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TRPM8 RECEPTOR ACTIVATION IMPROVES POST-TRAUMATIC RECOVERY OF RAT MUSCLE SOLEUS WITH FULLERENE THERAPY

The biomechanical parameters of muscle soleus of rats during the first 3 days of development of the posttraumatic syndrome caused by destruction of muscle cells by means of the mechanical compression are studied. Injections of both C60 fullerene antioxidant and menthol, which is the selective agonist of TRPM8 cold receptors, are used as therapeutic agents. Injections of an aqueous colloidal solution of C60 fullerene (at concentration of 1 mg/kg) into the damaged muscle improve its contractile function by 25– 30%. Application of combined injections of C60 fullerene and menthol (at concentration of 1 mkg/kg) improve this indicator by an extra 17–19%, while stabilizing the decrease in muscle strength observed throughout all experiments. The revealed synergy effect of menthol and aqueous solution of C60 fullerene on

posttraumatic process of restitution of skeletal muscle function opens up new prospects for the clinical application of such a combined therapy.

Analysis of the function of the TRPM8 cold receptor and its expression confirmed the existence of a close relationship between its activation and sensory responses of neurons responsible for causing acute or persistent pain. The biophysical and pharmacological characterization of these channels provided the technical basis for the development of new classes of pain relievers [1]. Cold water immersion (TRPM8 cold activation) after exercise is believed to reduce muscle fatigue and soreness and is thus a commonly used post-exercise recovery method [2]. A study of the functional, morphological and molecular adaptation of skeletal muscle to strength training with ten minutes of immersion in cold water and active recovery after each training also revealed a significant increase in muscle strength [3]. At the same time, it was shown that cold therapy does not decrease the rate of glycogen resynthesis in muscles during post-traumatic recovery [4]. In addition, local tissue cooling reduces edema and inflammatory response and may be beneficial in reducing the inflammatory response without inhibiting blood flow following skeletal muscle contusion [5]. The therapeutic effect of menthol is supported by a number of studies. So, in the early stages, soft tissue injuries are usually treated with ice or menthol gel. Several studies have compared the effects of these therapies on blood flow and muscle strength. In particular, it was shown that menthol has a faster and more short-term effect of reducing blood flow [6]. The use of an occlusive patch containing 3% menthol for the treatment of mild to moderate muscle pain in 208 patients showed significant pain relief compared to patients receiving placebo [7]. The results of using menthol-based gel in 197 outpatients showed that the time to resume functional activity was reduced, as a rule, by 2–6 days in case of moderate muscle damage [8]. At the same time, an increase in the temperature of the limbs or the whole body of rats significantly worsened their survival. A much lower survival rate was found in animals at the level of 0–10%, in which the hind limbs were warmed up during CS compression [9]. It has been shown that in the post-traumatic muscle, at the stage of alteration, at the site of

injury, a local vasodilation occurs, as a result of which blood supply increases, blood flow slows down and, as a consequence, there is a local temperature increase. An increase in the permeability of the capillary wall leads to the release of leukocytes, macrophages and the liquid part of blood (plasma) at the site of injury - edema, which in turn, squeezing the nerve endings, causes pain. Recent studies show that non-selective cationic TRPM channels of mammals (TRPM1-8) are expressed in endothelium and vascular smooth muscle. When these channels are activated, the membrane's permeability to sodium, potassium, calcium and magnesium increases, membrane depolarization occurs and, thus, vascular tone changes. Activation of the TRPM8 cold receptor with menthol regulates vascular tone, optimizing their normal physiological state and blood flow [10, 11]. It is possible that the effects we obtained are also influenced by this feature of the action of menthol, which confirms the need for further research. Thus, the obtained effects regarding the therapeutic effect of menthol injections into the injured muscle can be described by at least four components: a decrease in pain symptoms, a decrease in inflammatory reactions (probably synergistically with a similar effect of C60 fullerenes), an improvement in metabolic reactions, and a change in vascular tone. The revealed synergism of the therapeutic effect of menthol and C60 fullerenes on the post-traumatic process of skeletal muscle recovery requires further detailed research in order to conduct clinical trials.

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