.R. (1979). Cardiac effects of gentamicin in low-calcium or hypoxic conditions. *Fed. Proc.* **38**, Abs. 1593.

NAYLER, W.G., GRAU, A. & SLADE, A. (1976). A protective effect of verapamil on hypoxic heart muscle. *Cardiov. Res.*, **10**, 650–662.

NAYLER, W.G., YEPEZ, E.C., POOLE-WILSON, P.A. (1978). The effects of β-adrenoreceptor and Ca^{2+} antagonists drugs on hypoxia-induced increase in resting tension. *Cardiov. Res.* **12**, 666–674.

WINBURY, M.M. (1956). Influence of glucose on contractile activity of papillary muscle during anoxia. *Am. J. Physiol.* **187**, 135–138.

The pharmacological activity of some choline analogues and their acetylated derivatives

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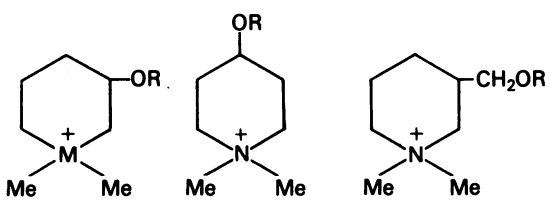
A study was made of some piperidine derivatives containing a choline like moiety to investigate their pharmacological properties on cholinergic transmission and to determine their potential as false neurotransmitters. The structural formulae of the compounds studied are shown below. The alcohols I (650 μg/ml), II (700 μg/ml) and III (300 μg/ml) were shown to produce a pre-junctional blocking action on the rat phrenic nerve hemidiaphragm preparation which was, in each case, reversed by choline. On the frog rectus abdominis muscle compounds I (450 μg/ml) and II (500 μg/ml) potentiated the responses to acetylcholine. On the same preparation compound III (200 μg/ml) had a direct depolarising action; its equipotent molar ratio to acetylcholine being 1,000:1.



The compounds were acetylated *in vitro* by choline acetyltransferase at a rate of I, 53%; II, 1%; and III, 2% compared to the acetylation of choline, 100%, at a concentration of 5×10^{-3} M.

Although the muscarinic activity of the acetylated compounds IV, V and VI has previously been studied, (Lewis, Barker, Fox & Mertes, 1973), the action of these compounds at the neuromuscular junction and their degradation by cholinesterase enzymes has not been fully investigated. The equipotent molar ratios of the acetylated compounds relative to acetylcholine in producing a contracture of the frog rectus muscle were shown to be IV, 57%; V, 60; VI, 105 and acetylcholine, 1. The degradation of the acetylated compounds by bovine erythrocyte acetylcholinesterase was investigated using a pH stat method. The relative rates of breakdown of the analogues at a concentration of 1.2 mM was found to be, acetylcholine, 1.0; IV, 0.75; V, 0.45 and VI, 0.6.

The results show that of the three piperidinols examined, compound I is acetylated *in vitro* by choline acetyltransferase; the acetylated product, compound IV is readily broken down by cholinesterase, however it is much less effective than acetylcholine

as an agonist at nicotinic receptors. The results provide a further indication as to the structural requirements for choline analogues being acetylated by choline acetyltransferase and for possibly acting as false cholinergic neurotransmitters.

Reference

LEWIS, N.J., BARKER, K.K., FOX, R.M. JR. & MERTES, M.P. (1973). Diacetoxypiperidinium analogues of acetylcholine. *J. Med. Chem.*, **16**, 156–159.

Is WB 4093 a selective presynaptic α_2-adrenoceptor antagonist?

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Kapur & Mottram (1978) have reported that WB 4093 is at least 1000 times more potent at blocking the stimulant effects of clonidine at presynaptic α_2-adrenoceptors than noradrenaline at postsynaptic α_1-adrenoceptors in the rat isolated vas deferens. If this is true WB 4093 would be a most valuable tool in the characterization of α-adrenoceptors, and so its potency at blocking α-adrenoceptors in other tissues has been investigated.

The pA_2 for WB 4093 was determined against noradrenaline at the post-synaptic α_1-andrenoceptors in the rabbit aorta (Apperley, Humphrey & Levy, 1976) after inhibition of uptakes$_1$ and $_2$ (cocaine, 10 μg/ml; cortiscosterone 10 μg/ml) and blockade of β-adrenoceptors (propranolol 0.3 μg/ml), and against clonidine at presynaptic α_2-adrenoceptors in the guinea-pig ileum (Drew, 1978). The mean (and 95% confidence limits) pA_2 values at α_1- and α_2-adrenoceptors were 6.97 (6.59–7.35: slope = 1.02; 0.64–1.40: $n = 4$) and 7.25 (7.02–7.48; slope = 1.20; 1.05–1.35: $n = 6$) respectively.

The effects of WB 4093 on postsynaptic α_1- and presynaptic α_2-adrenoceptors were also investigated in pithed rats (Drew, 1976). WB 4093, 1, 3 and 10 mg/kg caused a 4, 10 and 29 fold shift to the right in the phenylephrine dose-vasopressor response curve ($n = 4$); the dose-response curve to noradrenaline was shifted 2, 3 and 5 fold ($n = 5$). The clonidine dose-vasopressor response curve was shifted 4 and 28 fold to the right after pretreatment with 1 mg/kg ($n = 4$) and 10 mg/kg ($n = 5$) respectively of WB 4093. However, the presynaptic inhibitory effect of clonidine on the tachycardia produced by continuous stimulation of the cardiac sympathetic nerves at 1 Hz was little affected by either dose of WB 4093.

Thus *in vitro* WB 4093 shows no selectivity for α_1- or α_2-adrenoceptors; *in vivo* it is only weakly active at blocking α_1-adrenoceptors and almost inactive at blocking α_2-adrenoceptors. The reason for the difference between these results and those of Kapur & Mottram (1978) is unknown but it seems unlikely that WB 4093 will be useful in the characterisation of α-adrenoceptors.

WB 4093 was generously supplied by Dr P.N. Green of Ward Blenkinsop & Co. Ltd.

References

APPERLEY, E., HUMPHREY, P.P.A. & LEVY, G.P. (1976). Receptors for 5-hydroxytryptamine and noradrenaline in rabbit isolated ear artery and aorta. *Br. J. Pharmac.*, **58**, 211–221.

DREW, G.M. (1976). Effects of α-adrenoceptor agonists and antagonists on pre- and postsynaptically located α-adrenoceptors. *Eur. J. Pharmac.*, **36**, 313–320.

DREW, G.M. (1978). Pharmacological characterisation of the presynaptic α-adrenoceptors regulating cholinergic activity in the guinea-pig ileum. *Br. J. Pharmac.*, **64**, 293–300.

KAPUR, H. & MOTTRAM, D.R. (1978). A comparative study on the pre- and postsynaptic alpha-blocking activity of a series of benzodioxanes. *Biochem. Pharmac.*, **27**, 1879–1880.