EFFECTS OF PROLONGED ADMINISTRATION OF β-BLOCKING DRUGS ON SYMPATHETIC NERVE FUNCTION

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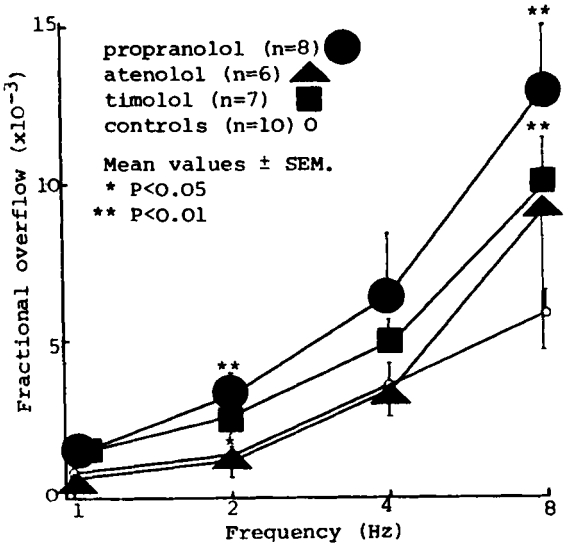
We have previously shown that prolonged administration of β-blocking drugs results in enhanced responses to sympathetic nerve stimulation (Qadus et al 1979). In the experiments reported here the rat anococcygeus muscle was used to elucidate further the effects of chronic treatment with β-receptor antagonists on sympathetic nerve function and transmitter release.

Male Wistar rats (University of Bath strain) were treated from 3 weeks of age with propranolol HCl (12mg kg^{-1} day^{-1}), atenolol (12mg kg^{-1} day^{-1}) and timolol maleate (1.2mg kg^{-1} day^{-1}) administered in the drinking water. After 11 weeks the animals were killed and the anococcygeus muscles were isolated and incubated in Krebs solution for 30 min with l-(7,8-^{3}H)-noradrenaline(NA)(12.2Ci/mmol $5x10^{-7}$M, Amersham). They were then held isotonically in air between two parallel electrodes and superfused with drug-free Krebs solution for 2 hours after which time each muscle received two periods of electrical stimulation, S_1 and S_2 (1msec, 2min, 20V) at 30 min intervals. S_1 and S_2 were delivered respectively at 1 and 4Hz for one muscle and at 2 and 8 Hz for the collateral muscle.

As shown in Figure 1, prolonged administration of propranolol, timolol, but not atenolol, resulted in an increase in the electrically-evoked overflow of ^{3}H from the anococcygeus muscle; there was a corresponding increase in the contractile response. It is unlikely that these results were due to blockade of NA reuptake by the β-blockers since the retention of ^{3}H by the anococcygeus was not impaired. Furthermore, desipramine (10^{-6}M) and normetanephrine (10^{-5}M), only marginally enhanced the electrically-induced ^{3}H overflow. If, however, the enhanced overflow of ^{3}H reflects an increase in the per pulse release of NA, it is possible that the decrease in sympathetic nerve drive, which follows the administration of β-receptor antagonists (Lewis & Haeusler 1975), may have resulted in a compensatory increase in facilitatory (or a decrease in inhibitory) prejunctional mechanisms for NA release in the anococcygeus muscle. The present findings would therefore suggest that the 'rebound phenomenon' observed after abrupt discontinuation of propranolol therapy in man may be a true hyperadrenergic rebound state following propranolol withdrawal, resulting from an enhanced excretion of catecholamines from nerves.

Figure 1. Overflow of tritium elicited by electrical stimulation



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Qadus, S. et al (1979) J. Pharm. Pharmac. 31 : 15P.

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