Malignant Hyperthermia Syndrome—Evidence for Denervation Changes in Human Skeletal Muscle

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The human malignant hyperthermia (MH) syndrome is an autosomally dominant inherited trait occurring during general anaesthesia [1, 2]. The syndrome, which has been classified as a sub-clinical myopathy [3], manifests itself as a rapid increase of body temperature to about 43°C simultaneously with development of severe muscular rigidity in most cases. It is fatal in at least 70% of reported cases. Britt et al. [4] have suggested that the basic biochemical lesion responsible for the MH syndrome resides peripherally in the skeletal muscles though the nature of the lesion is unknown. These workers implicated the sarcoplasmatic reticulum (SR) in the primary actiology of the syndrome because halothane (1-bromo, 1-chloro, 2,2,2-trifluoroethane) at anaesthetic concentrations was found to inhibit total calcium uptake by isolated SR from muscles of susceptible individuals while it had no effect on SR from normal human muscle. Thus halothane might trigger the MH syndrome by causing elevation of the sarcoplasmatic calcium ion concentration which would in turn activate myofibrillar ATPase resulting in sustained contraction. We examined the effect of halothane at anaesthetic concentrations on isolated SR from three cases of the MH syndrome [5] and found that the anaesthetic slightly stimulated net calcium uptake similar to the action of the anaesthetic on SR from normal muscle. Berman and Kench [6] investigating the effect of halothane on SR from muscles of MH susceptible Landrace pigs obtained similar results. For these and other reasons [7] we considered that the basic lesion in the MH syndrome must be elsewhere in the muscle fibre.

Evidence is now presented of distinct grouping of slow muscle fibres (type 1) and of abnormal mitochondria in the muscles of MH susceptible individuals. Further, it is shown that the rate of calcium uptake and Ca2+-dependent ATPase activity of the SR from susceptible muscle is lower than in normal human muscle while the ratio, rate of calcium uptake/ATPase activity, remains normal. A neuropathic basis for the syndrome is, therefore, indicated.

Methods

Biopsies of the Quadriceps muscle were taken under local anaesthesia from four susceptible individuals identified by finding elevated
Fig. 1. a Histochemical staining of NAD-diaphorase showing a group of small atrophic fibres. ×800; b Myosin ATPase showing area with grouping of type I fibres. ×200; c Area of myofibrillar disruption adjacent to some normal sarcomeres. ×20,000; d Area showing swollen mitochondria with some disruption of the cristae. ×14,200