Medical Hypotheses 120 (2018) 28–42

Contents lists available at ScienceDirect

Medical Hypotheses

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

# Intermittent living; the use of ancient challenges as a vaccine against the deleterious effects of modern life – A hypothesis

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ARTICLE INFO

*Keywords:*
Evolution
Intermittent
Hormesis
Hypoxia
Hypercapnia
Vaccine
Chronic
Low grade inflammation
Fasting
Preconditioning

ABSTRACT

Chronic non-communicable diseases (CNCD) are the leading cause of mortality in developed countries. They ensue from the sum of modern anthropogenic risk factors, including high calorie nutrition, malnutrition, sedentary lifestyle, social stress, environmental toxins, politics and economic factors. Many of these factors are beyond the span of control of individuals, suggesting that CNCD are inevitable. However, various studies, ours included, show that the use of intermittent challenges with hormetic effects improve subjective and objective wellbeing of individuals with CNCD, while having favourable effects on immunological, metabolic and behavioural indices. Intermittent cold, heat, fasting and hypoxia, together with phytochemicals in multiple food products, have widespread influence on many pathways related with overall health. Until recently, most of the employed challenges with hormetic effects belonged to the usual transient live experiences of our ancestors. Our hypothesis; we conclude that, whereas the total inflammatory load of multi-metabolic and psychological risk factors causes low grade inflammation and aging, the use of intermittent challenges, united in a 7–10 days lasting hormetic intervention, might serve as a vaccine against the deleterious effects of chronic low grade inflammation and it's metabolic and (premature) aging consequences.

## Introduction

The number of people with chronic diseases such as cardiovascular diseases (CVD), diabetes, respiratory diseases, mental disorders, autoimmune diseases (AID) and cancer has increased dramatically over the last three decades. The increasing rates of these chronic systemic illnesses suggest that inflammation [171,199], caused by excessive and inappropriate innate immune system (IIS) activity, is unable to respond appropriately to danger signals that are new from the perspective of evolution. The challenges lead to unresolved or chronic inflammatory activation in the body and a state of low-grade inflammation (LGI).

Known risk factors for LGI and chronic disease are premature aging, smoking, socioeconomic status, obesity, chronic psychosocial stress, sedentary lifestyle, toxins, insufficient sleep, nutritional factors (dose, composition, time, frequency), abuse of legal and illegal drugs, alcohol included, politics and economy [87,180,179,57,58]. These, mostly environment-driven, risk factors seem inevitable in current Western societies and their shares and intensities are most likely destined to further increase in the future. Importantly, many of these risk factors exhibit interaction, while contemporary humans are likely to suffer from these challenges in concert. This current 'conditions of existence' (Darwin) contrast with the stress factors experienced by traditionally living populations who still live in the environment of our ancestors. In that environment, they had to cope with short-term mono-metabolic danger factors (e.g. hunger, thirst, cold, heat), whereas modern humans are exposed to multi-metabolic risk factors that stimulate an energy conflict between organs and major systems [223]. The ensuing conflict between current experience and to what our genes and stress systems

*Abbreviations:* AA, arachidonic acid; AID, autoimmune diseases; ALAT, transaminases alanine aminotransferase; ARE, antioxidant response element; ASAT, aspartate aminotransferase; ADHD, attention deficit hyperactive disorder; BAT, brown adipose tissue; BMR, basal metabolic rate; CRP, C-reactive protein; CVD, cardiovascular diseases; CIRBP, cold-inducible RNA binding protein EPO; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HIF1, hypoxia inducible factor 1; IF, intermittent fasting; IL8, interleukin 8; IHT, intermittent hypoxia training; KEAP1, Kelch-like ECH associated protein 1; LFD, low food diversity; LGI, low-grade inflammation; MOP, mitochondrial oxidative phosphorylation; NFkB, nuclear factor kappa B; PON, plasma paraoxonase-1-arylesterase activity; mTOR, mammalian target of rapamycin; MOP, mitochondrial oxidative phosphorylation; Nrf2, N-erythroid derived -related factor 2; PD, panic disorder; PPARs, peroxisome proliferator activated receptors; RAAS, renin-angiotensin-aldosterone system; SAD, separation anxiety disorder; TNF-alpha, tumour necrosis factor alpha

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https://doi.org/10.1016/j.mehy.2018.08.002
Received 31 May 2018; Accepted 4 August 2018

are adapted is the basis of the so-called 'mismatch hypothesis' of 'typically Western' diseases.

Mono-metabolic stress factors have shaped adaptive mechanisms for survival and reproduction, such as short-lasting inflammation, insulin resistance, activation of the sympathetic nervous system and others. All of these responses emerged with the purpose to first protect the brain from damage and energy deficits [163]. Whereas mono-metabolic challenges increases basal metabolic rate, multi-metabolic risk factors may, on the other hand, cause LGI and a hypo-metabolic state [223]. The latter might be the principal reason for the deleterious effects of LGI, since a hypometabolic state causes energy deficits in multiple organs, and consequently multi-organ damage [198]. While among our ancestors, cold, heat, starvation and repetitive infections were among the major causes of death, exposure to mild cold, mild heat, short fasting periods and the regular consumption of small amounts of 'toxic' nutrients provided hormetic triggers. Mildly toxic insults, for example, derive from plant secondary metabolites, many with bitter tastes. The discovery of the Nrf2 receptor has revolutionized toxicology by unveiling the benefits of low amounts of toxins [16,83]. Ultimately, it is all about hormesis: every dose response curve is U-shaped (for further reading [22,142,138,137,26,21,20] (Calabrese, 2014)), as opposed to the saturation curves that are usually depicted in textbooks and lectures, and are the first to pop-up when entered into Google-pictures. Establishment of 'dietary reference intakes' (e.g. AIs, RDAs, ULs) have for long used dose–response curves, showing a dynamic intake range that initially causes deficiency and via adequacy moves into toxicity. The step to a general concept of 'what does not kill you makes you stronger' has, however, only recently become appreciated. This notion deserves rethinking of the definition of 'essential nutrients', but at the same time begs for extrapolation to non-nutritional lifestyle factors.

Mild triggers might at least in part reset physiologic and metabolic dysfunctioning in patients with 'typically Western' diseases [142,138]. In other words: they may provide low-cost opportunities for secondary prevention. Conversely, the chronic absence of mild stress factors may have rendered modern 21st century humans less resistant to major toxic insults and susceptible to the development of many, 'typically Western', chronic diseases of affluence, including metabolic disorders, some types of cancer, depression and cardiovascular diseases [142,138,27,140]. Re-introduction of exposure provides low-cost opportunities for primary prevention with huge favourable potential for the society as a whole. Many changes in lifestyle are involved and their adoption is not necessarily unpleasant, as is frequently claimed. For instance, a recent study suggested that men taking sauna bathing sessions at a frequency of 4–7 times/week have 63% lower risk of all-cause and CVD mortality, compared with those having one sauna session/week. There was also a significant trend of lower fatal CVD mortality of 19 min sessions, compared with sessions lasting less than 11 min [117]. A sauna session may be regarded as a mild, heat-based, stress factor with hormetic actions and broad protecting ability from the insults of the 21st century environment [183,170].

Several of our studies including the "Study of Origin" (see below) in the Spanish Pyrenees [166], a smaller one in Germany [70], and a third also in the Spanish Pyrenees (Pruimboom in preparation) showed that the combination of certain intermittent stress factors produce a hormetic early stress response with a compensatory improvement of multiple metabolic and immunological indices, and wellbeing. The employed hormetic triggers included: intermittent fasting, intermittent heat, intermittent cold, intermittent hypoxia, intermittent drinking and the consumption of a great number of nutrients with hormetic effects. Simultaneously, biorhythm became re-established by living in a natural environment without electric light. The influence of the latter was recently shown in a small observational study [197].

The use of intermittent challenges, combined in a homework-protocol, could serve as a vaccine against the deleterious effects of modern life. We named this concept "*intermittent living*", defined as the daily intermittent use of known ancient triggers for a period of seven days per month. We propose to use this concept as a basis for interventions for individuals with chronic disease and/or its prevention. Intermittent living is no more than the reintroduction of mild environmentally-based short lasting stress (including cold, heat, hunger, thirst,). It were those triggers that made us human, reflecting a part of the ancient lifestyle that in our ancestors produced a shift from strong to smart [155]. However, the feelings accompanying these hormetic stress factors are not necessarily comfortable. The resulting opponent emotion will nevertheless provide individuals with a higher level of well-being, health and even happiness [194].

## Hormesis; the role of Nrf2

Hormesis refers to the evolutionary conserved adaptive responses of all living organisms to mild environmental, nutritional or even voluntary challenges through which the system amends its tolerance to more dangerous stress factors [29]. Hormetic triggers, also named hormetins, stimulate multiple effects at cellular and systemic levels. Molecular mediators include hypoxia inducible factor 1 (HIF1), nuclear factor kappa B (NFkB), peroxisome proliferator activated receptors (PPARs) and N-erythroid derived -related factor 2 (Nrf2). Three of these are key-transcription factors for the hypoxia stress response (HIF1), inflammation (NFkB) and the adaptive stress response, respectively [168] (Lee, 2014). The discovery of the major evolutionary conserved transcription factor Nrf2 has been crucial for the understanding of the process of hormesis. Nrf2, also known as CNC in flies and SKN-1 in worms, exerts its functions via more than 270 different genes through binding to an antioxidant response element (ARE, [T/C] TGCTGA [C/G]) in the gene promotor [114].

Interestingly, the Nrf2 gene itself contains several AREs and is therefore subject to a positive biofeedback loop initiated by its agonists (ARE inducers) [121]. Nrf2 can either induce (230 genes) or repress (30–40 genes) the expression of its target genes [89]. Nrf2 is the key-transciption factor for the activation of redox and the detoxifying systems, including phase I, II and III enzymes [201]. Other genes involve intermediary metabolism, the production of growth hormones and inflammation [83]. During non-stress conditions, Nrf2 is deactivated by Kelch-like ECH associated protein 1 (KEAP1) that maintains a short Nrf2 half-life through polyubiquination and proteosomal degradation. However, upon stress (oxidative stress or otherwise, see below), changes in KEAP1 inhibit ubiquination and thereby Nrf2 degradation. The now activated transcription factor migrates into the cell nucleus where it binds to its target genes, eliciting expression of cytoprotective molecules [9].

Although oxidative stress is sufficient for activating the Nrf2 pathway, the presence of certain compounds with redox/electrophilic properties enhance Nrf2's activity to its full range [185]. Important members of such substances are sulforaphane in broccoli and curcumin in the turmeric plant [88]. Nrf2 stimulation exerts strong cytoprotective effects in multiple organs and tissues, including neuroprotection and maintenance of pancreatic beta-cells. Next to the cytoprotective effects, increased expression of Nrf2 exerts anti-inflammatory effects, induces detoxification of a wide range of xenobiotics, is anti-apoptotic, and influences metabolism through multiple pathways [120]. The relevant influence of Nrf2 on intermediary metabolic pathways has only recently been clarified. Effects range from inhibition of lipogenesis, facilitation of the pentose phosphate pathway, purine biosynthesis, NADPH regeneration, and support of beta-oxidation. The sum of these observations suggests that hormetic activation of Nrf2 helps the reprograming of metabolism during stress situations [83].

The hormetic response is usually biphasic and occasionally multiphasic. Knowledge of dose-responses is of crucial importance for the understanding of mechanisms in pharmacology, inflammation, aging and cancer [29]. An example of a hypothetical multiphasic hormetic response is the dosage of vitamin C in relation with mitochondrial viability and overall health (Fig. 1). Whereas a chronic vitamin C intake