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ORIGINAL ARTICLE/ARTICLE ORIGINAL

Neuromuscular excitability changes produced by sustained voluntary contraction and response to mexiletine in myotonia congenita

Modifications d'excitabilité neuromusculaire produites par une contraction volontaire prolongée et réponse à la mexilétine dans la myotonie congénitale

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KEYWORDS
Chloride conductance;
Myotonia;
Natural activity;
Sodium channel;
Weakness

Summary
Objective. — To investigate the cause of transient weakness in myotonia congenita (MC) and the mechanism of action of mexiletine in reducing weakness.
Methods. — The changes in neuromuscular excitability produced by 1 min of maximal voluntary contractions (MVC) were measured on the amplitude of compound muscle action potentials (CMAP) in two patients with either recessive or dominant MC, compared to control values obtained in 20 healthy subjects. Measurements were performed again in MC patients after mexiletine therapy.

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Results. — Transient reduction in maximal CMAP amplitude lasting several minutes after MVC was evident in MC patients, whereas no change was observed in controls. Mexiletine efficiently reduced this transient CMAP depression in both patients.
Discussion. — Transient CMAP depression following sustained MVC may represent the electrophysiological correlate of the weakness clinically experienced by the patients. In MC, the low chloride conductance could induce self-sustaining action potentials after MVC, determining progressive membrane depolarization and a loss of excitability of muscle fibers, thus resulting in transient paresis. Mexiletine may prevent conduction block due to excessive membrane depolarization, thus reducing the transient CMAP depression following sustained MVC.

MOTS CLÉS
Activité naturelle ;
Canal sodique ;
Conductance chlore ;
Faiblesse ;
Myotonie

Résumé
Objectif. — Étudier la cause de la faiblesse transitoire dans la myotonie congénitale (MC) et le mécanisme d'action de la mexilétine pour la réduire.
Méthodes. — Les modifications d'excitabilité neuromusculaire produites par 1 min de contraction volontaire maximale ont été mesurées sur l'amplitude du potentiel global d'action musculaire (PGAM) chez deux patients présentant une MC récessive ou dominante, comparativement aux valeurs témoins obtenues chez 20 sujets sains. Les mesures ont été effectuées à nouveau chez les patients MC après traitement par la mexilétine.
Résultats. — La réduction transitoire de l'amplitude maximale du PGAM était évidente pendant plusieurs minutes après contraction volontaire maximale chez les patients MC, alors qu'aucun changement n'était observé chez les témoins. La mexilétine a efficacement réduit cette dépression transitoire du PGAM chez les deux patients.
Discussion. — La dépression transitoire du PGAM après contraction volontaire maximale soutenue peut représenter la corrélation électrophysiologique de la faiblesse observée cliniquement chez les patients. Dans la MC, la faible conductance du chlore pourrait induire des potentiels d'action auto-entretenus après contraction volontaire soutenue, déterminant une dépolarisation membranaire progressive et une perte d'excitabilité des fibres musculaires, résultant alors en une parésie transitoire. La mexilétine pourrait empêcher le bloc de conduction d'apparaître en raison d'une dépolarisation membranaire excessive, réduisant ainsi la dépression transitoire du PGAM après contraction soutenue.

Introduction

Myotonia congenita (MC) is an inherited disorder characterized by delayed muscle relaxation and stiffness after voluntary activation. It is caused by mutations of *CLCN1*, which encodes the CLC-1 chloride channel of skeletal muscle fibers. Both autosomal dominant (Thomsen's myotonia) and autosomal recessive (Becker's myotonia) forms are known [17].

The major clinical manifestation of MC is muscle stiffness (myotonia) resulting from abnormal membrane over-excitation. With repeated movements, the intensity of myotonia diminishes over seconds to minutes and may even become asymptomatic, a phenomenon called ''warm-up''. The chloride conductance ensures the electrical stability of the human muscle membrane and is crucial for countering the depolarizing effect of K^+ accumulation in T-tubules during the action potential. In MC subjects, the tubular potassium accumulation resulting from the initially driven activity and the low chloride conductance of myotonic muscle fibres appear to be responsible for the initiation of the myotonic discharge [32].

Additional common symptoms of MC include pain, weakness and fatigue [36—38]. In particular, MC patients complain of transient weakness that appears when the muscles are activated after a period of rest; moreover, in some cases the force in relation to muscle volume is constantly reduced [4,8,22,24,35]. However, transient weakness is only rarely reported by patients, who are usually unable to distinguish the stiffness secondary to myotonia from fatigue and weakness following muscle activity.

Brown [4] first observed that a decremental evoked compound muscle action potential (CMAP) was noticeable when myotonic patients attempted sustained activity after rest. The fade of the evoked response was correlated with the timing of a previous conditioning stimulus train or voluntary contraction [4]. At present, the analysis of CMAP size variations in response to short or long exercise tests has become useful in differentiating muscle channelopathies and improving knowledge about their pathogenesis [10,17,27,31].

In the present paper, CMAP changes were recorded before and after 1 min of maximal voluntary contraction (MVC) in two subjects with MC, one with Thomsen's myotonia and another with Becker's myotonia. The results were compared with those of 20 healthy subjects. In both patients, the study was repeated after introduction of mexiletine therapy. Although the effectiveness of mexiletine on both stiffness