

THE RESPONSES OF VASCULAR TISSUE AFTER PROLONGED TREATMENT WITH β -ADRENOCEPTOR BLOCKING DRUGS

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When rats are given β -adrenoceptor blocking drugs continuously for several weeks, there is evidence of an increased release of noradrenaline (NA) from the sympathetic nerve-endings of the anococcygeus muscle when they are electrically stimulated in vitro (Carr et al 1981).

In order to assess the relevance of these chronic changes to clinical responses to β -adrenoceptor blockers we have turned our attention to sympathetic function in vascular tissue. In these experiments either propranolol HCl 120 mg.l⁻¹ or timolol maleate 12 mg.l⁻¹ was given in the drinking water for up to 10 weeks to 3-4 week old male Wistar rats. (approximate daily doses 12 mg.kg⁻¹ and 1.2 mg respectively). At the end of the treatment period, the rats were killed and the superior mesenteric vascular beds excised and perfused in vitro essentially by the method of McGregor (1965). In some experiments a bipolar platinum electrode was used to stimulate the sympathetic nerve plexus closely associated with the superior mesenteric artery. Stimulus parameters were 400 pulses, over a range of 10-40 p.p.s., at 80 volts and 5 m.sec duration.

Unlike their effects on the anococcygeus preparation, chronic treatment with β -adrenoceptor blockers decreased responsiveness of the superior mesenteric blood vessels to both nerve stimulation and exogenous NA. Measured in terms of maximum response, the sensitivity of the tissue changed little with time, whereas the EC₅₀ value showed a significant time-dependent decrease, maximal after 8 weeks, (Table 1).

Table 1. Maximum response and EC₅₀ values for NA in the superior mesenteric vascular bed.

	<u>TIMOLOL</u>			<u>PROPRANOLOL</u>		
	EC ₅₀ (μ g)	Max. response (mm. Hg)	n.	EC ₅₀ (μ g)	Max. response (mm. Hg)	n.
control	2.17	200 \pm 16	8	2.17	200 \pm 16	8
4 weeks	2.79 n.s.	137 \pm 15 p < 0.02	6	5.24 p < 0.01	165 \pm 6 n.s.	6
6 weeks	3.51 n.s.	188 \pm 18 n.s.	5	6.80 p < 0.05	153 \pm 19 n.s.	6
8 weeks	7.77 p < 0.001	193 \pm 12 n.s.	6	7.24 p < 0.01	192 \pm 1 n.s.	6
10 weeks	3.48 p < 0.05	132 \pm 17 p < 0.02	4	4.22 p < 0.05	195 \pm 16 n.s.	6

Blood-vessel diameter in the mesenteric vascular bed is predominantly controlled through α -receptors. The observed changes must presumably therefore either reflect changes in tissue sensitivity which are secondary to the action of the β -adrenoceptor blockers elsewhere, or result from direct actions on sympathetic nerve endings. It is further suggested that the differences between the results obtained here and in the anococcygeus muscle reflect differences in the extent of local tissue reaction to the primary actions of the drugs, i.e. differences in presynaptic autoregulation and in changes in post-synaptic receptor populations. At the same time, the differences in the rate of disappearance of drugs from the isolated tissues, and consequent differences in tissue re-adaptation cannot be ruled out.

Carr, S.R. et al(1981). J. Pharm. Pharmac. 33: 92P.
McGregor, D.D.(1964) J. Physiol. 177:21-30.