Medical Hypotheses 89 (2016) 79–83

Contents lists available at ScienceDirect

Medical Hypotheses

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

Promising link between selenium and peroxisome proliferator activated receptor gamma in the treatment protocols of obesity as well as depression

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ARTICLE INFO

Article history:
Received 23 October 2015
Accepted 7 February 2016

ABSTRACT

Considerable interest has been given to the significance of peroxisome proliferator activated receptors (PPARs) in macronutrient metabolism, however, there is not sufficient data concerning the interactions between PPARs and micronutrients. Investigations performed on PPARγ and one of the essential micronutrients selenium (Se) have shown that both parameters may lead to alterations in obesity-related or mood disorders. Therefore, it is plausible to consider PPARγ and Se together as a powerful combination during the treatment of two associated diseases; obesity and depression.

PPARγ has been shown to be involved in the antidepressant-like activity. It is also an important parameter to be considered in obesity as the master regulator of adipogenesis. The mechanism of action of PPARγ is initiated by ligand binding which induces a conformational change in the receptor. Se is capable of alleviating inflammatory signaling pathways. Obesity is associated with chronic low-grade inflammation. Depression is also defined as an inflammatory disorder. Inflammatory mediators such as tumor necrosis factor-alpha (TNFα) participate in the progression of depression. They are also obesity-associated parameters. Due to TNFα induced depressive-like behaviors and the positive association between this proinflammatory cytokine and obesity, TNFα-activated signaling pathways and those inhibiting them have recently gained importance as potential targets and therapeutic tools, respectively.

More studies are necessary to develop compounds with therapeutic nature against depressive disorders and obesity. PPARγ is an important signaling pathway that occurs at the crossroads of depression and obesity. Se, aside from its anti-inflammatory, anticarcinogenic and antioxidative nature, affects also the way of PPARγ action. Se supplementation or fortification as well as the development of the partial agonists of PPARγ in which lipophilic Se compounds are used as ligand followed by experimental trials and human studies using the newly developed compounds will be promising approaches for future hope during the treatment of these diseases.

Introduction

Peroxisome proliferator activated receptors (PPARs) are the members of the ligand-dependent nuclear hormone receptor superfamily. As the ligand activated nuclear transcription factors, they regulate the gene expression of proteins involved in glucose and lipid metabolism [1–3]. One of the approaches related to the hypothesis for obesity is the interaction of polyunsaturated fatty acids with the transcription factors, PPARs, which maintain the balance between oxidation and storage of lipids [4]. Recent studies have emphasized on PPARγ as a therapeutic target for improvement of cognitive performance [5]. They also regulate several physiologic processes. Of its three major isoforms, α, β and γ, PPARγ exerts its function in a variety of tissues including adipose tissue. The nuclear transcription factor PPARγ is a key mediator of insulin sensitivity [6]. It acts primarily as a key regulator of metabolic genes and improves insulin sensitivity through glucose/lipid uptake and storage in peripheral tissues, such as skeletal muscle, liver and adipose tissue [7,8]. It is a master regulator of adipogenesis and also acts as a modulator of inflammation [1,2,9]. It also regulates adipose-tissue related energy homeostasis, the levels of adipokines such as adiponectin, correlates circadian rhythm and metabolism [8,10]. Ligand stimulated activation of this factor improves insulin sensitivity. Therefore, PPARγ ligands have been recognized as the most powerful anti-diabetic drugs [2,3,5,11]. While 15d-prostaglandin J2 is one of the natural ligands

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http://dx.doi.org/10.1016/j.mehy.2016.02.008
0306-9877/

of PPARγ, thiazolidinediones (TZDs) are potent exogenous agonists. Due to their insulin-sensitizing properties 2 TZDs, rosiglitazone and pioglitazone are designed for type 2 diabetes (T2D) treatment. TZDs also appear to induce significant neuroprotection [12]. The need for the identification of physiologically relevant endogenous ligands for PPARγ is of utmost importance. So far, dietary intermediates are examined as PPARγ ligands ameliorating inflammation and therefore treating T2D or obesity. Monounsaturated fatty acids, eicosapentaenoic acid (EPA), capsaicin could be novel agonists [13]. Particularly EPA acting as a PPARγ agonist and inducing PPARγ expression plays roles in the neuroendocrine-immune network, may improve depression by suppressing inflammation, and normalize the glutamatergic systems [14–17]. Also, icosapentethyl, a pure EPA, correlated to lowering of triacylglycerols [18], a parameter which is important for obesity, metabolic syndrome and cardiovascular diseases (CVDs).

Trace elements are required for normal body function and a deficiency or overabundance may lead to a diverse range of diseases such as psychiatric disorders as well as obesity [19,20]. The role of selenium (Se) in neurological function and its relationship with obesity are still under investigation. Dietary Se, as either inorganic (selenite, selenate) or organic (selenomethionine, selenocysteine) species is metabolised to selenide (Se^{2-}) and then, selenophosphate (SeH_3PO_3), which is incorporated into proteins via a unique tRNA pathway [21,22]. Se is incorporated into selenoproteins in the form of the 21st amino acid, selenocysteine. They provide a key defense against oxidative stress. Many of them are expressed in the brain and several are required for normal brain development. Se administration attenuates oxidative stress, prevents neurodegeneration and counters cell signaling mechanisms known to be dysregulated in certain disease states [23].

Since its identification in the early 1990s, considerable amount of investigations has focused on PPARγ. It received particular attention in macronutrient metabolism, however, its significance on micronutrient metabolism particularly that on Se remains inconclusive.

The hypothesis

PPARγ, as a ligand activated transcription factor of the nuclear receptor superfamily, controls the expression of a variety of genes involved in fatty acid metabolism, adipogenesis and insulin sensitivity. PPARγ has been shown to be involved in the antidepressant-like activity [24]. It is also reported as the master regulator of adipogenesis [3]. Therefore, it is also an important parameter to be considered in obesity studies. The mechanism of action of PPARγ is initiated by ligand binding domain and activation domain which cause its translocation to the nucleus [1,25].

Patients with type 1 diabetes (T1D) show increased plasma cytokine levels such as tumor necrosis factor (TNF) α, interleukin (IL) 6 as a result of beta cell destruction and hyperglycemia. Patients with major depressive disorder (MDD) show similar increases in immune activity. Pro-inflammatory cytokines may mediate the relationship between T1D and depression [26]. TNF-α is involved in the pathology of T1D. It is required for antigen-specific effector T cell induced diabetes. Interferon-γ can play a dominant role in diabetes induction. T1D patients showed elevated Th17 cells and Th17 activities at T1D onset [27]. There are some models proving the possible role of IL-1β in T2D onset. IL-1Ra is a naturally occurring inhibitor of IL-1β, and it is reduced in poorly controlled T2D patients. All effects of IL-1β are blocked by IL-1Ra. IL-1Ra competes with IL-1β for the receptor. It is suggested that the prediabetic state can be restored by combined glucose-lowering and IL-1Ra therapy [28,29].

Depression and obesity are both characterized, to an extent, by behavioral expressions of disordered motivation towards food in obese individuals and towards pleasant stimuli and reward among those with depression. It is possible that blunted reactivity may be a physiological marker of such motivational dysregulation. There is evidence about a long-term impact of stressful life experience on the reactivity of the human stress axis [30–34].

Stress impacts the hypothalamus–pituitary–adrenal (HPA) axis and contributes to inflammation, a key biological contributor to the pathogenesis of diabetes and its associated complications such as neuropathy, cognitive decline and depression. Stress can influence the onset of T2D secondary to obesity and metabolic syndrome [35,36].

Pro-inflammatory response, altered blood flow, hyperglycemia are involved in the etiology of peripheral neuropathy. In experimental studies, reduced blood flow to the nerve is seen within the first few days of the induction of diabetes. The loss of blood flow results in neuronal hypoxia sufficient to initiate neurodegeneration. Hypoxia induced neuronal changes may play a role in the development of neuropathy [37,38].

Insulin resistance (IR) may play role as a potential link between diabetes and depression as well as cognitive decline [26,39]. Neuroendocrine signaling, through hyperactivity of the HPA axis, is thought to cause or exacerbate depression in diabetics [40]. Obesity and its comorbidities are closely related to the inflammatory milieu created by expanded adipose tissue. Several mechanisms trigger inflammation in adipose tissue, including excess fatty acids, hypoxia, and activation of the inflammasome [41].

Striking similarities exist between the structural and functional abnormalities of the central nervous system (CNS) in depression and T1D including decreases in hippocampal volume, decreased cerebral perfusion and glucose metabolism and also similar patterns of neurocognitive deficits [26].

Stress induces chronic, low-grade inflammation, a risk for the development of obesity and diabetes. This may increase the physiological alterations leading to neuropathy and contribute to behavioral symptoms, including depression, cognitive impairment [42].

Epidemiologic evidence suggests that the benefits of the essential micronutrient Se are, in part, contributed by the ability of Se to alleviate inflammatory signaling pathways [43,44]. Obesity is associated with chronic low-grade inflammation. Depression is also defined as an inflammatory disorder. Inflammatory cytokines, e.g., TNFα, IL1β, and prostaglandin E_2 (PGE_2) interact with various stages relevant to depression. These are also obesity-associated parameters [45,46].

Therefore, it is plausible to consider PPARγ and Se together as a powerful combination during the treatment of two associated diseases; obesity and depression.

Evaluation of the hypothesis

Due to TNFα induced depressive-like behaviors and the positive association between this proinflammatory cytokine and obesity, TNFα-activated signaling pathways and those inhibiting them have recently gained importance as potential targets and therapeutic tools, respectively.

IR induced by chronically elevated TNFα is involved in the inhibition of neuronal survival signals. This may contribute to neuronal damage in mood disorders. Obesity, frequently associated with IR, may lead to CNS dysfunction in MDD or bipolar disorder (BD) via a similar mechanism [47].

Elevated TNFα levels were reported during depressive and manic states [48,49] as well as in BD [50]. In a similar manner, in a very recent study, in peripheral blood mononuclear cells of obese