

## Cromakalim, pinacidil and RP 49356 activate a tolbutamide-sensitive K<sup>+</sup> conductance in human skeletal muscle fibres

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### Introduction

Cromakalim (BRL 34915), pinacidil and RP 49356 belong to a new class of drugs characterized as "K<sup>+</sup> channel openers" (Weston and Abbott 1987). The present study was concerned with two experimental questions. (a) Do K<sup>+</sup> channel openers influence electrophysiological parameters of human skeletal muscle? In particular, effects on diseased human muscle would be of interest and may lead to new therapeutic strategies. (b) How do these drugs activate the K<sup>+</sup> conductance of skeletal muscle? To answer these questions we performed electrophysiological recordings from human skeletal muscle biopsies maintained *in vitro* (Iaizzo and Lehmann-Horn 1988; Spuler et al. 1989).

### Methods

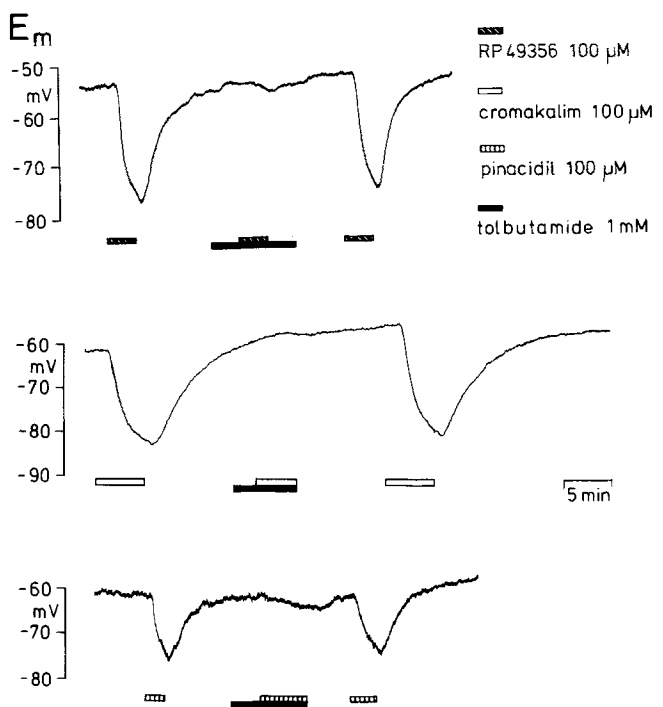
Fibre segments (4–6 cm long) from human skeletal muscle biopsies were placed into a perspex chamber (volume 2 ml, flow rate 6–8 ml/min) and superfused at 36°C with a Bretag solution (Bretag 1969). Intracellular recordings were performed with conventional microelectrodes. Drugs were applied via the bathing solution.

### Results and discussion

Resting membrane potentials in fibres from human skeletal muscle biopsies varied between -55 and -85 mV. However, in spite of this wide range in resting potential, an uniform effect was seen when cromakalim, pinacidil, or RP 49356 at a concentration of 100 µM were applied via the bathing solution. The effect consisted of a membrane hyperpolarization and an increase in membrane conductance. The change in membrane potential was dependent on the difference between resting and K<sup>+</sup> equilibrium potential. Only small effects were seen in fibres with resting potentials around -85 mV. Furthermore, current-voltage relationships were determined before and during the action of K<sup>+</sup> channel openers. These measurements revealed a reversal potential close to the K<sup>+</sup> equilibrium potential. All these observations indicate an increase in membrane K<sup>+</sup> conductance.

In another series of experiments, the effects of the K<sup>+</sup>

channel blocker tolbutamide were explored. It was found that tolbutamide strongly antagonized the effects of cromakalim, pinacidil and RP 49356. Fig. 1 illustrates this interaction on three different muscle fibres (upper and lower traces from a patient with myotonic dystrophy, middle trace from a patient with hypokalaemic periodic paralysis). Tolbutamide on its own had no effect on membrane potential or conductance (Spuler et al. 1989).



**Fig. 1.** Effects of K<sup>+</sup> channel openers on the membrane potential ( $E_m$ ) of human skeletal muscle fibres. The recordings are from three different cells. For further information see text.

In conclusion, human skeletal muscle fibres possess tolbutamide-sensitive (probably ATP-regulated; Sturgess et al. 1985) K<sup>+</sup> channels which are closed under normal circumstances. Cromakalim, pinacidil and RP 49356 are able to activate this conductance. A similar conclusion was drawn in a recent study about the effects of cromakalim on cardiac myocytes (Escande et al. 1988).

An exogenous activation of membrane  $K^+$  conductance may be of therapeutic benefit in situations in which a membrane depolarization causes muscle paralysis.

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