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Insulin action in the human brain: evidence from neuroimaging studies

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Running Head: Brain insulin action

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Abstract

Thus far, little is known about insulin action in the human brain. Nonetheless, recent advances in modern neuroimaging techniques, as functional magnetic resonance imaging (fMRI) or magnetoencephalography (MEG), have made it possible to investigate brain insulin action in humans providing new insights into the pathogenesis of brain insulin resistance and obesity. Using MEG, the clinical relevance of brain insulin action was first identified linking cerebral insulin resistance with peripheral insulin resistance, genetic predisposition and weight loss success in obese adults.

While MEG is a suitable tool to measure brain activity mainly in cortical areas, fMRI provides high spatial resolution for cortical as well as subcortical regions. Thus insulin action can be detected within all eating behavior relevant regions, which include regions deeply located within the brain as the hypothalamus, midbrain and brainstem as well as regions within the striatum.

In this review, we will outline recent advances in the field of neuroimaging to investigate insulin action in the human brain using different routes of insulin administration. fMRI studies have shown a significant insulin induced attenuation predominantly in occipital and prefrontal cortical regions and the hypothalamus, successfully localizing insulin sensitive brain regions in healthy mostly normal-weight individuals. However, further studies are needed to localize brain areas affected by insulin resistance in obese individuals, which is an important prerequisite to selectively target brain insulin resistance in obesity.

Introduction

While insulin action has been mainly attributed to peripheral organs, as the liver, muscle and adipose tissue, the importance of insulin signaling in the brain has long been overlooked. Even though insulin is not required for glucose uptake into the brain (1), it is an important neuroregulatory peptide. More than 30 years ago, though, Woods et. al. (2) showed for the first time that intracerebroventricular infusion of insulin decreased food intake and body weight in baboons. Since then brain insulin signaling has been extensively studied in rodent models identifying insulin receptors throughout the brain with the highest expression in the olfactory bulb, cortex, cerebellum, hippocampus, and hypothalamus (for a recent review please see (3)). Insulin from the blood enters the brain via a receptor-mediated transport, with lower insulin concentrations in the cerebrospinal fluid in subjects with peripheral insulin resistance (4). Binding to the insulin receptor has diverse effects on functions of energy homeostasis, growth, reproduction and neural plasticity (5). In humans, however, the relevance of brain insulin signaling on energy metabolism has only been recently identified since modern neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) or magnetoencephalography (MEG), have emerged as valuable tools. In this review, we will outline recent advances in the field of neuroimaging to investigate insulin action in the human brain.

Brain insulin signaling is mainly investigated in healthy adults, with a special focus on obesity and peripheral insulin sensitivity, and patients with type 2 diabetes or dementia related diseases. The latter is based on the fact that type 2 diabetes is associated with an increased risk to develop dementia and accelerated cognitive decline with age (6-8). Furthermore, brain insulin action is impaired in Alzheimer's disease and first evidence suggests that insulin administration can decrease

cognition decline (9). In this review, we will exclusively focus on brain insulin action in healthy individuals (with and without obesity), to avoid brain alterations due to comorbidities of type 2 diabetes such as cognitive impairments or hyperglycemia, which have a strong effect on brain metabolism (10) (for review on cognition, insulin resistance and dementia please see (11)).

Insulin administration

In animals, direct infusion of insulin into the brain, for example via direct injection into brain tissue or the ventricular system, is readily employed. In humans, however, the application of insulin is more complex and different routes of administration are used. Systemic intravenous infusion by means of hyperinsulinemic euglycemic clamp and oral glucose tolerance test (oGTT) are standard methods to investigate peripheral insulin sensitivity and have been used whilst simultaneously evaluating brain activity. The oGTT uses oral glucose ingestion, thereby physiologically elevating blood glucose as well as insulin. Glucose has its peak at around 30 min while insulin is still significantly elevated 120 min after ingestion of 75g of glucose. By measuring brain activity 120 min post load gives the possibility to evaluate mainly insulin driven effects. The hyperinsulinemic euglycemic clamp, on the other hand, keeps plasma glucose concentration stabile while insulin concentration is acutely raised to postprandial levels. For both methods, peripheral insulin sensitivity can be assessed and then correlated with brain activity making interferences on brain insulin sensitivity. However both methods make it difficult to decipher insulin from glucose, and other circulating factors, as well as peripheral from central insulin effects. The intranasal insulin administration technique, on the other hand, makes it possible to selectively study cerebral insulin action by delivery of the hormone directly into the brain, without major effects on peripheral glucose concentrations (12). After

intranasal application, insulin enters the cerebrospinal fluid compartment with a significant cerebrospinal fluid increase in insulin as early as 20 min after application (12). Thus the preferential path is assumed to be the extracellular passage through the intercellular cleft of the olfactory epithelium.

Effect of brain insulin action investigated by MEG

We first described brain insulin action by means of MEG, which is a non-invasive method to detect magnetic fields generated by electric activity of neurons with high temporal and spatial resolution in cortical areas (range of cm). In obese compared to lean adults, increasing insulin levels failed to enhance intrinsic as well as stimulated brain activity by means of hyperinsulinemic euglycemic clamp as well as intranasal insulin application (13-15). This cerebral insulin resistance was also linked to specific peripheral tissues and signals. Increasing body mass index (BMI) and specific fat depots (visceral fat and liver fat) were correlated with a decreased theta brain activity to insulin, which is a frequency band mainly generated by the hippocampus associated with memory performance. Interestingly, independent of visceral and liver fat, saturated nonesterified free fatty acid levels (NEFAs) were associated with theta brain activity, suggesting NEFAs as an independent predictor for brain insulin resistance (16). Furthermore, risk-allele carriers of genes associated with an increased risk of obesity (FTO and MC4R) (17, 18) and type 2 diabetes (IRS-1) (13) showed a diminished brain response to insulin in the theta and beta frequency band, indicating augmented brain insulin resistance with genetic predisposition. Additionally, brain insulin sensitivity was a predictor for weight loss after a dietary intervention. Consequently, individuals with high insulin sensitivity showed the greatest loss of visceral adipose tissue 9 months after the intervention (19). While the mechanisms by which NEFAs or visceral fat depots and specific genetic

backgrounds may be a cause of brain insulin resistance are not known, these studies confirm however the clinical importance of insulin signaling in the brain.

Effect of brain insulin action investigated by fMRI

While MEG is a suitable tool to detect insulin action in cortical areas, its spatial resolution for subcortical regions is extremely limited. However, cerebral processes essential for the control of food intake and eating behavior are also deeply located within the brain as the hypothalamus, midbrain and brainstem as well as regions within the striatum. The hypothalamus has profound regulatory influences in energy homeostasis integrating peripheral signals to provide critical feedback on energy abundance or the lack thereof. Furthermore, hormones essential for eating behavior, such as insulin, directly modulate dopaminergic circuits within the midbrain and striatum to stimulate or inhibit food intake (20). Hence, neuroimaging tools with higher spatial resolution are needed to localize insulin action and resistance in cortical and subcortical regions of the brain. For this purpose, fMRI is a valuable tool measuring metabolic changes related to neuronal activity using blood-oxygen-level-dependent contrast (BOLD) imaging or cerebral blood flow (CBF). BOLD detects increases in brain activity resulting from an enhanced release of glucose and oxygen changing the ratio between oxy- to deoxyhemoglobin. Compared to BOLD fMRI, quantitative measurement of CBF provides a well characterized physiological parameter in physiological units (ml/100g brain tissue/min). By combining fMRI (BOLD or CBF) with insulin application, brain activity was evaluated either in response to food cues or under resting-state condition, in response to a peripheral increase in insulin levels using an oGTT or direct application into the brain by means of intranasal insulin.

fMRI studies have shown a significant insulin induced attenuation predominantly in occipital and prefrontal cortical (PFC) regions and the hypothalamus in healthy mostly normal-weight individuals (Figure 1) (21-25). Furthermore, some studies also identified striatal regions (25, 26), the insula cortex (25, 26) and the cingulate cortices to be insulin responsive (24, 25). While visual food cues, varying in caloric content and palatability, are used in order to provoke eating behavior related brain activity, resting-state fMRI is particularly useful to avoid any task specific effects. Especially brain activity within the occipital cortex (mainly the fusiform gyrus) decreases in response to insulin when visual food cues are evaluated (15, 21, 24). Concomitantly, the posterior fusiform gyrus has been shown to be the most concurrent brain region activated by food cues, eliciting also an enhanced response to high compared to low caloric foods (27-29). Nonetheless, the hypothalamic and prefrontal response to insulin have been identified independently of the fMRI design (resting-state or task based). Heni et al. (24) showed that after glucose ingestion the prefrontal cortex response to food cues correlated with the change in insulin 120 min post load in normal-weight and obese participants. As a result, individuals with higher insulin sensitivity revealed a stronger decrease, while the obese insulin resistant participants showed an increase in PFC activity. But also in normal-weight participants, individuals' serum insulin levels can determine the reactivity of the prefrontal cortex after glucose ingestion in response to food cues (21, 25) as well as under resting-state condition after intranasal insulin; here normal-weight women responded with an increase in PFC activity the higher their individual BMI (23). The prefrontal cortex plays a crucial role in cognitive control and decision making, including inhibitory control towards food cues after food intake (30). Thus, we postulate that brain insulin resistance of the PFC could contribute to overeating

behavior. However, this hypothesis needs to be investigated by further studies since very little is known about insulin action in obese insulin resistant individuals using fMRI.

The task-independent insulin induced decrease in the hypothalamus could lead to an increase in satiety attenuating the response to food. Most studies reporting a hypothalamic response have used glucose ingestion identifying a profound decrease with increasing glucose levels (24, 31-33). Moreover, altered hypothalamic processing after glucose ingestion was observed in obese adults and patients with diabetes type 2 with a diminished attenuation (34, 35). However, these hypothalamic effects were reported in studies using glucose ingestion making it difficult to distinguish glucose from insulin mediated effects.

Thus besides the fMRI paradigm, the method by which insulin is administrated could potentially affect brain activity. Only by means of glucose ingestion, brain areas within the striatum correlate with the change in insulin levels (24, 25, 33), pointing to a rewarding effect due to glucose ingestion. Generally, obese individuals show an augmentation in the striatum to food cues. Therefore, it is important to investigate insulin action using a method that circumvents peripheral glucose effects. By means of intranasal application, insulin action can be selectively studied by delivery of the hormone directly into the brain without an effect on brain vasculature (measured by global CBF) (36). By this means, selective brain insulin action was identified within the hypothalamus, prefrontal and occipital cortex confirming an insulin and not glucose mediated effect in these brain regions (21-23). Of note, brain glucose metabolism is not stimulated by insulin after increasing insulin above fasting levels (37). Hence the selective insulin-activated brain regions most likely reflect direct insulin action. In addition it was shown that glucose concentration in the brain is

insulin independent (1). Concomitantly, in normal-weight women, the influence of nasal insulin on hypothalamic, striatal and orbitofrontal cortex activity correlated with peripheral insulin sensitivity (22), providing further evidence that peripheral and central insulin sensitivity are highly linked processes.

Thus far, modern neuroimaging studies have shown a significant insulin induced brain response mainly in occipital and prefrontal cortical regions and the hypothalamus, successfully localizing insulin sensitive brain regions. Yet, only the hypothalamic and prefrontal response to insulin was identified independent of the study design (resting-state or task-based) as well as insulin administration, mostly in healthy normal-weight individuals. Conversely, selective brain insulin action in obese humans still remains ill-defined. Hence further studies are needed to localize brain areas affected by insulin resistance in obese individuals, which is an important prerequisite to selectively target brain insulin resistance in obesity. For this purpose, we propose the combination of fMRI with the intranasal administration of insulin as a particularly useful instrument to investigate region specific insulin effects in health and disease.

Figure legend

Figure 1

Insulin sensitive brain regions displayed on a standard anatomical template. Modern neuroimaging studies revealed a significant insulin induced brain response mainly in the occipital cortex (light blue), prefrontal cortex (magenta) and the hypothalamus (yellow).

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