Medical Hypotheses 102 (2017) 61–64

Contents lists available at ScienceDirect

Medical Hypotheses

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

Pathophysiological explanation of cardiovascular benefits of sodium-glucose cotransporter-2 inhibitors by neurotrophic theory

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ARTICLE INFO

Article history:
Received 11 July 2016
Accepted 26 February 2017

Introduction

In 1986, Prof. Rita Levi-Montalcini was awarded the Nobel Prize for Physiology and Medicine for her fundamental discovery of nerve growth factor (NGF) and neurotrophins that was subsequently developed as Rita Levi-Montalcini's neurotrophic theory. Nowadays it is used in many fields of biomedical science. During the next 20 years, a lot of scientific facts have been accumulated and the neurotrophic theory has been transformed into clinical practice as neurotrophic hypothesis of pathogenesis of metabolic syndrome (MS) and type 2 diabetes mellitus (T2DM) [1,2].

Meanwhile, our hypothesis [1] was positively evaluated in the world literature on MS. Up-to-date, this paper occupied in *Scopus* (the Netherlands) the 7th place among top 25 hottest articles published in *Medical Hypotheses* between April and June 2006 but in *Web of Science* (Thomson Reuters, USA) it is the 11th most cited article among all the 608 papers published in 2006 in this journal. As of December 2016, it has been cited in *Web of Science* 44 times. A more recent review article of mine [3] summarizing the transition of the neurotrophic hypothesis to a theory of MS has already received five citations in *Web of Science*. The history of the neurotrophic theory of MS was subsequently systematized in a monograph [4].

Neurotrophic hypothesis of MS

An increasing number of researchers of MS assume that many mechanisms are involved in its complex pathophysiology such as an increased sympathetic activity, disorders of the hypothalamo-pituitary-adrenal axis, the action of chronic subclinical infections, proinflammatory cytokines, the effect of adipocytokines, or psychoemotional stress. There is growing evidence of the role of the neurotrophins and mastocytes in the pathogenesis of inflammatory and immune diseases. Recently, it has been proved that neurotrophins and mast cells exert metabotrophic effects and take part in the carbohydrate and lipid metabolism. Neuroimmune mediators such as NGF, brain-derived growth factor (BDNF), leptin and mast cells might be involved in the development of cardiovascular diseases and related disorders [5] (Chaldakov GN).

In early MS stage (with three components available), we establish a statistically significant increase of plasma NGF levels while in generalized one (MS-ge) (more than three components available) there are statistically significantly decreased plasma neurotrophin levels than in healthy controls [6]. It is likely that the neurotrophin deficit plays a significant pathogenic role in the development of the metabolic anthropometric and vascular manifestations of MS-ge. So, we suggest a hypothesis for MS etiopathogenesis based on the neuro-immuno-endocrine interactions.

The specific pathogenic pathways of MS development include: i) increased tissue and plasma levels of proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) caused by inflammatory and/or emotional distress; ii) increased plasma neurotrophin levels caused by the high IL-1, IL-6 and TNF-α levels; iii) high plasma NGF levels which enhance the activation of the autonomous nerve system – vegetodystonia (disbalance of neurotransmitters), neuropeptide Y (NPY)-enhanced feeding, obesity and increased leptin plasma levels; hypothalamo-pituitary-adrenal axis-increased corticotropin-releasing hormone (CRH) and cortisol (hormonal disbalance); immune cells – increased number and degranulation of mastocytes (MC) – immunological disbalance, and iv) DM occurrence resulting from is confirmed by the results obtained after 6-months non-steroid anti-inflammatory treatment of patients with MS [6].

Metformin and neurotrophins in MS

According to the aforementioned paper [6], metformin (Mf) exerts specific metabolic effects on neurotrophins in MS-ge (Table 1).

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http://dx.doi.org/10.1016/j.mehy.2017.02.021
0306-9877/

Table 1
Metabolism-related parameters in MS-ge before and after treatment with Mf.

Parameter	MS-ge (n = 20)	
	Before Mf	After Mf
BMI (kg/m^2)	42.1 ± 0.3	40 ± 0.3‡
Waist circumference (cm)	121.9 ± 3.8	118.5 ± 3.8
CRP (mg/L)	10.6 ± 1.4	9.2 ± 1.2
NGF (pg/mL)	21.4 ± 16.8	15.7 ± 9.9*
BDNF (pg/mL)	2721.1 ± 878.1	2850.2 ± 124.2

$^{*}p < 0.05$, $^{†}p < 0.01$, $^{‡}p < 0.001$; BMI – body mass index; CRP – C-reactive protein.

Despite the positive Mf effects on BMI and adipose tissue quantity, hyponeurotrophinemia is exacerbated at MS-ge, i. e., it deals with a minimal effect and cardio-metabolic risk factors progress.

Cardiovascular benefits of sodium-glucose cotransporter-2 inhibitors (SGLT-2) in the light of the neurotrophic theory

MS is the cause of disease in 89% of T2DM patients and in 20% of type-1 DM (T1DM) ones. Neurotrophic theory of the pathogenesis of T2DM, visceral obesity and MS places the chronic inflammatory and/or psycho-emotional distress as major etiological factor. It is related to increased tissue and plasma levels of the proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, and TNF-α. They result in changes of plasma levels of neurotrophins NGF/BDNF - from their compensating increase at the early development of disease to significant reduction – hyponeurotrophinemia in patients with T2DM and MSD [1,2]. The neurotrophic hypothesis of the early development of atherosclerosis as a consequence of hyponeurotrophinemia in T2DM and MS is confirmed, too [2]. As of now, all researchers unanimously agree on the following theses:

Thesis 1: Adipose tissue is an endocrine organ. IN T2DM and MS, visceral adipose tissue is increased and there exists a low-level inflammatory status along with systemic inflammation in abdominal adipose tissue producing adipocytokines. These are proinflammatory and antiinflammatory cytokines, growth factors, neurotrophins, hormones, etc.

Thesis 2: Insulin resistance, a major pathogenetic factor, exists in T2DM and MS.

Thesis 3: CRP is a typical indication of T2DM and MS. CRP indicates significant relation with insulin resistance and cardiovascular complications [1–3,6].

Thesis 4: IL-1, IL-6, and TNF-α enhance insulin resistance and hyperinsulinemia.

Thesis 5: Sympathicotonia exists in T2DM and MS.

Thesis 6: Hyponeurotrophinemia exists in T2DM and MS.

Thesis 7: Hypothalamus-pituitary-adrenal axis is over-activated resulting in hormonal imbalance in T2DM and MS manifested by hyperleptinemia, hyperinsulinemia, hypercortisolemia, hyposomatotropism, hypothyroidism and hypogonadism in men and increased testosterone levels in women.

Thesis 8: T2DM and MS are chronic progressive diseases. With advancing age, there is a rising number of its components (hypertension, hyperuricemia, dyslipidemia, and visceral obesity increases, while hyperglycemia gets worse). Mortality risk increases by increasing the number of such components [7,8].

Thesis 9: Immunosuppression and common focal infections exist in T2DM and MS.

Thesis 10: Macro- and microvascular damages, early atherosclerosis with elevated risk of cardiovascular complications progress in T2DM and MS.

Recent investigations show that SGLT-2 inhibitors effectively improve the glycemic control by lowering the blood glucose and glycated haemoglobin (HBA1c); by lowering triglycerides and increasing HDL-cholesterol; by lowering blood pressure; by reducing hyperuricemia, adipose tissue and body weight and cardiovascular mortality as well [9].

How does it work? the answer is the following: By the neurotrophic theory

By decreasing hyperglycemia through a non-insulin dependent mechanism, SGLT-2 inhibitors also reduce insulin secretion; this reduces lipogenesis and visceral adipose tissue. This is the first key point and results in reduction of plasma and tissue levels of adipocytokines, IL-1, IL-6, and TNF-α. Then, insulin resistance reduction follows. The second key point is the answers to theses Nos 1, 2, 3, and 4. Increased sensitivity of insulin receptors follows and this further helps the process of normalizing plasma glucose and T2DM control.

Proinflammatory cytokines, in addition to their involvement in the insulin resistance, cause dysfunction and possible destruction of pancreatic β-cells [10–12]. Therefore, by reducing visceral adipose tissue and proinflammatory cytokines, SGLT-2 inhibitors improve β cellular secretion of insulin and secretion of neurotrophins. The increased insulin secretion is carried out in the presence of calcium. Movement of calcium ions from plasma to β-cells occurs. There is an open calmodulin that combines ionized calcium and serves as reservoir and regulator of calcium ions release needed by insulin secretion.

Visceral adipose tissue reduction leads to lowering leptin levels. According to the neurotrophic theory, just hyperleptinemia, hyperinsulinemia and increased lipogenesis cause sympathicotonia.

Lowered levels of insulin, leptin, and reduced lipogenesis under the effect of SGLT-2 inhibitors reduce sympathetic tone. This decreases arterial hypertension, tachycardia, vasoconstriction and expands vascular lumen, thus improving perfusion and oxidative stress. Sympathicotonia reduction results in diminished appetite (at the hypothalamus level), additional lowering visceral adipose tissue, and hence additional reduction of the proinflammatory cytokines and chronic inflammation being the answer to thesis 5.

All the positive effects referred to herein are a consequence of SGLT-2 inhibitory effect on glucose reabsorption and hyperglycemia reducion, notwithstanding with endogenous insulin secretion. However, the other component of SGLT-2 inhibitory activity, namely the inhibition of sodium reabsorption takes part in the process of sympathetic tone reduction. Increased natriuresis is followed by reduced kaliuresis, and a process of calcium ions redirecting to β-cells exist. This changes the plasma potassium/calcium ratio in a direction of potassium elevation. The autonomic nervous system tone is determined by this ratio that is, normally, between 1.9 and 2.06. When it is below 1.9 there is sympathicotonia. Its elimination is the third key point in the effects of SGLT-2 inhibitors.

How do SGLT-2 inhibitors affect hyponeurotrophinemia?

Today, neurotrophins are known as mediators of many biological phenomena caused by their neurotrophic, metabotrophic, epitheliotropic, and immunotrophic effects. These effects are extremely important for maintaining the cardiometabolic homeostasis (glucose and lipid metabolism, energy balance, cardioprotection, neuroprotection, and renoprotection).

NGF and BDNF are signal molecules of nervous, endocrine and immune systems and maintain balance between them. Nervous,