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A simple *in vitro* preparation of mammalian tissue exhibiting properties of slow tonic skeletal muscle

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Guinea-pig cremaster muscle can be set up as an isolated preparation (Ninomiya, 1975; Dale, Evinc & Vine, 1976). It gives dose-related contractures with acetylcholine which, on the basis of the affinity constants obtained with (+)-tubocurarine and atropine, involve nicotinic not muscarinic receptors (Dale *et al.*, 1976). Set up as a simple nerve-muscle preparation, with isometric recording, the muscle manifested twitches to single supra-maximal stimuli. Repetitive stimulation at 20 Hz resulted in fused tetanus, but maximum tension (40 G) only developed above 60 Hz. The ratio of twitch tension to maximum tetanic tension was approximately 0.1. The muscle was singularly resistant to fatigue, tetanic contraction at 20 Hz being maintained up to 10 minutes.

KCl (0.1 M) produced a sustained increase in tension, and depolarizing neuromuscular blocking agents (10^{-6}—5×10^{-5} M) evoked slow, dose-related contractures, up to 70% of the maximum response to KCl. When added during repetitive nerve stimulation, succinylcholine, at low concentrations, produced a sustained increase in tension but, initially, no inhibition of twitch; total neuromuscular block involving both twitch and tension increase, occurred at 4×10^{-5} M. (Figure 1).

Tetrodotoxin (10^{-7} M) modified the dose-response curve to acetylcholine and succinylcholine, but substantial responses to these agents could still be obtained. On the nerve-muscle preparation, tetrodotoxin eliminated the twitch leaving the tension increase virtually unaltered. With tubocurarine it could be shown that these tetrodotoxin-resistant responses involved nicotinic not muscarinic receptors. It thus appears that the tissue contains skeletal muscle

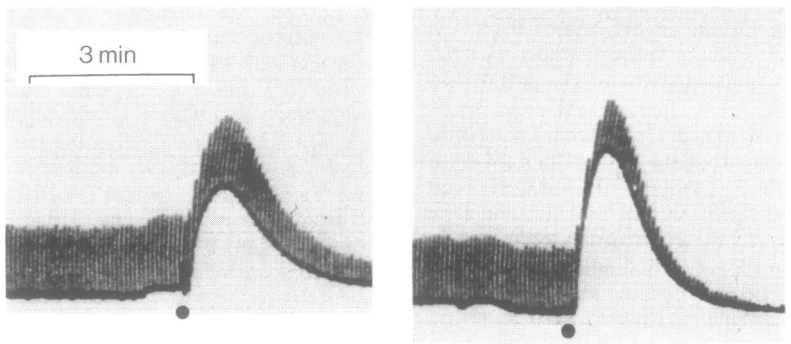

Figure 1 The response of the guinea-pig cremaster nerve/muscle preparation to succinylcholine. Bathing fluid: oxygenated Krebs-Henseleit solution at 32°C. Isometric recording with a Pye-Ether UFI transducer and George Washington Oscillograph 400 MD/2. Stimulation, using a Grass SD5 stimulator: 4 V, 0.2 Hz, 0.1 ms pulse duration.

fibres which do not require a propagated action potential for contraction.

These responses resemble those of mammalian extra-ocular muscles (Bach-y-Rita & Ito, 1966; Browne, 1976) and show some similarity to frog rectus and to avian muscle (Ginsborg, 1960) – all of which contain slow tonic skeletal muscle.

Preliminary histochemical studies of cholinesterase in cremaster muscle suggest that some fibres have innervation different from the typical 'en plaque' end-plates found in focally-innervated muscle.

Rigorous proof of the existence of a type of slow tonic muscle in the cremaster requires electro-physiological and electronmicroscopic studies. But the responses described above suggest fairly strongly that fibres of this type are present.

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Fitting a general sigmoid model to pharmacological response curves

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In order to evaluate potency and drug activity it is necessary to quantify the relationship between the response and the dose. However, in some sets of data problems arise in a log-dose transformation and some of the data may have to be omitted.

Many attempts have been made to derive models from pharmacological principals (Ariens, 1954; Clark, 1937; Paton, 1961; Stephenson, 1956) but the most successful involve a function that can only be determined empirically, i.e. the efficacy.

Parker & Waud (1971) used the logistic curve

$$Y = \frac{1}{1 + A \exp(-bX)},$$

showing that it could be rearranged to give:

$$R(X) = M\frac{X^B}{X^B + C^B} \qquad (1)$$

Equation (1) has some of the required characteristics

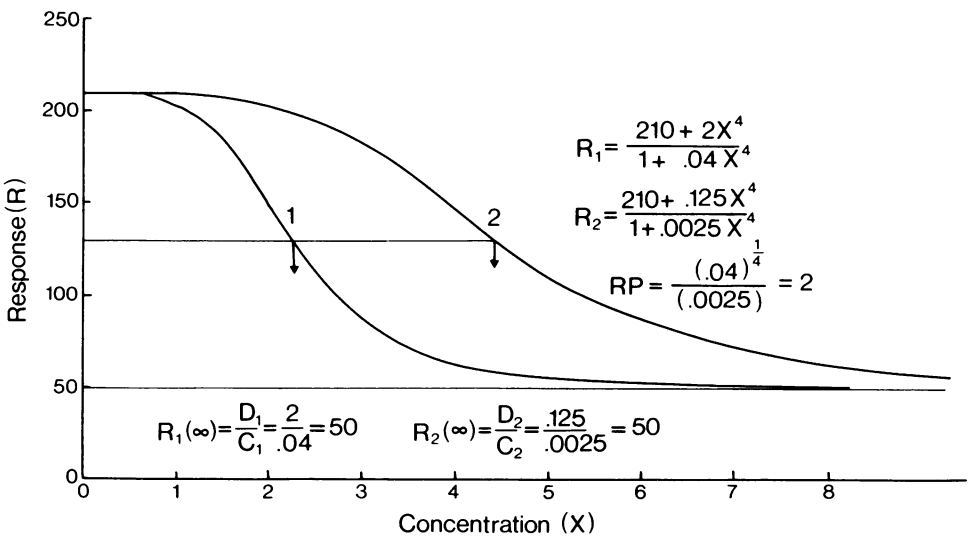

Figure 1 Parallel sigmoid curves.