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Can Giant Cell Arteritis be Prevented and Ameliorated with Magnesium and a Recently-Discovered Biologic, HDFx?

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Introduction

Giant cell arteritis (GCA) is characterized as an inflammatory condition of the body's large and medium arteries. GCA can be considered a form of vasculitis, and it usually is found in people older than the age of 50, being more prominent in women [1]. GCA is a disease that causes inflammations of various arteries with no known etiology and is most frequently found in people of Northern European origin [1,2]. GCA is thought to be an autoimmune disease affecting arterial vessels in the head, temporal lobes and neck and often, primarily those arterial vessels in the eyes accompanied by intense headaches, fever, and jaw pain while eating [1-3]. It often leads to permanent loss of vision in one or both eyes in 20-50% of the affected victims. In a number of patients, GCA has been associated with central arterial occlusions and hemorrhages in the retinas of the eyes and strokes [4,5]. GCA has also been associated with cardiac dysrhythmias and myocardial infarctions [1-5]. Often, the symptoms are very sudden in onset. GCA, in many cases, attacks arterial vessels going to the aorta leading to aneurysms within the artery and a great risk of rupture of this large blood vessel. In some patients, rapid treatment with aspirin and high-dose steroids can ameliorate many of the symptoms [1-3]. Do these pathophysiological events have any common, potential physiological and biochemical underlying etiologies?

Recently, it has been pointed out that macular degeneration and central vein occlusion in the eyes are associated with a magnesium deficiency and a potential release of ceramides and platelet-activating factor (PAF) [6]. Working with a variety of mammals, including sub-human primates, it has been discovered that a heretofore unknown naturally-occurring conserved biologic host-defense molecule, termed HDFx, is characterized with multiple anti-inflammatory attributes as well as regenerative properties [7-20]. Below, we posit why the combined use of HDFx and Mg may be therapeutically-effective in GCA and other forms of vasculitis diseases.

Discovery and Virtues of HDFx

Our laboratories have been working on a new approach to develop host-defense factors that stimulate/inhibit various arms of the innate and adaptive immune systems. To this end, a new host -defense factor , termed "HDFx", which is a conserved protein found, has been discovered in mice, rats, guinea-pigs, rabbits, dogs, and sub-human primates [7-21]. We assume it is also present in humans since it is a conserved molecule. More than 135 years ago, Elie Metchnikoff, the great father of immunology, hypothesized that the body under stressful conditions might produce powerful immune -stimulants which perforce would act on different arms of the innate immune system and serve to protect against major injuries, inflammatory reactions, and diseases [22]. Metchnikoff's early studies pointed to the importance of macrophages and phagocytic leukocytes to natural (innate) resistance against pathogenic bacteria and other microorganisms. Over the past 30-40 years, a considerable body of evidence has accumulated to support a strong relationship between the functional (physiological) state of the microcirculation, macrophages-phagocytes, natural killer (NK) cells, the reticuloendothelial system (RES), and "pit cells" in the liver to host defense and resistance to pathogens, trauma, circulatory shock, wounding, and combined injuries [23-35].

Studies from our laboratories have clearly shown that HDFx is protective (to different degrees) against a variety of systemic bodily insults ranging from hemorrhage, trauma, endotoxins, a variety of lethal bacteria (e.g., *E. coli, S. enteriditis, C. welchii*) to fungi such as *candida, aspergillis, and fumigates microorganisms* [7-10, unpublished findings]. HDFx is a conserved 35-40 kD protein [7]. A unique

attribute of HDFx is that it accelerates wound healing [9], an attribute probably vital to the healing needed in the inflammatory reactions, blood vessel ruptures, and macular degeneration found in GCA. Most importantly, HDFx has been demonstrated to inhibit the release of multiple cytokines (i.e., IL-2, IL-6, IL-8, Il-1 beta, IFN-gamma) and chemokines (i.e., macrophage factors, MCP-1) observed in GCA [7]. It has been shown that HDFx can either prevent or ameliorate the intensity of "cytokine storms" under a variety of conditions [7,10,11,16,18,19, unpublished findings] which normally produce intense inflammatory responses, severe tissue injury, and bleeding events that eventually compromise and kill the host from GCA.

Since it has been demonstrated that HDFx appears to "supercharge" macrophages, phagocytic leukocytes, RES cells, as well as "pit cells", against injury and infections, produced by multiple microorganisms [7-10, unpublished findings], we believe HDFx would be therapeutically-effective, or at least ameliorative, against many of the tissue injuries seen in GCA.

Potential Combined Use of Magnesium in GCA

Next to potassium, Mg is the second most abundant intracellular cation and the fourth most abundant cation in the body. Mg is a co-factor for more than 500 cellular enzymes involved in cellular energy production. In addition, Mg is involved membrane functions such as hormone-receptor bindings, gating of Ca^{2+} channels, transmembrane fluxes of ions, regulation of adenylate cyclases, numerous structural functions, stabilization of cell membranes, regulation of cell growth processes, regulation of cardiac and smooth muscle tone, regulator of neurotransmitter release, regulation of blood pressure, and regulation of DNA, RNA, proteins, carbohydrates, and lipids [35-41]. Mg also plays multiple roles in programmed cell death (i.e., apoptosis, necroptosis, and ferroptosis) [42-44]. Mg plays a pivotal role in control of neuronal activity, cardiac excitability, neuromuscular transmission, vasomotor tone, and microcirculatory blood flows and capillary distribution, all important factors in preventing dysfunctions in GCA. Mg sulfate has been utilized as an anti-inflammatory agent ever since its discovery at Epsom Downs, England, almost four centuries ago. Mg is a potent vasodilator, an effect which should help to keep blood vessels patent in GCA. Prophylactic use of Mg with HDFx would be expected to limit the incidences of arrhythmias, ventricular fibrillation, and heart attacks associated with GCA, as the syndrome often demonstrates all of the latter effects; Mg therapy has been shown in animals and humans to thwart these effects [35-41]. HDFx has recently been demonstrated to inhibit complications to the pulmonary-respiratory tract and reduce pulmonary arterial hypertension, often seen in GCA [21]. Furthermore, HDFx has recently been found to inhibit inflammatory responses in the lungs (e.g., reduced release of cytokines and chemokines; reduced infiltration of lung tissues by leukocytes, macrophages, and dendritic cells; and reduced thromboses) produced in experimental pulmonary hypertension [21, unpublished findings].

Daily Dietary Intakes of Mg Demonstrate a Marked Deficiency in this Mineral

Dietary, daily intakes of Mg in the USA, UK, and Europe indicate there are shortfalls amounting to 35-40% of normal (i.e., 150-235 mg/day of Mg compared to a normal level of 375-450 mg/day of Mg) [21,38-41]. Whether these severely- low levels of Mg intake is a potential causal agent in GCA remains to be investigated. However, using our data, the World Health Organization has recommended that all diets should attempt to include enough Mg to overcome the current shortfalls [42].

Conclusions

We believe our findings on HDFx and Mg should be helpful in understanding some of the pathophysiological mechanisms underlying GCA and may prove useful in aiding the treatment of patients with GCA. We, thus, believe that clinical trials to test our hypothesis should be mounted.

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