Dehydroepiandrosterone Sulfate (DHEAS) Therapy for Myotonic Dystrophy Type 1 and Myotonia

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Myotonic dystrophy type 1 (DM1), which is an autosomal dominant disorder based on expanded CTG repeat located in the 3’-untranslated region of the DMPK gene (1) with distally predominant muscular atrophy and myotonia, features multiple organ involvement including various endocrinological abnormalities (2). Occasional testicular atrophy and reduced serum testosterone level have been considered common, but little attention has been paid to adrenal androgens, major components of which are dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS).

These adrenal androgens are steroid hormones present in abundance in humans. The serum concentrations of DHEA and DHEAS have clearly shown age-related decreases in adult humans (3). The anti-aging effects of these hormones have been studied, however the physiological effects of DHEA and DHEAS, other than the weak androgenic effect of DHEA, remain unclear.

The serum concentrations of DHEAS are lower in patients with DM1 (4). We found that the serum concentrations of DHEAS and DHEA in DM1 were more than 60% lower than those in age-and sex-matched healthy controls (unpublished data). The open trial of intravenous administration of a DHEAS preparation (200 mg/day for 8 weeks) in patients with DM1 as replacement therapy showed improvement of activities of daily living (ADL) with increased muscular strength, decreased myotonia, and decreased cardiac conduction block and premature beats. Especially, improved grip and percussion myotonia was observed in eight of the 11 subjects, and completely eliminated myotonia in four during DHEAS therapy (5). However, the mechanism of action is still unknown.

Mankodi et al reported the decrease of Cl channel and appearance of myotonia in skeletal muscles from transgenic mice of DM1, which had aberrant splicing of pre-mRNA encoding Cl channel by accumulation of mRNA carrying large CUG repeat in the nuclei (6). Nakazora and Kurihara reported the effect of DHEAS on myotonia by using myotonic mice, whose Cl channel did not develop due to stop codon (7).

They showed that DHEAS markedly suppressed insertion myotonia in a dose-dependent manner by intracellular recordings on the diaphragm preparations of myotonic mice and decreased isometric twitch tension in Wistar rats much smaller than mexiletine (7). These results suggested that DHEAS is a favorable agent to treat myotonia of DM1 because it could abolish myotonia without reducing muscle power.

It is noteworthy that the appearance of effect on myotonia required a high concentration of DHEAS. This may account for the finding that the intravenous administration of DHEAS was effective but its oral administration of DHEA (50 mg/day) was negative in a small size of clinical trial for DM1 (unpublished data). The effects of DHEAS on muscle cells appeared quickly but were eliminated by washing out in experimental studies (7, 8), but the persistent effect was observed after discontinuation of DHEAS therapy for DM1.

Recently, new findings with action mechanism of DHEAS for DM1 have accumulated. Tsuji et al suggested the direct action of DHEAS by the identification of specific DHEAS binding sites in C2C12 myocytes and human skeletal muscles (9). Furuya et al reported that DHEAS prevents the cis-effect and cytotoxicity of toxic RNA with expanded CUG repeats in a neural cell line (10). Recent advances in molecular biology have revealed the genetic basis of DM1, but no effective treatment has been established for this disease. As DHEAS is the first agent found to improve ADL, further study is needed to clarify the mechanism of action of DHEAS on DM1.

References

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