THE EFFECT OF PROLONGED ADMINISTRATION OF β-BLOCKING DRUGS ON RESPONSES OF THE RAT ANOCOCCYGEUS MUSCLE

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Inspite of their increasingly wide-spread clinical use, the mode of action of β-blockers in hypertension remains obscure. One possible mechanism is suggested by the observation that, in animal experiments, β-blockers decrease responses to sympathetic nerve stimulation (Barret & Nunn, 1970). However, it has not yet been established how much of this effect is due to a direct action on sympathetic nerves and how much results from decreased sympathetic outflow for the CNS. We have used the rat anococcygeus muscle to investigate the effect of long-term treatment with β-blockers on sympathetic nerve function. This tissue was chosen because only α-receptors are found post-synaptically (Gillespie, 1972).
Propranolol(△), atenolol(■) and timolol(□) were administered in the drinking water at an approximate daily dose of $12mg.kg^{-1}$ and $1.2mg.kg^{-1}$ respectively, to groups of male Wistar rats (University of Bath strain). After 8 weeks, the animals were killed, the anococcygeus muscles were set up as described by Gillespie (1972) and the responses of the tissue to nerve stimulation and exogenous drugs, were compared to those of control tissues (○).

From Fig. 1 it can be seen that after 8 weeks there was significant potentiation of the effect of nerve stimulation by all 3 drugs(1a). In contrast, responses to noradrenaline (NA) were only potentiated at high dose levels(1b), and in fact propranolol appeared to decrease sensitivity of the tissue to low doses of NA. Responses to methoxamine, a 'pure' α-receptor against, and not a substrate for presynaptic uptake processes, were also potentiated(c), suggesting changes in post-synaptic receptor population, perhaps an increased sensitivity arising indirectly from prolonged decrease in transmitter release. Such an effect would be expected if a central action of β-blockers results in decreased sympathetic outflow. However, the relative lack of potentiation of NA compared to methoxamine, and the observation that nerve stimulation is potentiated significantly more than either amine suggests additional local changes in the presynaptic terminal. Estimation of the NA concentration of the tissues by fluorimetric assay failed to show anysignficant changes in concentration after administration of β-blockers for 8 weeks. Therefore, at this stage we are unable to state whether the increased responses to nerve stimulation are caused by an effect on presynaptic β-responses, or by changes in the dispostion and avilability of NA within the presynaptic terminals.

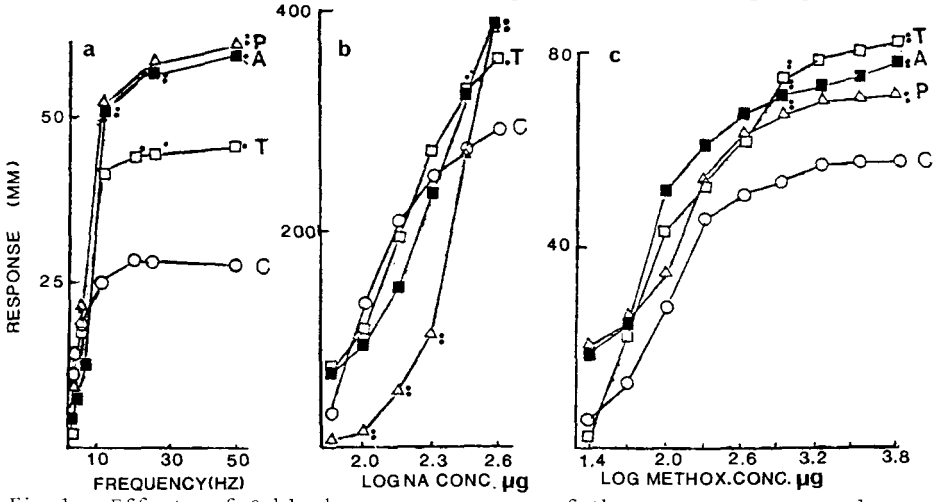

Fig 1. Effects of β-blockers on responses of the anococcygeus muscle

Barrett, A.M., Nunn, B. (1970) J. Pharm. Pharmacol. 22: 806-810
Gillespie, J.S. (1972) Br. J. Pharmacol. 45: 404-416