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# COMMENT ON: PATHOPHYSIOLOGICAL EXPLANATION OF CARDIOVASCULAR BENEFITS OF SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS BY NEUROTROPHIC THEORY. MEDICAL HYPOTHESES102 (2017) 61-64

Pathophysiology

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KEYWORDS

sodium-glucose cotransporter-2 inhibitors, NGF syndrome

In connection with the published hypothesis about cardiovascular benefits of sodium - glucose cotransporter - 2 inhibitors, I present my own results from treatment with Empagliphlozin 10 mg added to Metformin 2x1000 mg in a small group of patients with type 2 diabetes mellitus and metabolic syndrome [1].

Before and after 12 months of treatment, 23 patients (13 females, 10 males - mean age of 59.61 ± 9.91, mean BMI 39.00 ± 7.86 kg/m²) and 20 healthy controls (10 females, 10 males - mean age 57.5 ± 8.51) were studied. Serum levels of neurotrophins were tested by ELISA of CUSABIO, China and adiponectin - by ELISA, BIO Vendor Laboratory.

Data were statistically processed by variation and correlation analyses using IBM SPSS v. 19 statistical package.

The cardioprotective and nephroprotective effects of Empagliphlozin have been demonstrated by the results of a large multicenter study [2]. I present the explanation of the effects of Empagliphlozin on my patients through the results in 7 consecutive steps:

**1. Restoration of the balance of the autonomic nervous system and control of sympathicotonia through increased natriuresis, osmotic diuresis, decreased plasma volume and changes in the potassium/ calcium ratio.**

| | Before treatment | After treatment | |
|---|---|---|---|
| Potassium/calcium ratio | 1.80±0.16<br>In sympathicotonia | 2.01±0.09<br>In normotonia | p 0.000 |

**2. Reduction of immunosuppression by lowering acety lcholinesterase, leading to increased acetylcholine and cholinerigic anti- inflammatory reflex.**

| | | | |
|---|---|---|---|
| Acetyl cholinesterase(U/L) | 10368.43±2470.5 | 9127.09±2250.4 | p 0.044 |

**3. Reduction of the central depot of visceral adipose tissue and local depots around the heart, kidneys, adrenal glands, blood vessels, lymph nodes, ovaries, eyes.**

Increased glucosuria reduces the substrate for adipogenesis.

| | | | |
|---|---|---|---|
| BMI (kg/m²) | 39.00±7.86 | 34.57±6.20 | p 0.042 |
| Waist circumference (cm) | 116.13±14,36 | 107.22±12.10 | p 0.035 |

**4. Inflammation is reduced due to the reduced volume of visceral adipose tissue and the proinflammatory cytokines (adipocytokines) produced by it** [3, 4, 5].

| | | | |
|---|---|---|---|
| CRP (mg/L) | 7.86±9.31 | 6.13±8.23 | p 0.439 |

**5. Insulin resistance decreases.**

| | | | |
|---|---|---|---|
| HOMA-index | 9.37±5.98 | 3.45±3,05 | p 0.000 |

**6. Plasma levels of NGF increase in response to the restored balance of the autonomic nerve system through an increase of acetylcholine transferase.**

BDNF and adiponectin plasma levels are decreased in all patients after treatment.

| | | | |
|---|---|---|---|
| NGF (pg/mL) | 44.30±22.18 | 51.87±20.10 | p 0.128 |
| BDNF (ng/mL) | 2.20±1.67 | 0.65±0.23 | p 0.000 |
| Adiponectin (ng/mL) | 3.77±1.87 | 3.32±1.48 | p 0.409 |

**7. Restoration of the balance in the hypothalamic - pituitary - adrenal axis and control of the hormonal imbalance.**

| | | | |
|---|---|---|---|
| IRI (мкU/ml) | 18.58±9.57 | 11.58±7.28 | p 0.006 |
| Cortisone (мkg/dL) | 20.76±7.07 | 16.25±5.09 | p 0.014 |

- Plasma levels of immunoreactive insulin and cortisol are reduced.
- Improvement of hypertension, hyperglycemia, hyperlipidemia and hyperuricemia.

Elevated plasma levels of NGF increase its neurotrophic, metabotrophic, immunotrophic and epitheliotrophic effects. Secreted by adipocytes in the peripheral fat depots, NGF acts in a paracrine way on the heart, kidneys, blood vessels and others. Taken together, the presented results confirm the previous hypotheses that NGF is an important factor in reducing hypoxia, inflammation, fibrosis, thrombosis and oxidative stress, it is an important factor in the cardioprotective and nephroprotective effects of SGLT2 - inhibitors in the treatment of patients with metabolic syndrome - with or without type 2 diabetes. Future research in this area is needed.

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The author declares that she has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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