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Translating whole-body cryotherapy into geriatric psychiatry – A proposed strategy for the prevention of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD), which is the most common form of dementia, constitutes one of the leading causes of disability and mortality in aging societies. Currently recommended medications used in treating AD include cholinesterase inhibitors and the NMDA antagonist – memantine, but poorly counteract progression of the disease. According to current knowledge, the neuropathological process underlying the etiology of AD begins many years, if not decades, before the development of overt symptoms of dementia. Mild cognitive impairment (MCI) is regarded as the first detectable manifestation of cognitive decline. Nowadays, there is a general consensus that vascular alterations, oxidative stress and inflammatory response contribute to the development of AD. Following these mechanisms and tracing the anti-inflammatory and anti-oxidative effects of cryostimulation, we postulate that whole-body cryotherapy (WBCT) might be utilized as a means of preventing AD. WBCT is a relatively safe and cost-effective procedure, which is widely applied in various medical specialties. Thus, there is an urgent necessity to evaluate the long-term effectiveness of WBCT in the prevention of AD in patients with MCI and healthy individuals.

Introduction

Several large-scale surveys have indicated that Alzheimer's disease (AD), which is the most common form of dementia, constitutes one of the leading causes of disability and mortality in aging societies. According to current knowledge, AD affects 35.6 million people worldwide and this figure is expected to increase in the next few years [1]. In a recent large study, commissioned by the European Brain Council (EBC), the total costs of dementia for Europe in 2010 were estimated at 105.2 billion € [2]. To make things worse, the treatment of AD leaves much to be desired. Current therapeutic options include cholinesterase inhibitors and the NMDA antagonist – memantine, which poorly counteract the progression of AD.

Therefore, numerous hypotheses regarding the etiology of AD have been strongly criticized over the past decade. However, there are several biological alterations including vascular malfunction, oxidative stress, mitochondrial damage, chronic inflammation and aberrant neurotransmission, which constitute potential therapeutic targets for AD [3,4]. Interestingly, some of these patomechanisms overlap at several points with the etiology of depression. Thus, emerging hypotheses suggest the existence of a common etiological background for AD and depression [5]. Tracing biological alterations connected to depression, the research team from our scientific unit has previously performed, for the first time, a controlled pilot study on the role of whole-body cryotherapy (WBCT) in the treatment of depression and anxiety disorders [6]. Despite several limitations, the positive results of this trial led to the assumption that WBCT might be considered as an adjunct treatment of depressive and anxiety disorders. Subsequently, Miller et al. [7] investigated the effects of WBCT on various parameters of oxidative stress in depressive patients with multiple sclerosis. The results obtained indicated that WBCT suppresses oxidative stress in this group of patients and this mechanism might slow down progression of the disease.

Exposure to extremely low temperatures was introduced into medicine at the end of the 1970s by Toshiro Yamauchi, who constructed the first cryogenic chamber [8]. Currently, cryostimulation is being applied increasingly often in medicine as an adjunct treatment of rheumatic diseases [9], traumatic injuries [10], neurological diseases with spasticity [11] and distinct dermatological entities including psoriasis [12–14]. Notably, the results on dermatoses linked by psychosomatism e.g. psoriasis, as well as depression and anxiety disorders could suggest that WBCT may improve cognition in humans. However, this field is still in its infancy and requires further investigation to determine underlying mechanisms in animal models.

WBCT relies on exposure to extremely low temperatures, between −110 and −160 °C, in cryogenic chambers. According to current experience, WBCT is a safe procedure, performed under the supervision of a physician after consideration of some contraindi-

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cations. The exact mechanisms underlying the action of extremely low temperatures remain incompletely elucidated and have been determined on the basis of preliminary experimental studies. The anti-inflammatory effects of cryostimulation may arise from increasing the level of anti-inflammatory cytokines, such as IL-6 and IL-10, and down-regulating the production of pro-inflammatory cytokines, including IL-1α, IL-2, and IL-8 [15–17]. In turn, antioxidant action may be the result of an increase in the activities of glutathione peroxidase and glutathione reductase, as well as an increase in the concentrations of antioxidants, particularly extraerythrocyte hemoglobin and uric acid [18]. There are also single reports with regard to the influence on hormone metabolism manifesting in increased concentration of catecholamines, adrenocorticotropic hormone, cortisone, pro-opiomelanocortin (POMC) and β-endorphins [19]. Finally, WBCT may lead to beneficial changes in the lipid profile [20]. However, the exact mechanism of this phenomenon remains unclear. It might be assumed that alterations in the metabolism of lipids result from increased production of IL-6, which is a lipolytic molecule, i.e. produced by adipose tissue [17].

Hypothesis

We hypothesize that WBCT may be applied in geriatric psychiatry and utilized as a potential means of preventing AD. Nowadays, there is an accumulating number of expert opinions that the effective treatment of AD might be possible only in patients without overt cognitive decline and during the preclinical course of dementia [21]. In view of this, we assume that the early stages of AD neuropathology, including mild cognitive impairment (MCI), may be the logical target for WBCT. Given that WBCT is a cost-effective and relatively safe procedure, the application of this strategy with regard to AD seems to be an attractive approach. Several patomechanisms underlying the molecular background of AD, particularly vascular neuropathology, support our hypothesis. Briefly, the vascular hypothesis of AD states that reactive oxygen species, generated as a consequence of inflammation or other insults, may induce vascular hypoperfusion, mitochondrial malfunction, manifested as energy failure, endothelial damage and the subsequent disruption of the blood brain barrier (BBB), leading to neuronal loss at the molecular level, and cognitive decline as a clinical outcome [3]. In view of this, there is a general consensus that oxidative stress precedes irreversible hallmarks of AD, which are principally represented by the deposition of amyloid-β (Aβ) [22,23]. On the other side, Aβ aggregation may itself promote oxidative stress creating a vicious cycle [24,25]. It is noteworthy that the enhancement of lipid peroxidation and nucleic acid oxidation is not limited to brain, but has been also found in peripheral blood and urine of patients with MCI [26–28]. Similarly, accumulating evidence indicate that a low-grade inflammatory state is indispensably associated with AD etiology and has been widely observed in brain and at the periphery [29]. However, clinical trials with anti-inflammatory medications failed to prove beneficial effects indicating that AD is not a consequence of a single insult, but rather a complex clustering of alterations in various biological pathways. Hence, it is necessary to search for treatment strategies displaying systemic activity in multiple fields of AD neuropathology. In view of this assumption, WBCT fulfills the criterion of being a multidirectional therapeutic approach, which possesses high antioxidant and anti-inflammatory power. Moreover, emerging data indicate that WBCT may promote a release of pro-hormones with local and systemic effects [19], as well as affect the lipid metabolism [20].

There is also convincing evidence supporting the neuroprotective role of low temperatures, which originates from experimental studies on the application of therapeutic hypothermia in infants and adults with hypoxic-ischemic cerebral injury [30]. There is a growing debate as to whether hypothermic coronary bypass grafting is more beneficial than the normothermic procedure with regard to postoperative behavioral recovery, neurological outcome and cognitive functions [31,32]. Following these clinical findings, it should be noted that there are several mechanisms underlying the effectiveness of therapeutic hypothermia, which might slow down neurodegeneration. Hypothermia has been reported to suppress glutamate release, silence the action of inflammatory transcription factor (NFκB) and display antiapoptotic effects via various mechanisms, reviewed in detail by Yenari et al. [33]. Interesting arguments supporting our potential therapeutic strategy were provided by Salerian and Saleri [34]. They noted that physical fitness lowers body temperature and increases brain volume in humans. In turn, lower body temperature has been linked to a longer life expectancy in many species.

Testing of the hypothesis and further consequences

Firstly, our hypothesis should be confirmed in animal models mimicking cognitive impairment and AD. Experimental studies in animal models should focus not only on the effectiveness of WBCT, but also on the putative targets for cryostimulation. However, the possibility of improving cognitive functions in patients with AD raises many doubts due to advanced neuropathological lesions, which seem to be irreversible. Thus the next step should focus on long-term, observational, case-control studies of subjects with MCI or cognitively healthy controls. A comprehensive approach linking reliable clinical assessment to advanced neuroimaging techniques and so-called "omics" analysis, which refers to exhaustive evaluation of biological pathways at various levels of gene expression and posttranslational mechanisms, should be adopted to perform the testing of our hypothesis.

Conflict of interest statement

None declared.

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