A novel condition of mild electrical stimulation against inflammatory-related and autoimmune diseases

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Over the last few years, the practicality of physical therapy has been attracting attention around the world. The forms of physical therapy can be diverse, such as electrical or thermal stimulation, exercise, etc. Despite the effectiveness of physical therapy, lack in knowledge of scientific evidence and safety issues hinder its usage in clinical settings. In order to generalize the use of physical therapy for disease treatment, it is important to expand science-based evidence.

Previously, in our laboratory different modes of exogenous electrical stimulation at physiological strength has been applied to various diseases. We extensively demonstrated the usability of mild electrical stimulation (MES) with low frequency pulse current at 55 pulses per second (MES_{55}) for several disease conditions. However, the effective and applicable conditions of MES on immune system is still unexplored. Here, to resolve this question, I investigated the effect of different MES conditions on immune cells (Research 1), and expanded my investigation on animal models of concanavalin-A-induced hepatitis mouse model (Research 2) and C-protein-induced myositis (CIM) mouse model (Research 3).

1. The effect and mechanism of MES_{5500} on immune cells

To determine whether MES has effects on immune system, first, I checked different MES conditions on overexpressed cytokine levels. Here, I showed that MES with high frequency pulse-current (5500 pulse per second; MES_{5500}) suppressed the overproduction of inflammatory cytokines induced by phorbol myristate acetate/ionomycin in Jurkat T cells and primary splenocytes. The molecular mechanism underlying these effects included the ability of MES_{5500} to induce modest amount of hydrogen peroxide (H_2O_2) and control multiple signaling pathways important for immune regulation, such as NF-κB, NFAT and NRF2. These results indicated the crucial role of MES_{5500} to manage excessive inflammation and immune response. This finding led me to investigate the effect of MES_{5500} on *in vivo* models of concanavalin-A-induced acute hepatitis and autoimmune inflammatory muscle disease.

2. MES_{5500} ameliorated inflammation in concanavalin-A induced hepatitis mouse model

The concanavalin-A (ConA)-induced hepatitis is a model of acute inflammatory liver disease, caused by activation of T cells through TCR stimulation. The injection of ConA significantly increased T cell-derived expression of IL-2, IFN-γ and other cytokines. In this study, I showed that two times MES_{5500} treatment (20 min, before and after ConA injection) suppressed the overproduction of inflammatory cytokines both in liver and spleen, improved liver damage and reduced mouse spleen enlargement. The comparison of MES_{5500} effect with currently practiced immunosuppressive drug cyclosporin A (CsA) showed analogous, slightly milder effect. Moreover, MES_{5500} treatment slightly increased blood serum H_2O_2, indicating one mechanistic possibility for the anti-inflammatory effect of MES_{5500} in *in vivo* studies that correlated with *in vitro* data. These findings showed that MES_{5500} ameliorated acute hepatitis and proved the validity of MES_{5500} treatment *in vivo*.

3. MES_{5500} improved pathophysiology in CIM mice of PM

Polymyositis (PM) is an autoimmune inflammatory muscle disease. The pathogenesis of PM involves adaptive and innate immunity as well as non-immune pathways. The current treatments with high-dose corticosteroids or immunosuppressive drugs show limited success, with high risk of side effects. To assess the effect of MES_{5500} treatment on polymyositis, I used the C-protein-induced myositis (CIM) mouse model. C-protein emulsified in complete Freund's adjuvant (CFA) induced mild myositis with immune cell infiltration in muscle tissue, leading to muscle inflammation. Interestingly, MES_{5500} treatment (10 min twice/week) significantly reduced immune cell infiltration and muscle inflammation and suppressed IL-1β mRNA expression. MES_{5500} treatment enhanced the mRNA expression of myogenic factors (MyoD, myogenin) and suppressed myostatin, which are important for muscle cell differentiation and regeneration. MES_{5500} treatment also improved enzyme levels (CK, Cre, AST, ALT), which are upregulated during disease and indicate muscle damage. Moreover, MES_{5500} treatment showed improvements in behavioral tests of mouse muscle function. These results suggested that MES_{5500} treatment ameliorated the pathology of polymyositis through inhibiting muscle inflammation and enhancing muscle cell regeneration.

Collectively, these studies suggest that physical medicine in the form of MES_{5500} may be considered as a novel therapeutic tool or as adjunctive therapy for inflammatory and immune-related diseases.