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A novel combination of mild electrical stimulation and hyperthermia: General concepts and applications

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Abstract
This review discusses the basic concepts, effects and applications of hyperthermia and mild electrical stimulation (MES) using low-intensity direct current. It also proposes a novel combinatorial use of MES and hyperthermia, and briefly outlines the rationale and the effects of MES and hyperthermia combination treatment on certain diseases (diabetes, hepatic ischaemia/reperfusion injury and gastric ulcer). The integrated modalities of MES and hyperthermia might find therapeutic applications to stress-induced diseases and intractable diseases of dysregulated signalling pathways.

Keywords: *hyperthermia, mild electrical stimulation, low-intensity current, heat shock, Hsp72*

Introduction

The effectiveness of many drug therapies for various diseases is sometimes hampered by their high degree of toxicity. Thus, the search for efficacious cure with few side effects is an on-going process in the fields of medicine, pharmacy and biochemistry, among others. Interestingly, some treatment modalities that have been determined to produce relatively positive results with less toxicity are not chemical in nature but rather mechanical, such as the application of mild electrical stimulation (MES) and mild heat or hyperthermia [1, 2]. The effects of these interventions have already been explored in pre-clinical and clinical trials for treatments of diseases that range from cancer to inflammation and wound healing. While to a certain extent these approaches are successful, there is certainly room for improvement. In this review we focus on the effects of MES and hyperthermia as well as on their applications. We also briefly explore the possibilities of the application and the benefits of combined treatment of MES and hyperthermia on diabetes, gastric ulcer and ischaemia-reperfusion injury. This new combinatorial strategy may open up a new avenue of an alternative therapeutic approach to a host of diseases.

Mild electrical stimulation

Physiological relevance

In the past century it has been recognized that exogenous and endogenous electrical currents exert some influence over how cells behave and interact with one another at the cellular and organismal levels. For instance, as early as 1770, electrical experiments were popularized in Japan by Hiraga Gennai and Sakuma Shozan in which one of the electrical phenomena investigated was the electrical conductivity through the human body. In 1831, an electrical battery constructed by Utagawa Yoan, based on the one invented by Volta in 1800, was used in medical experiments based on the belief that

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electricity could help cure illnesses. The existence of endogenous electrical current in skin wounds was first determined by the German physiologist Emil Du-Bois Reymond in 1843 [3]. It has since then been confirmed that wounds produce a surrounding electrical current or 'injury potential' with an intensity of less than $10\,\mu A\,cm^{-2}$, and that this electrical current plays an important role in wound healing [4, 5]. The endogenous electrical current stimulates and directs epithelial cell proliferation and cell migration at the wound edge and in this way promotes wound healing [6]. In addition to wound healing, nerve regeneration is also controlled by endogenous electrical current in vivo [7]. The seminal work of Borgens, et al. showed that steady direct-current electrical field of opposite polarity to the injury potential induced increased branching and faster regeneration of naturally regenerating axons. This finding has been applied to promoting mammalian spinal cord repair [8]. Applied physiological electrical current also induces a striking reorientation of some cells such as endothelial cells and myoblasts [9, 10], and guides the directional migration of hippocampal neurons and of neuronal stem cells [11, 12]. In vitro and in vivo studies revealed that electrical currents regulate cell movement and orientation during mitosis, an effect that may result in the shaping of tissues and organs [13, 14]. The effects of electrical current on cell behaviour and motility has been discussed in a review by McCaig et al. [15]. From the increasing number of studies on micro-electrical currents, either endogenous or applied, it is clear that electrical currents have significant physiological relevance.

Definition and technical specification

Applied current or electrical stimulation may vary in form and parameters, such as direct currents and alternating currents, among others; but this review focuses on low-intensity direct current or MES because it resembles the currents produced by the human body and is the most common type of electrical current used in research [16]. Applied electrical field of physiological strength or MES is defined as current with an intensity that is less than or equal to 1 milliampere (mA). MES is produced by low-voltage generators or electrotherapy units that can generate a range of waveforms, from monophasic square to biphasic rectangle, and with a range of frequencies from 0.3 to 50 Hz. Pulse duration may vary from 1 to 500 milliseconds (ms) at low frequencies [17]. Low-intensity direct currents of less than 1 mA usually do not produce muscular contraction or significant sensory stimulation [18].

Clinical effects

Positive clinical effects of applied low-intensity electrical current have been reported. Aside from wound healing, these effects include alleviation of pain, bone fracture healing, reduced inflammation and amelioration of osteoarthritis [19–22]. Given the mounting evidence on the positive effects of electrical current, it is not surprising that applied current or MES has been used clinically to treat non-healing skin wounds and bone fractures [23, 24]. Electrical stimulation has been employed in the clinical setting to treat delayed unions and non-unions of bone fractures with 64–85% success rates [24, 25]. A systematic review and meta-analysis of randomised placebo-controlled trials of applied low-intensity electrical current in patients with osteoarthritis of the knee revealed clinically relevant short-term pain relief for these patients [26]. Despite the positive effects of MES in clinical trials, its molecular mechanism of action is largely unexplored.

Mechanism of action

The process of wound healing can be ascribed to increased cell proliferation, tissue regeneration and new capillary formation. As mentioned above, low-intensity current enhances cell proliferation [6] and therefore tissue regeneration. It was also previously reported that applied current could initiate capillary formation [27]. In the elegant experiment by Zhao et al., they demonstrated that low-intensity electrical signals activate the phosphatidylinositol-3-OH kinase-γ (PI(3)Kγ) pathway, which mediates the process of wound healing. The activation of PI(3)K signalling subsequently induced the phosphorylation of extracellular-signal-related kinase (ERK), p38 mitogen-activated kinase (MAPK), Src and Akt but not Janus kinase JAK1, indicating that electric currents activate certain defined signalling pathways [4]. Indeed, it has been hypothesized that electrical signals may activate signal-transduction mechanisms and this underlies the therapeutic effects of applied electrical current not only on wound healing but also on other diseases [28]. While the influence of low-intensity current on cell migration and directional cues and its subsequent effect on wound healing is well known, other processes that low-intensity current might impact on, such as the signal-transduction pathways, and the consequential effects on physiological and/or pathological states are less explored. Because signalling cascades such as PI(3)K/Akt affect a broad range of cellular processes, the effects of applied low-intensity electrical current may be far-reaching. For instance, PI(3)K and its downstream target molecule Akt are central mediators of the effects of insulin [29].

Interestingly, we have demonstrated that MES enhances the phosphorylation of Akt that resulted in the amelioration of insulin resistance [18], which is consistent with the hypothesis that MES may affect signal transduction mechanisms. Our laboratory has also investigated the effects of MES on cellular functions and we have shown that MES increased the expression of ubiquitinated proteins and inhibited the proteasomal degradation of the molecular chaperone, heat shock protein (Hsp) 72 [30] whose turnover is regulated by the ubiquitin/proteasome pathway (Figure 1). Whether the activation of signalling pathways and the suppression of proteasomal degradation by MES are interdependent or unrelated is still unknown but these are proofs of principle that MES impacts on basic signal transduction pathways and cellular processes, which may produce the observable therapeutic effects of applied electrical current.

But due to technical limitations it might be difficult to measure the extent of electrical conductance in cells and tissues. Electrotherapeutic units of low voltage may produce currents of intensities up to a few microamperes and milliamperes, but measuring the current distribution of an applied electrical current in biological tissues is hampered by several factors. Electrical charges in tissues are transferred by multiple mechanisms such as the migration of ions, membrane capacitance, and rotation of polar molecules. Moreover, these electrical properties vary between tissues. Different cell types show subtly different responses to direct current electrical field due to variable local tissue resistances, the extracellular matrix composition, the coexistence of growth factors and neurotransmitters, and the level of second messengers within the cells [31]. Notwithstanding the technical difficulties of determining electrotherapeutic currents in tissues, various studies have demonstrated the effectiveness of applied low-intensity electrical field in clinical settings [1].

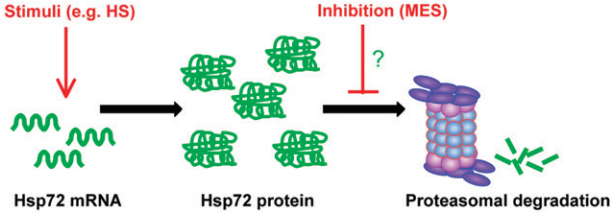

Figure 1. The effect of HS and MES on the synthesis and fate of HSP72. HSP72 mRNA induction is stimulated by stress such as heat shock (HS), leading to the production of HSP72 protein, which is subject to proteasomal degradation. Through an as yet undefined mechanism, MES inhibits the degradation of HSP72 and this leads to increased expression of HSP72.

Hyperthermia and Hsp72

Physiological relevance and applications

As mentioned above, we previously reported [30] that MES inhibited the degradation of Hsp72, which is particularly interesting because Hsp72 is well known for its cell protective functions [32]. Hsp72 acts as a molecular chaperone by assisting the proper refolding of misfolded proteins and helping in their elimination if they become irreversibly damaged, which is not uncommon when cellular stress occurs. Hsp72 also appears to play a critical role in the development of thermotolerance and protection from cellular damage associated with stress. The lack of Hsp72 synthesis in the presence of cellular stress is associated with exponential cell death, thus, Hsp72 regulates cellular homeostasis and promotes cell survival [33]. Hsp72 is rapidly synthesized in response to a variety of stresses, such as increase in temperature. For review of Hsp72 synthesis and mechanism of action, see Mayer and Bukau [34].

Considering that heat induces cell stress, it seems untenable to employ a modality wherein heat is applied to increase the body temperature in the treatment protocol of hyperthermia [2]. Yet, the number of studies on the effects and applications of hyperthermia is increasing. Most notably, hyperthermia is used as an adjunct to an already established treatment modality for malignant tumour such as chemotherapy or radiotherapy [35]. Several reports on hyperthermia in tumour therapy vary in the treatment protocol including the heating temperature used and exposure time. In some procedures, the core temperature of the animal or patient is raised to a high temperature range, usually between 41°C–42°C, and maintained for 30 min to 2 hr [36, 37]. Other protocols utilise low temperature or fever-like mild hyperthermia with a temperature range between 39°C–40°C applied for longer periods of time [38, 39]. It was reported that the advantage of the latter protocol is the improved anti-tumour effects with less toxicity [38].

Although hyperthermia is mostly known for its use as adjuvant in tumour therapy [40], it is also employed to induce preconditioning in ischaemia/reperfusion experimental settings [41]. Studies in cardiac muscles have shown that small priming episodes of stress, such as mild hyperthermia, are followed by an increase in the expression of stress-related Hsp72 and this often correlated with improved survival of ischaemic/reperfused muscle [42]. Activation of the heat shock proteins (HSPs) by mild heat shock apparently allows cells to withstand subsequent cellular insult that would otherwise be lethal [43]. The important role of Hsp72 in preconditioning was confirmed using molecular techniques to block or increase Hsp72 synthesis [44, 45]. Cells exposed to sub-lethal heat shock develop an initial rapid thermo-tolerance that

results in a desensitization of the Hsp72 response to a second sub-lethal heat shock. When cells have been acclimatized, an altered threshold for Hsp70 production results in an accelerated rate of Hsp72 transcription when exposed to acute heat shock [46].

Distinct yet related to preconditioning, the induction of Hsp72 by hyperthermia has found an application to hormesis, which in turn is beginning to be recognized as one of the underlying mechanisms for the anti-aging and longevity effects of certain genetic and environmental factors [47, 48]. Aging is associated with inefficiency and failure in stress response, cellular maintenance, function and repair mechanisms resulting in the accumulation of cellular damage. But a proper dosing of stress or hormesis, which is defined as an adaptive response of cells and organisms to a moderate (usually intermittent) stress, increases stress tolerance and longevity in both cellular and organismal models [49]. The mechanism of hormetic effects of heat shock is the activation of key proteins involved in stress response, mainly, though not restricted to, the HSPs [50], which provide protection to the cells.

Another lesser known, but nevertheless important, function of Hsp72 is its ability to inhibit the activation of c-Jun N-terminal kinase (JNK) by Hsp72 binding to JNK [51]. JNK can phosphorylate a key serine residue (serine 307) in insulin receptor substrate-1 (IRS-1), which is a crucial substrate for activated insulin receptor (IR) (Figure 2). The phosphorylation of IRS-1 by JNK renders IRS-1 a less suitable substrate for IR and this compromises the insulin signalling pathway [52]. Importantly, it has been noted that the skeletal muscles of patients with insulin resistance or type 2 diabetes have low expression of Hsp72 [53, 54]. Thus, the induction of Hsp72 may have the potential to ameliorate insulin resistance by inhibiting the phosphorylation activity of JNK on IRS-1 [55]. Indeed, it has been shown that overexpression of Hsp72 protected test animals against diet- or obesity-induced insulin resistance through prevention of JNK phosphorylation [56]. It appears then that the protective functions of Hsp72 extend to the preservation of insulin signalling transduction mechanism.

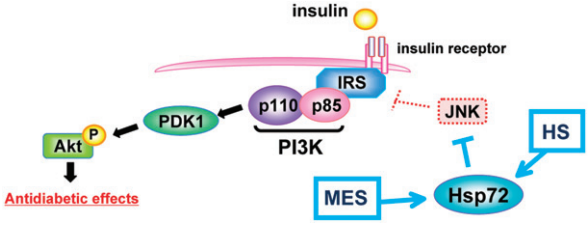

Figure 2. The effect of HS and MES on the insulin signalling pathway. Insulin activates the insulin receptor, initiating a signalling cascade that results in activation of the protein kinase Akt. Increased AKT phosphorylation regulates different metabolic pathways including activation of glucose uptake in muscle and fat. JNK increases serine phosphorylation of insulin receptor substrate (IRS) to impair the insulin signalling pathway. On the other hand, MES and HS increase the expression of Hsp72, which is known to inhibit JNK. Thus, the effect of MES and HS is to enhance insulin signalling by inhibiting JNK through Hsp72.

Combining mild electrical stimulation and hyperthermia

Rationale

Based on the premise that MES and hyperthermia each affect signalling pathways and Hsp72 expression, we hypothesised that the combination of MES and hyperthermia might produce an additive complementary effect on the alleviation of diseases caused by dysregulated signalling mechanism and/or stress-induced diseases, such as insulin resistance and ischaemia/reperfusion injury, respectively.

Applications and future potential

Work in our laboratory has focused on investigating the effects of combination treatment of MES (10 μA; 12 V) and mild HS (<42°C) on hyperglycaemia, hepatic I/R injury and gastric mucosal ulcer using the apparatus shown in Figure 3. Our recently published report showed that the combination of MES and mild HS significantly ameliorated insulin resistance in the animal models of hyperglycaemia through the dual

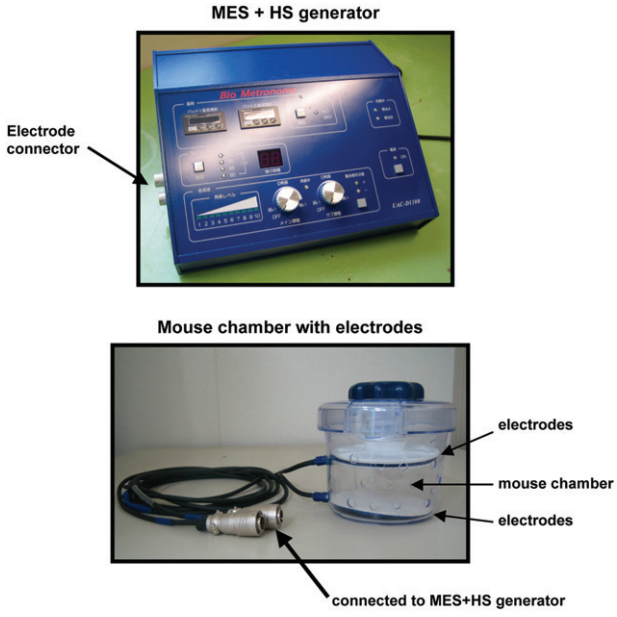

Figure 3. The apparatus for MES + HS treatment. The upper panel shows the generator or Biometronome™ that delivers MES and/or heat shock in which current and heat can be controlled. The lower panel shows the apparatus used in our experimental work for in vivo treatment. The mouse is placed in the well ventilated chamber in contact with moistened cloth-padded rubber electrodes which are connected to the Biometronome™.

effects of increased Akt phosphorylation and enhanced Hsp72 expression (Figure 2) [18]. Our investigations also yielded recently published results in which pre-conditioning with MES + mild HS significantly attenuated ischaemia/reperfusion-induced liver injury in mice [57]. In addition, our as yet unpublished study showed that MES + mild HS preconditioning also ameliorated indomethacin-induced gastric ulcer. Collectively, these observations suggest promising effects of MES + mild HS combination treatment on certain diseases. The mechanism of the positive effects of this treatment is yet unclear. Since low-intensity current and hyperthermia have an impact on many cellular processes and functions [28, 58, 59] aside from induction of Hsp72, further investigation on the possible regulation of other signalling molecules by MES and hyperthermia may be necessary to provide deeper mechanistic insight into the effects of these treatments.

Low-intensity current as well as hyperthermia have been applied as treatment modalities for a range of diseases with relatively few side effects [1, 35]. Assessment of the long-term effects of the combination treatment of MES and HS is necessary, as with any other modalities. There is potential each for MES and hyperthermia alone as therapeutic modalities. Their combination could yield even more enormous potential. A rewarding field yet awaits.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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