The origin of the repetitive firing of mammalian skeletal muscle after anticholinesterase drugs

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Experiments have been made on the phrenic nerve-diaphragm preparation of the rat maintained *in vitro* in a physiological saline at 37°C (Ferry & Soo Lin Geh, 1977). The bioelectric responses of muscle cells to stimulation of the nerve were recorded with a micropipette filled with 3 M KCl located intracellularly at the endplate region, or with a silver wire electrode or a saline-filled pipette located extracellularly. With extracellular electrodes the response recorded under control conditions at the endplate was a biphasic negative-positive potential due to the initiation of an action potential and its propagation away from the endplate.

After ecothiopate (0.5 μM), the action current was followed by a prolonged inward endplate current which was recorded as a negativity. Repetitive spikes appeared on this negativity 3–5 msec after the initial action current, and with the same biphasic negative-positive potential sequence at first. Later, the repetitive activity, but not the initial action current became mainly positive-going monophasic potentials. At this time an electrode placed 0.2–0.3 mm away from the endplate, along the longitudinal axis of the muscle cell, recorded the initial action current as a triphasic positive-negative-positive potential sequence, with a smaller endplate current and the repetitive activity as a biphasic negative-positive potential.

Records made with an intracellular electrode showed that after ecothiopate, the action potential was followed by an endplate potential prolonged for up to 50 ms. Repetitive action potentials could be grouped into those (a) which arose from, and were associated with, second and subsequent endplate potentials. Repetitive activity of this type was frequently seen in reduced [Mg^{2+}] saline (b) which did not arise from another endplate potential but from the depolarising phase after the peak of the positive after potential of a previous action potential. Repetitive activity in normal physiological saline with [Ca^{2+}] 2 mM, [Mg^{2+}] 1 mM, was mainly of this type.

It is concluded that the repetitive activity in muscle cells *in vitro* bathed in physiological saline most frequently stems from the prolonged endplate potential after ecothiopate. These repetitive action potentials are first generated at the endplate region, but late in the course of ecothiopate action, the locus of initiation of repetitive action potentials moves 0.2–0.3 mm away from the endplate.

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Reference

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Effect of 4-aminopyridine on muscle contractility in the cat

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4-Aminopyridine facilitates neuromuscular transmission by increasing the evoked release of acetylcholine (see, for example, Lundh, 1978). It is used as an anticurare agent in Bulgaria (Stoyanov, Vulchev, Shturbova & Marinova, 1976), and has been shown to restore transmission in the Eaton-Lambert syndrome (Lundh, Nilsson & Rosén, 1977; Agoston, van Weerden, Westra & Broekert, 1978). The compound may also enhance skeletal muscle contractility through a direct action on the muscle fibres, although there appears to be a species difference with regard to this effect. It is reported to be very effective on the rat diaphragm (Bowman, Khan & Savage, 1977), only slightly so on the chick biventer cervicis (Bowman, Harvey & Marshall, 1977), and ineffective on the rabbit tibialis anterior muscle (Lemeignan & Lechat, 1967).

Experiments were performed on the tibialis anterior and soleus muscles of cats under chloralose anaesthesia. Isometric twitches and tetani were evoked by stimulation of the motor nerves, or by direct stimulation of the fully-curarized or chronically denervated muscles. Gross muscle action potentials (belly-tendon leads) were recorded simultaneously with the contractions of the indirectly stimulated muscles as an indication of any changes in the number of contributing muscle fibres or of any repetitive firing.

4-Aminopyridine, in doses of 0.5 mg/kg i.v. and above, produced a slowly-developing increase in the