MOTOR AXONS EXCITABILITY CHANGES PRODUCED BY SUSTAINED NATURAL ACTIVITY AND RESPONSE TO MEXILETINE IN MYOTONIA CONGENITA

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Background: Myotonia congenita (MC) is a disorder characterized by delayed muscle relaxation and stiffness after voluntary activation. It is caused by mutations of *CLCN1*, which encodes the skeletal muscle chloride channel CLC-1. More than 100 different *CLCN1* mutations causing MC have been described, and the inheritance of the disease can be autosomal dominant (Thomsen's myotonia) or recessive (Becker's myotonia). Our objective was to investigate the cause of the transient weakness that occurs in MC, by exploring the changes in excitability of motor axons; in addition, we aimed at understanding the mechanism by which that sodium channel blockers improve both myotonic stiffness and weakness.

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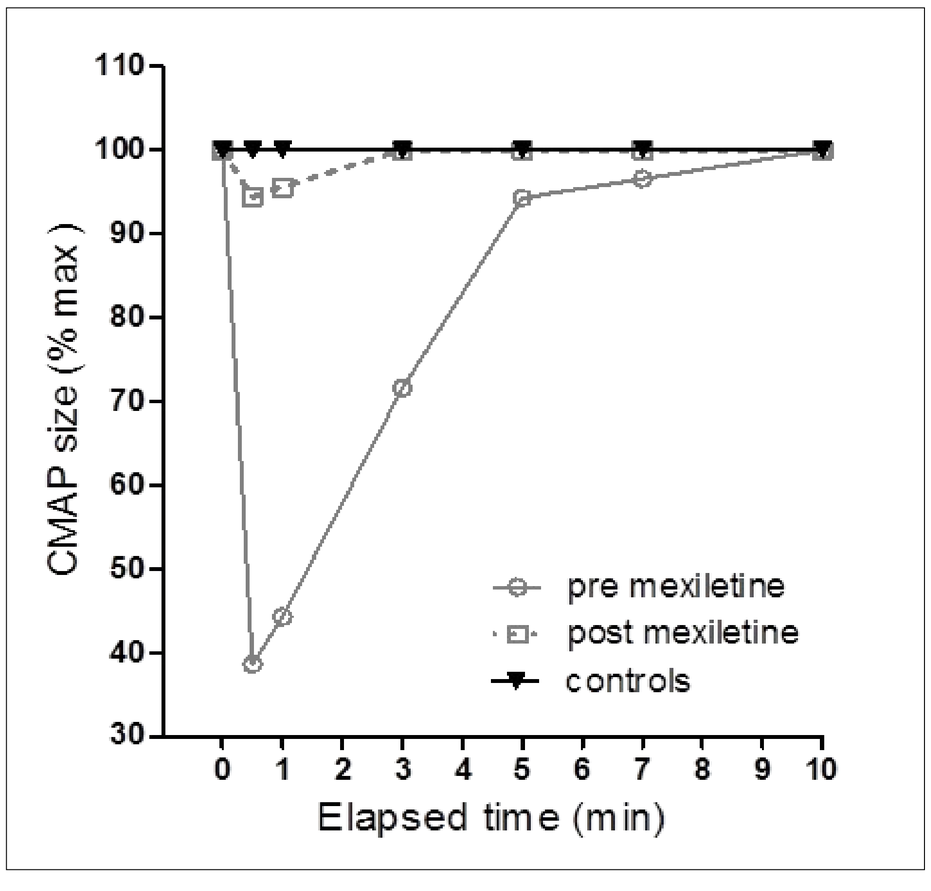
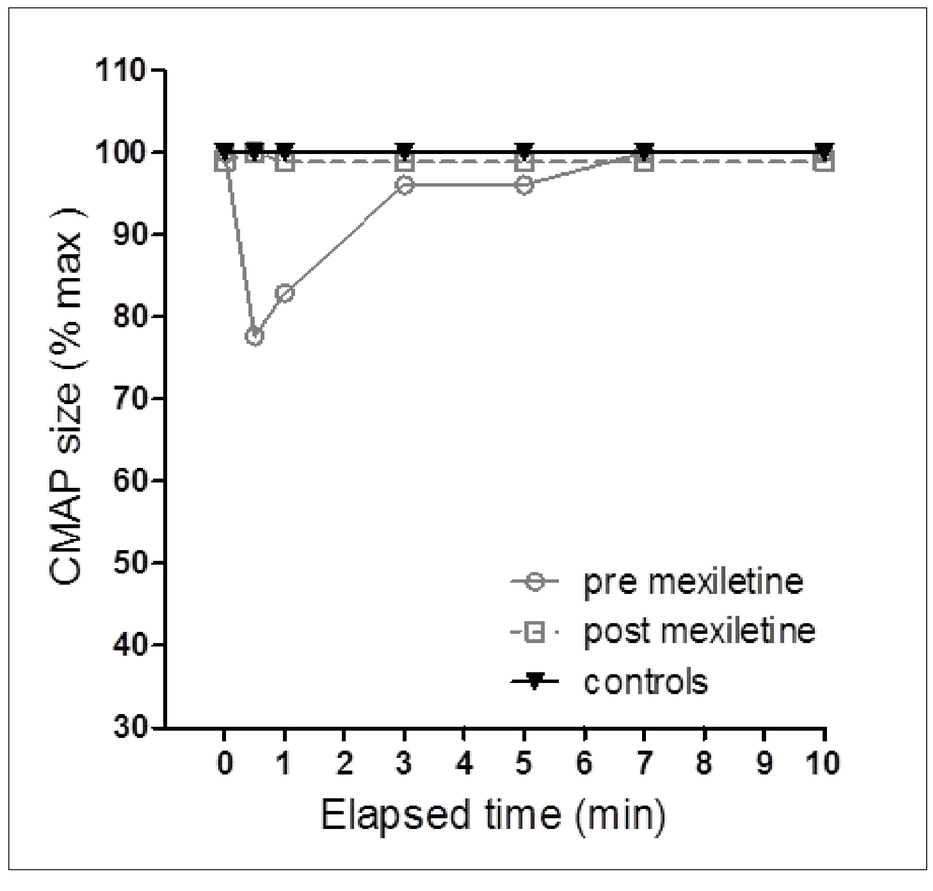
Methods: Studies on compound muscle action potential amplitude (CMAP) changes were undertaken before and after 1 minute of maximal voluntary contraction (MCV) of abductor digiti minimi in two subjects with MC, one with Thomsen's myotonia and another with Becker's myotonia. The data were compared with those of 20 healthy subjects. In both patients the study was repeated after therapy with mexiletine.

Results: A transient reduction in maximal CMAP lasting several minutes was evident in MC patients, while it was absent in healthy controls. Mexiletine therapy markedly reduced the transient CMAP depression in both subjects.





Test CMAP (100% of maximum) from ADM, following 1 minute MCV.

The ulnar nerve was stimulated at the wrist at a fixed intensity

Discussion: In MC subjects, during protracted muscle contraction, the low chloride conductance induces a progressing depolarization causing a loss of excitability of the muscle fiber membrane and thereby a transient paresis of a number of muscle fibers. Mexiletine blocks the myotonic discharge and may prevent the membrane block due to cumulative depolarization, thus reducing the depression of the CMAP following MCV. In MC a proportion of muscle fibers cannot maintain their response to stimulation after sustained voluntary activity: this phenomenon likely represents the physiological counterpart of the weakness. The remarkable recovery of motor axons excitability following mexiletine suggests a common mechanism underlying the myotonic stiffness and the weakness in MC.

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