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Impaired Brain Insulin Signalling, a Potential Cause of Obesity: A Review of Literature

ABSTRACT

Objective: Obesity is a major health problem in the modern world, which together with other conditions such as cardiovascular disease, hypertension and type 2 diabetes, can pose a direct threat to health and life. Obesity is often accompanied by insulin resistance, which has been shown to occur in both peripheral and central tissues. Brain insulin resistance is a less well understood and less described phenomenon than peripheral insulin resistance, but equally important and worthy of attention.

Materials and methods: This review was written using the PubMed database. Articles were searched using keywords such as: insulin resistance, dopamine, obesity, cerebral insulin resistance, mesolimbic pathway, insulin, hypothalamus, feeding. The results of the studies within each phenomenon were analysed, compared and, on this basis, common conclusions were drawn.

Results: Available scientific data indicate a correlation between insulin signalling in the brain and the function of the hypothalamic centres of hunger and satiety and the dopaminergic mesolimbic pathway, which is part of the reward system. The phenomenon of hyperphagia in obese individuals with insulin resistance can be explained by potentially reduced hypothalamic satiety signalling with simultaneously increased hunger signalling, and impaired dopaminergic transmission within the mesolimbic pathway, due to impaired insulin activity in the brain.

Conclusions: The purpose of this article is to show a new potential direction for future obesity research and treatments, which would be based on the function of insulin-dependent brain centres regulating food intake. Improving insulin signalling in these areas could contribute to reduction in hyperphagia as well as reduction in excessive body weight. (Clin Diabetol 2022; 11; 5: 346–351)

Keywords: insulin resistance, dopamine, obesity, cerebral insulin resistance, mesolimbic pathway, insulin, hypothalamus, feeding

Introduction

Obesity is one of the major health problems in the modern world. According to World Health Organization (WHO) data from 2017, the number of overweight people is 1.9 billion, with about 650 million of them being obese. Given the above, it was decided to review the literature to investigate a potential obesity causal factor of cerebral insulin resistance. It is well known that obesity disease is the result of an imbalance between the number of ingested kilocalories and the amount of spent energy, which in case of positive energy balance results in an increase in body weight; however, the cause of the hyperphagia occurring in in this group of patients is not clear. It is a condition that also co-occurs with other disease entities such as heart disease, hypertension, and type 2 diabetes, which are consequences of obesity and which are collectively referred to as "silent killers" [1]. One of the treatments currently used for obesity is bariatric surgery. However,

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this method is stressful for the patient, interfering with the homeostasis of the organism by affecting gastrointestinal hormone levels [2]; therefore the search for less invasive methods of treatment appears to be a future direction of research on obesity. Along with obesity-related disease, there often occurs a condition of reduced tissue sensitivity to insulin called insulin resistance. In fact, it affects not only the peripheral tissues but also the brain tissues of obese individuals, which has been documented in both animals and humans [3]. The state of peripheral insulin resistance in obesity, caused by a high-fat diet, occurs together with central insulin resistance [4]. Insulin resistance is closely related to eating habits. Overeating "tasty" food is associated with obesity and type 2 diabetes, the prevalence of which is increasing dramatically [5]. A high-fat meal affects the reduction of insulin permeation across the blood-brain barrier, compared to a low-fat meal [1]. It has been suggested that a low-fat diet may help restore normal insulin signalling in brains affected by insulin resistance [6]. A diet based on "tasty" foods also increases the concentration of hypothalamic hunger peptides such as orexin or neuropeptide Y and occurs with simultaneously suppressed insulin-, leptin- or cholecystokinin-dependent satiety signalling [1].

Materials and methods

A literature review was performed using the PubMed database. Keywords such as obesity, dopaminergic system, insulin resistance, cerebral insulin resistance, hemispheric nucleus, insulin, striatum, nutrition, arcuate nucleus, and hypothalamus were used. Articles were searched for publications within the last decade, but it should be noted that some of those used in this review do not meet this condition.

Insulin in the central nervous system

Insulin is released into the blood in a constant and phasic manner. By interacting with insulin receptors, it is an important regulator of cell differentiation, growth and metabolism [7]. Due to a meal-related stimulus, such as the smell of food, the hormone's production increases [8]. Under physiological conditions, as a result of eating a meal, insulin is released into the bloodstream, with peripheral and central effects. Once it crosses the blood-brain barrier, this hormone regulates food intake by affecting the dopaminergic system as well as the hypothalamus [9]. Insulin receptors have been demonstrated in many brain centres including: dopaminergic neurons of the ventral tegmental area [10], striatum [11], cerebellum, hypothalamus [12].

Increased extracellular dopamine levels as a response of the brain to nutrient stimulus

The food-related stimulus that is food presentation increases extracellular dopamine levels in the striatum [13], which suggests the importance of this process in triggering an individual's drive and motivation to get food. The dorsal striatum has been proven to regulate food intake as a determinant of survival, while the ventral striatum, the acquisition of food to provide pleasure [13]. Both of these processes are closely linked to an increase in extracellular dopamine concentration. The ingestion of a high-fat, and therefore "palatable", meal resulted in rats showing an increase in dopamine levels in the region of the nucleus accumbens [14]. Food, being one of the natural rewards, increases dopamine release in the area of the nucleus accumbens which is part of the mesolimbic pathway [15]. Given the above, it would seem that the purpose of dopamine signalling within the dorsal striatum is to produce a drive, which through an increase in dopamine concentration in the area of the nucleus accumbens, as a result of its satisfaction, would determine the production of a feeling of pleasure, thus positively reinforcing the stimulus in question. Positive reinforcement of a particular stimulus could prompt an individual to seek it out in the future.

The effect of insulin on the dopaminergic system

In the rat model, intraventricularly administered insulin increased the amount of mRNA for the dopamine active transporter (DAT) within the ventral tegmental area of the caudate and the compact part of the black matter [16]. Insulin signalling inhibits the gene expression for dopamine-degrading monoamine oxidases [17] and increases dopamine release in the area of the nucleus accumbens by interacting with receptors of striatal cholinergic interneurons [18]. Therefore, since the ingestion of a meal generates an increase in dopamine concentration within the area of the nucleus accumbens and thus its arousal, and insulin, which increases dopamine reuptake in the ventral tegmental area via the DAT after reaching a state of satiety [10], it can be presumed that there is a negative feedback between these two systems. Insulin injected directly into the ventral tegmental area affects the reduction of satiated food intake and decreases somatodendritic dopamine concentrations in this area [5]. Mice with dopamine deficiency, developed by selective inactivation of the tyrosine hydroxylase gene in dopaminergic neurons, starved to death several weeks after birth [19]. Restoration of dopamine signalling within the dorsal striatum, but not within the Nucleus

Accumbens (NAc), sustained feeding with the regular laboratory food mixture, and restoration of this signalling within the nucleus accumbens, resulted in return of the preference to eat tasty, sweet food, but without a tendency to sustain long-term feeding [13]. Since a meal is accompanied by the release of insulin into the blood, which after crossing the blood-brain barrier contributes indirectly (with the participation of striatal cholinergic interneurons) and directly (by inhibiting the gene expression for dopamine-degrading enzymes) to an increase in dopamine levels in the area of the nucleus accumbens, reaching the satiety state — presumably dependent on the intensity of dopamine stimulation of this nucleus — is conditioned by dopamine reuptake through DAT, whose synthesis also depends on insulin. It can be assumed that this hormone plays a role in the control of the food drive, participating in both its positive reinforcement and its quenching.

Regulation of food consumption dependent on insulin signalling in the hypothalamus

The arcuate nucleus of the hypothalamus is responsible for regulating the feeling of hunger and satiety by influencing the satiety centre located in the ventral-posterior nucleus and the hunger centre located in the lateral hypothalamic area. The arcuate nucleus contains two types of neurons that secrete the orexigenic peptides AgRP (agouti-related peptide)/NPY (neuropeptide Y) and the anorexigenic POMC/CART (proopiomelanocortin/cocaine and amphetamine regulated transcript). Stimulation of the hunger or satiety centre is mediated by these neuropeptides, due to signalling of the arcuate nucleus. Satiety signals suppress hunger signalling [1]. Insulin has the ability to penetrate brain regions such as the hypothalamus and the pons [20]. Insulin receptors have been found in the arcuate nucleus of the hypothalamus [21]. Neurons sensitive to glucose-related signalling are located in the ventral medial nucleus of the hypothalamus [22]. Neurons of the POMC system and AgRP of the arcuate nucleus are sensitive to insulin signalling [23]. Administering insulin to the arcuate nucleus area may affect the reduction of food intake by decreasing the activity of anabolic AgRP/NPY neurons, and increasing the activity of the α-MSH (α-Melanocyte Stimulating Hormone)-dependent pathway [24], a product of POMC. Intraventricular administration of insulin decreases the expression of AgRP/NPY neurons while stimulating POMC/CART [24]. If food intake increases the concentration of insulin in blood, which is able to pass through the blood-brain barrier and affect the arcuate nucleus of the hypothalamus, whose signalling through neurons synthesising

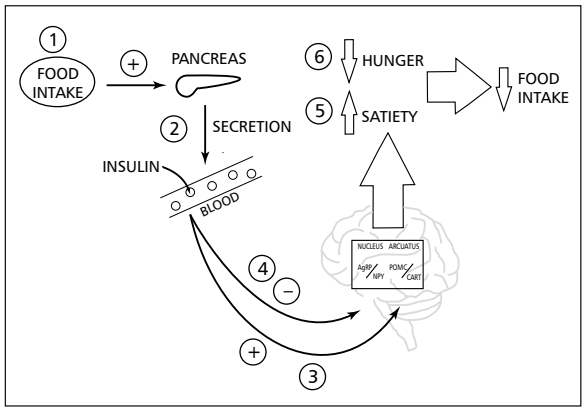

Figure 1. Insulin Action in the Hypothalamic Centre of Hunger and Satiety
As a consequence of consumed food (1), insulin is released into the blood. (2) After crossing the blood-brain barrier, insulin influences the hypothalamic centre of hunger and satiety by stimulating anorexigenic POMC/CART neurons (3) and inhibiting orexigenic AgRP/NPY neurons (4), resulting in satiety signalling (5) with simultaneous suppression of hunger signalling (6)

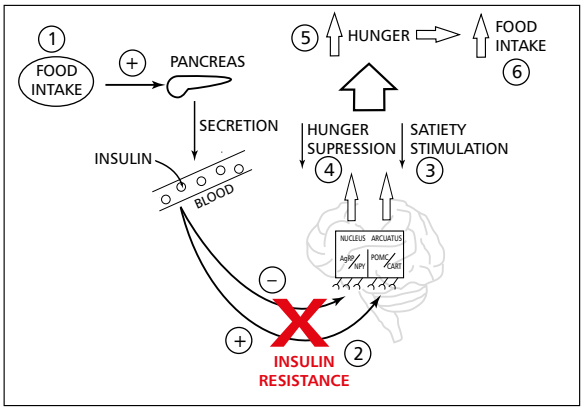

Figure 2. Hypothetical Effect of Cerebral Insulin Resistance on the Food Intake Regulation
Insulin is released into the blood as a result of food ingestion (1), which, due to cerebral insulin resistance (2), could result in lower excitation of anorexigenic POMC/CART neurons and therefore lower satiety signalling (3) with concomitant lower inhibition of orexigenic AgRP/NPY neurons (4) and thus higher hunger signalling (5). Brain insulin resistance can presumably lead to an increase in food consumption due to the regulatory changes described above (6)

anorexigenic peptides influences the feeling of satiety, it can be assumed that the interaction of insulin with the arcuate nucleus of the hypothalamus plays a role in the control of food intake. Therefore, if in obese individuals, insulin resistance involves both peripheral tissues and the brain, it is possible that insulin-dependent hunger and satiety signalling in the hypothalamus is also affected. Since intraventricular administration of

insulin stimulates the activity of POMC/CART neurons and decreases that of AgRP/NPY neurons, resulting in increased satiety signalling and decreased hunger signalling, it seems that a state of decreased insulin sensitivity in the brain may be associated with insufficient satiety signalling and increased hunger signalling, which might provide an explanation for the phenomenon of hyperphagia observed in obese individuals.

The correlation between insulin resistance and lower dopamine levels in obese individuals

Phasic and tonic dopamine release closely depends on factors such as the dopamine precursor availability, receptor density and availability, DAT activity and concentration, dopamine synthesis activity by tyrosine hydroxylase, and the level of dopamine-degrading enzymes such as COMT (catechol-o-methyltransferase), or MAO (monoamine oxidase) [25]. As mentioned above, under physiological conditions, insulin indirectly increases dopamine release, inhibits gene expression for monoamine oxidases, and increases the amount of DAT by increasing the synthesis of mRNA for this transporter. It can be speculated that the concentration of dopamine-degrading enzymes will be higher in the brains of obese individuals as a result of central insulin resistance. Among adult men with a body mass index (BMI) above 30.4 and women with a BMI above 28.5, significantly higher concentrations of the dopamine metabolite homovanillic acid and the serotonin metabolite 5-hydroxyindoleacetic acid have been reported compared to individuals with lower BMI [26]. Mice with knockout of the brain insulin receptor showed increased levels of monoamine oxidases A and B in the striatum and nucleus accumbens, resulting in increased dopamine turnover in these areas [17].

These findings provide support for the hypothesis above. In rats predisposed to obesity, a reduced dopaminergic response has been shown in the dorsal striatum and prefrontal cortex after stimulation, suggesting the presence of a central presynaptic dopamine deficit in these animals [27]. Rats fed the cafeteria diet, in comparison to those consuming the laboratory diet, became obese while exhibiting lower extracellular dopamine concentrations in the area of the nucleus accumbens. Furthermore, in obese rats, the laboratory meal, compared to the cafeteria meal, did not induce dopamine release in the area of the nucleus accumbens [28]. Rats over-consuming a high-fat diet show lower basal extracellular dopamine concentrations in the region of the nucleus accumbens compared to non-obese rats. In addition, rats predisposed to obesity showed lower total dopamine levels in the region of the nucleus accumbens after eating a high-fat meal compared to the obesity-resistant group, suggesting the need for this group to consume significantly more food in order to achieve the same dopamine concentration as rats in the comparison group [14]. Excessive consumption of high sugar and high fat foods leads to neuronal insulin resistance, dysregulation of dopamine homeostasis, and HRDS (hypodopaminergic reward deficiency syndrome) in the brain [11]. Brain insulin resistance appears to reduce the activity of the dopaminergic system, particularly the mesolimbic reward system, by increasing the dopamine-degrading enzymes MAO A and MAO B and COMT, which may result in reduced dopamine concentrations in the cerebra of obese people. Lower dopamine availability due to neuronal insulin resistance could underlie the brain reward deficit syndrome found in this group of patients and contribute to excessive food intake as a compensatory mechanism for lowered dopamine concentrations. One might suspect that, as a result of reduced dopamine availability, arousal of regions involved in food reward would also be lower, which would provide a potential explanation for the hyperphagia among obese individuals as well.

Brain insulin resistance and its impact on peripheral insulin resistance

Animal studies have shown that central insulin activity contributes to the regulation of peripheral insulin sensitivity [29]. The hypothalamus appears to play an important role in this process. Insulin activity in the brain, may improve glucose metabolism in peripheral tissues under hyperinsulinaemia by suppressing endogenous glucose synthesis as well as enhancing glucose uptake by tissues [30]. However, these effects were not observed in overweight subjects, which may suggest an altered brain insulin response in this group of patients. High brain insulin sensitivity is associated with weight loss following lifestyle changes and beneficial body fat distribution [31].

Clinical implications

1. Increasing the concentration of dopamine in the neurons of the mesolimbic system, which is reduced due to insulin resistance in the brain, could result in the restoration of its appropriate concentration in the synapse when a food stimulus is triggered, and thus in a faster achievement of the food satisfaction threshold.
2. Improving insulin signalling in the brains of obese people with insulin resistance, could act on the homeostatic, resulting from feelings of hunger, as well as the hedonistic, dependent on the rewarding properties of food, need to eat it. Restoration

of proper nutritional balance could result in reduced hyperphagia with a possible decrease in excess body weight.

3. Given the evidence and argument presented, it does not appear that the cause of obesity is food addiction in the strict sense.
4. It seems that in order to achieve improvement in peripheral insulin sensitivity, one should also focus on the treating brain insulin resistance, which is another potential line of treatment for this condition.

Future directions

The validity of the considerations above would need to be verified under real-life conditions. A possible challenge, and another direction for obesity research, may be attempting to restore correct insulin signalling in the brain and assessing the effectiveness of this in the context of regulating food intake. At the same time, it is worth mentioning that there are currently no studies showing a direct link between cerebral insulin resistance and obesity. Another limitation of these considerations is the selected data obtained based on animal models.

Ethical permission

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Conflict of interest

None declared.

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