Pathogenetic Roles of Intracellular Calcium and Magnesium in Membrane-Mediated Progressive Muscle Degeneration in Duchenne Muscular Dystrophy

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1. INTRODUCTION

Duchenne muscular dystrophy (DMD) in humans is a progressively crippling X-linked recessive neuromuscular disease with no effective treatment (Rowland, 1980; Moser, 1984). It is characterized by profound biochemical (Kar and Pearson, 1976; Bertorini et al., 1982; Bhattacharya and Crawford, 1985), electrocardiographic (Sanyal and Johnson, 1982), histopathological (Bodensteiner and Engel, 1978; Emery and Burt, 1980; Bertorini et al., 1982, 1984), and ultrastructural (Mokri and Engel, 1975; Oberc and Engel, 1977) abnormalities of skeletal and cardiac muscle, and a 70–80% reduced life expectancy. Although a “vascular hypothesis” implicating abnormal microvasculature has been presented in the past to explain many aspects of the dystrophic pathophysiology, the most tenable mechanism for the classical muscle degeneration in DMD is now widely attributed to a generalized functional and structural defect(s) in the plasma membrane integrity of myofibers (Mokri and Engel, 1975; Schotland et al., 1977) and erythrocytes (Araki and Mawatari, 1971).

This “membrane hypothesis” suggests a sarcolemmal abnormality which results in an increased cellular ingress of Ca$^{2+}$ and Na$^{+}$, and a leakage of Mg$^{2+}$, K$^{+}$, creatine kinase (CK), and lactate dehydrogenase (LD) to the extracellular compartment. Cumulative evidence indicates that among the multitude of discernible pathogenetic events which transpire between the initiation of membranous changes and ultimate toxic cell death in DMD (Carpenter and Karpatt, 1979; Schanne et al., 1979), membrane-mediated excessive intracellular Ca ac-
cumulation (EICA) represents one of the earliest detectable biochemical events (Emery and Burt, 1980; Bhattacharya and Crawford, 1985). Excessive intracellular Ca accumulation appears to be the most crucial factor in the pathogenesis of muscular dystrophy in both DMD and animal models (Wrogemann and Pena, 1976; Brambati et al., 1980; Bertorini et al., 1984; Bhattacharya et al., 1984).

In this chapter, we will briefly discuss (1) the roles of intracellular Ca and Mg in the pathogenesis of membrane-mediated progressive muscle degeneration in DMD and in animal models of muscular dystrophy, (2) the interrelationships of EICA with other pathobiological aspects of progressive muscle degeneration, and (3) the potential pharmacological regulation of EICA in degenerating cardiac and skeletal muscles affected by hereditary muscular dystrophy.

2. PATHOGENETIC ROLES OF CALCIUM AND MAGNESIUM IN PROGRESSIVE MUSCLE DEGENERATION IN HEREDITARY MUSCULAR DYSTROPHY

The biological roles of Ca and plasma membranes in cellular and subcellular functions are well characterized in numerous physiological processes (Ebashi and Sugita, 1979); however, the intricacies of their abnormalities in a variety of pathogenetic conditions are far from completely understood (Carpenter and Karpati, 1979; Chizzonite and Zak, 1981). In the mammalian system, extracellular [Ca\(^2+\)] is 10\(^{-3}\) M, whereas that in the intracellular milieu is approximately 10\(^{-7}\) M. This 10,000-fold [Ca\(^2+\)] gradient is maintained by active transport, and is augmented by the functional and structural integrity of the plasma membrane. Likewise, [Ca\(^2+\)] in the intracellular compartments is regulated by the mitochondrial (MIT) and sarcoplasmic reticulum membranes which maintain the intraorganelle [Ca\(^2+\)] at 10\(^{-4}\) and 10\(^{-6}\) M, respectively.

These subcellular organelles participate in the regulation of intracellular Ca to meet specialized cellular functions which are vital for the interaction and synchronization of many biochemical and physiological processes within the cell. The MIT primarily function as a cellular power house for ATP synthesis, serve as a reservoir for intracellular Ca\(^2+\), and regulate the intracellular [Ca\(^2+\)] within a narrow physiological threshold during acute and transient Ca accumulation. Sarcoplasmic reticulum (SR), on the other hand, is involved in the release and uptake of Ca\(^2+\) during excitation–contraction coupling of myofibers in response to neurotransmitter-mediated stimuli for muscle contraction.

There are many mechanisms by which cells maintain electrolyte equilibrium. These mechanisms include passive diffusion; membrane-bound ATPases such as Na\(^+\), K\(^+\)-ATPase, Mg\(^{2+}\)-ATPase, and Ca\(^{2+}\)-ATPase which are present in sarcolemmal, mitochondrial, and SR membranes; slow inward Ca\(^2+\) channels which allow the influx of Ca\(^2+\); and the 2Na\(^+\) ↔ Ca\(^{2+}\) exchange channels (Ebashi and Sugita, 1979). A normal cell also has at least two distinct pools of Ca. The intracellular free Ca exists in the ionized form and is freely transported between the intra- and extracellular compartments, whereas the bound Ca may remain complexed with ATP, lipids, phosphates, proteins, or other biomolecules. The initial abnormalities in degenerating muscle presumably are expressed in the cellular and subcellular membranes, and may be characterized by a decreased transmembrane potential and increased membrane permeability. Under a partially depolarized state, uncontrolled amounts of extracellular Ca\(^2+\), Na\(^+\), and water can passively diffuse into the cells, while K\(^+\) and Mg\(^{2+}\) leak out along with intracellular enzymes such as CK and LD (Fig. 1). Thus, whenever cells