

Our Psycho-Neurodiabetological Concept

Abstract

Since 2001 we know, that the blocking of the serotonin 2C, 3 receptor can simultaneously decrease the production of the incretin hormones [1], this relates to the beta-cell-function [2] nevertheless on a cellular level it also strenghtens the cellular insulin resistance [3]. Perhaps this receptor is the central diabetes-controller-accordingly, maybe in both types of diabetes.

Keywords: Vasopressin; Serotonin; Incretins; Hypothalamus; Neuroendocrinology; Psychiatry; Neurodiabetology; Psychosomatics; Diabetes

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Abbreviations: D4DR: Dopamine D4 Receptor Gene; 5-HT receptors: Serotonin Receptors; GLP-1: Glucagon-Like Peptide-1; DPP-4 Inhibitors: Dipeptidyl Peptidase 4 Inhibitors; ACTH: Adrenocorticotrophic Hormone; CRH: Corticotropin-Releasing Hormone

Introduction

Statistically, if someone takes clozapin for 3 years, there is a 30 % chance of a type two diabetes [4] olanzapin is less aggressive on this field [5] but it is common in the USA that the psychiatrist - at his own discretion - gives a usual minidose of 2x200 mg metformin as an adjuvant. Interesting, that this diabetesizing effect regress after 2-3 years and the increased body weight decrease even without metformin, there is 12 years of experience in this. However, it has only turned out from clozapin, which has been used since 1994. For example, risperidon slightly has such an effect, as it bonds to/ with the 5-HT_{2C} receptor much less, than to the 5-HT_{2A}, it does not bond to the 5-HT₃ receptor at all [6]. But we must not forget, that diabetes one is an autoimmune disease [7].

Discussion

Unusual Systems

We must build upon the connection between the hypothalamus and the limbic system, through the vasopressin-dopamine-serotonin, etc. cycle, as the thermostatic function of the hypothalamus can control psychoimmune, e.g. autoimmune reactions: let us not forget the function of the nucleus supraopticus and the nucleus paraventricularis in the operation of secretin.

If we put the puzzle together, the beta-cell function and the incretins, and the inner dynamics of the peripheral insulin resistance, going back to the highest level of neuroendocrin and psychoimmune reactions and their probably - joint cerebral control - beyond the ordinary endocrinology, humorously: the insulin based diabetology gets replaced by a more complex neuroscience, where the insulin or the metformin means only a basic intervention.

Our Neurodiabetological concept in therapy too

In the course of the research of the DPP-4 inhibitors today we can already talk about "incretin-axes" [8]. The glucagon-like peptide-1 (GLP-1) can be traced in the brain as well in a relatively high concentration, namely in the hypophysis, in the hypothalamus and in the nucleus reticularis thalami, a peptide consisting of 31 aminic acid.

It holds back the glucagon production of the alpha-cells, while it intensifies the insulin production of the beta-cells, but only in the basis of the ingested glucose, as it does not cause hypoglycemia, for which there are several enzyme explanation as well, but I would also like to give a neural explanation for it in order to account for this hypothesis.

Because the ingested sugar releases insulin, which on the other hand releases serotonin in the dorsal and medial raphe nuclei. Accordingly, the 5-HT_{2C}, 3 activity increases, which results in more incretins: therefore the cerebral and medical process are already synchronized here. The endorphine excess presses down [9] the hypothalamical-hypophyseal D4 and V3 activity [10]. Glucose creates a state of mental-physical satisfaction. At the same time GnRH also increases, as it does not get press down by endorphine, that is, the neuroendocrin "pleasure-seeking" begins again.

The low V3 vasopressin receptor activity (unstressed entactogenesis [11]), high D4 dopamine receptor activity (especially the length of D4DR candidate gene: adventure seeking [12]) and low serotonin level (dissatisfaction [13]) result in a new endorphine cyle, which, in order to be self-sufficient require sugar again, the CRH-ACTH-adrenaline-corticosteroid axis increases with the beta endorphine, once again "demanding" sugar. And this complex neuroendocrinological cycle reproduces itself. Thus the incretin system has a very serious neural controller as well, in accordance with endocrinology, quasi in sync.

So much the more as the cycle's main neurochemical switches the: "I am open, I am looking for new ways" vasopressin in the

brain, the "I want" dopamine, the "I am enjoying it" endorphine, and "the sugar has come, I am satisfied" serotonin can be related to psychological states. But the cycle's balance can be disrupted both in neural and endocrine way, e.g. "I am starving", "I suffer from bulimia".

On the basis of our current knowledge this searching cycle is probably opened by the cerebral vasopressin, whose receptors, the V1/V3, can be found in the hypothalamus and in the hypophysis, also where GLP-1 is; and GLP-1 can also be found in the nucleus reticularis thalami, which region is the afferentation center between the brainstem (see serotonin-raising) and the cortex (see endorphine-release). Is it a coincident?

The DPP-4 inhibitors are treating diabetes innovatively, perhaps with the V1/V3-regulating the psychological desire for sugar could be increased or reduced in eating disorders, so, that we are in control of the whole chain of neuro-diabetes, and not only in the way that is widely known, but in the way, that we invasively dive into more invasive serotonin-systems (see sibutramine [14]), presumably more complexly, naturally and with less side effects.

Conclusion

According to our supposition, this not only could play a role in the reduction of appetite as sibutramine in the appropriate biofeedback-cycle can even treat the psychological increase of appetite, but the neuroendocrine incretinerg and even the medical alpha, beta-cell function can too be positively influenced with it: it would be a theoretical combination of 5-HT_{2C} agonist lorcaserin [15], sibutramine, metformin and the therapies after metformin, between Psychiatry and Neuroendocrinology [16].

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