Medical Hypotheses 80 (2013) 548–552

Contents lists available at SciVerse ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Physical activity, by enhancing parasympathetic tone and activating the cholinergic anti-inflammatory pathway, is a therapeutic strategy to restrain chronic inflammation and prevent many chronic diseases

Heidi L. Lujan, Stephen E. DiCarlo *

Department of Physiology, Wayne State University, School of Medicine, Detroit, MI 48201, United States

ARTICLE INFO

Article history:
Received 18 September 2012
Accepted 13 January 2013

ABSTRACT

Chronic diseases are the leading cause of death in the world and chronic inflammation is a key contributor to many chronic diseases. Accordingly, interventions that reduce inflammation may be effective in treating multiple adverse chronic conditions. In this context, physical activity is documented to reduce systemic low-grade inflammation and is acknowledged as an anti-inflammatory intervention. Furthermore, physically active individuals are at a lower risk of developing chronic diseases. However the mechanisms mediating this anti-inflammatory phenotype and range of health benefits are unknown. We hypothesize that the "cholinergic anti-inflammatory pathway" (CAP) mediates the anti-inflammatory phenotype and range of health benefits associated with physical activity. The CAP is an endogenous, physiological mechanism by which acetylcholine from the vagus nerve, interacts with the innate immune system to modulate and restrain the inflammatory cascade. Importantly, higher levels of physical activity are associated with enhanced parasympathetic (vagal) tone and lower levels of C-reactive protein, a marker of low-grade inflammation. Accordingly, physical activity, by enhancing parasympathetic tone and activating the CAP, may be a therapeutic strategy to restrain chronic inflammation and prevent many chronic diseases.

Introduction

Exercise, the wonder remedy and prophylactic

It seems as if hardly a week goes by without a headline touting the benefits of regular exercise for everything from cancer to heart disease; for high blood pressure, diabetes and high cholesterol, or to lose weight, relieve joint pain, reduce anxiety or increase libido. It seems as if exercise is beneficial for everything and anything that ails us [23,48,80,83]? And it may be, since there is a linear relationship between physical activity and health. Specifically, individuals who maintain an active lifestyle live longer, healthier lives [10]. Furthermore the capacity to exercise is a strong predictor of overall mortality rates [58]. In sharp contrast, as we in the developed world have become less physically active, the incidence of many chronic diseases has increased and a sedentary lifestyle is a major risk factor for many chronic conditions [26,50]. How is it possible that being physically active has such a positive impact on multiple health conditions and what is the common mechanism?

Chronic inflammation linked with chronic disease

Chronic diseases are the leading cause of death in the world and chronic inflammation is a key contributor to many chronic diseases [75]. For example, inflammation plays a key role in heart disease, arthritis, diabetes, irritable bowel syndrome, Alzheimer's disease, Parkinson's disease, asthma and many others. Furthermore, several reports investigating various markers of inflammation in different population groups have confirmed an association between low-grade systemic inflammation and chronic diseases [6,21,25,27,30,32,44,60,66,67,78,94]. Thus, persistent, low-grade inflammation is an important contributor to the pathophysiology of several chronic health conditions, and many chronic health conditions are considered inflammatory disorders [56]. Accordingly, interventions that reduce inflammation may be effective in treating multiple adverse chronic conditions. For example, aspirin, the miracle or wonder drug, is effective for many chronic conditions (heart attacks, stroke, cancer, pain and many other conditions) due, in part, to its anti-inflammatory properties [98].

The cholinergic anti-inflammatory pathway

Mammals maintain homeostasis by balancing the activities of pro-inflammatory and anti-inflammatory pathways. This is

* Corresponding author. Address: Wayne State University, School of Medicine, 540 E. Canfield Ave., Detroit, MI 48201, United States. Tel.: +1 313 577 1557; fax: +1 313 577 5494.
E-mail address: sdicarlo@med.wayne.edu (S.E. DiCarlo).

0306-9877/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.mehy.2013.01.014

necessary because inflammatory cells release cytokines that are potentially injurious. The autonomic nervous system interacts with the immune system to modulate and restrain the inflammatory process [13,73]. For example, in 2000, Tracey and colleagues documented the role of efferent parasympathetic (vagal) nerve signaling in modulating inflammation [13]. The authors named this neural-immune interaction the "cholinergic anti-inflammatory pathway" (CAP). The CAP is an endogenous, physiological mechanism by which acetylcholine from the vagus nerve, via the α7 subunit of the *nicotinic* acetylcholine receptor (α7nAChR), interacts with the innate immune system to *modulate and restrain* the inflammatory cascade [13,34].

Specifically, acetylcholine, the principle vagal neurotransmitter, attenuates the release of pro-inflammatory cytokines [tumor necrosis factor (TNF), interleukin (IL)-1β, IL-6 and IL-8], but not the anti-inflammatory cytokine IL-10, in lipopolysaccharide- stimulated human macrophage cultures [13]. Furthermore, direct electrical stimulation of the peripheral vagus nerve during lethal endotoxemia in rats inhibited TNF synthesis in liver, attenuated peak serum TNF amounts, and prevented the development of shock [13]. Thus vagal nerve signaling, via the α7 subunit of the nicotinic acetylcholine receptor (α7nAChR), is critical for the anti-inflammatory response [1,28,35,81,96]. Similarly, clinical studies indicate that nicotine administration is effective for treating some cases of inflammatory bowel disease [41,84] and that pro-inflammatory cytokines are significantly decreased in the colonic mucosa of smokers with inflammatory bowel disease [86].

Nicotine and anti-inflammation

It is well accepted that cigarette smoking is associated with significantly increased rates of cardiovascular disease and premature death [76]. Furthermore, cigarette smoking is a strong and independent risk factor for the development of heart failure [46,77,90,99]. However, despite these well established facts, paradoxically, a number of studies have documented that the short-term mortality rates are lower in smokers compared with non-smokers after acute coronary syndromes [3,4,40,45,55]. Although, this 'smoker's paradox' has been explained, in part, by the younger age and fewer coexisting risks in smokers, many studies have shown that the paradox persists with comprehensive covariate adjustment [4,29,40,55]. A similar paradoxical relationship with smoking and short-term outcomes has also been observed in patients presenting with ischemic stroke [72]. Thus, although it is clear that cigarette smoking has multiple adverse effects on the cardiovascular system including endothelial dysfunction, platelet dysfunction, increased coagulation, increased heart rate, increased blood pressure, increased myocardial oxygen demand and vasoconstriction [59,68,69,79,93], paradoxically, "smoking cessation" measures for individuals with heart failure have never been shown to be beneficial [22]. In sharp contrast, chronic activation of nicotinic receptors is beneficial in dogs with heart failure [7]. Similarly, vagal stimulation, through its nicotinic actions, limits infarct size and the inflammatory response to myocardial ischemia and reperfusion in anesthetized, open chest rats [17]. Taken together, activation of nicotinic acetylcholine receptors has a profound anti-inflammatory effect [13].

Physical activity and chronic disease

Physically active individuals are at a lower risk of developing chronic diseases [11,18,20,57,89]. Furthermore, as people in the developed world have become less physically active, the incidence of many chronic diseases has increased. Physical in-activity has been linked to obesity, cardiovascular diseases and diabetes, as well as immune-system dysfunction. Accordingly, a sedentary lifestyle is a major risk factor for many chronic conditions [26,50]. In contrast, the capacity to exercise is a strong predictor of overall mortality rates [58] and increasing the amount of physical activity prevents many chronic diseases.

Many chronic diseases are associated with a persistent, low-grade inflammation. For example, inflammation is correlated with the development of insulin resistance and type 2 diabetes [49], cardiovascular diseases [42,63], neurodegenerative diseases [92], Alzheimer's disease [102], and many other chronic conditions. Since inflammation is implicated in the pathogenesis of many chronic conditions and physical activity reduces the incidence of many chronic diseases, perhaps the therapeutic benefits of exercise are due, in part, to the well-established anti-inflammatory effects of regular exercise [14,53,75,100]. For example, regular exercise reduces levels of inflammatory cytokines and protects against cardiovascular disease and type 2 diabetes [5,38,51,64,70]. Although, physical activity reduces the level of systemic inflammation [37], the mechanism mediating the anti-inflammatory effects of regular exercise is unknown.

Physical activity enhances parasympathetic tone

Daily exercise alters the autonomic nervous system resulting in an *increase* in cardiac parasympathetic tone [9,12,15,82]. For example, resting bradycardia [8,15,19,39,61,71,82,85,88] and reduced heart rate at submaximal workloads [2,8,12,15,16,36,39,61,62,87,88] are well-established consequences of daily exercise. Furthermore, acetylcholine content and choline-acetyltransferase are increased in the hearts of trained rats [19,91]. Accordingly, the anti-inflammatory phenotype and range of health benefits associated with daily exercise may be mediated, in part, by acetylcholine activation of the cholinergic anti-inflammatory pathway. In this context, stimulation of the efferent vagus nerve inhibits pro-inflammatory cytokine release and protects against systemic inflammation [13,74].

The hypothesis

Physical activity, by enhancing parasympathetic tone and activating the cholinergic anti-inflammatory pathway, may be a therapeutic strategy to restrain chronic inflammation and prevent many chronic diseases (Fig. 1). Specifically, higher levels of physical activity are associated with enhanced parasympathetic (vagal) tone. Importantly, parasympathetic tone activates the "cholinergic anti-inflammatory pathway". The Cholinergic Anti-inflammatory pathway is an endogenous, physiological mechanism by which acetylcholine from the vagus nerve, interacts with the innate immune system to *modulate and restrain* the inflammatory cascade. In this context, physical activity is documented to reduce systemic low-grade inflammation and is acknowledged as an anti-inflammatory intervention. Accordingly, the "cholinergic anti-inflammatory pathway" mediates the anti-inflammatory phenotype and range of health benefits associated with physical activity.

Implications of the hypothesis

Physical inactivity is the major public health problem of our time costing the world hundreds of billions of dollars and millions of lives [65]. According to the World Health Organization, 31% of adults aged 15 and over were insufficiently active in 2008 (men 28% and women 34%); and approximately 3.2 million deaths each year are attributable to insufficient physical activity [97]. Importantly, a strong relationship exists between time spent in inactivity (e.g., television viewing time, sitting in a car, overall sitting time) and all-cause and cardiovascular disease mortality [24,54,95].