Central nervous pathways of insulin action in the control of metabolism and food intake in humans

Stephanie Kullmann, PhD [1,2,3], André Kleinridders, PhD [2,4], Prof Dana M. Small, PhD [1,5,6], Prof Andreas Fritsche, MD [1,2,3], Prof Hans-Ulrich Häring, MD [1,2], Prof Hubert Preissl, PhD [1,2,3,7,8], Prof Martin Heni, MD [1,2,3]

1) Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, Tübingen, Germany.
2) German Center for Diabetes Research (DZD e.V.), Neuherberg, Germany.
3) Department of Internal Medicine, Division of Endocrinology, Diabetology, Angiology, Nephrology and Clinical Chemistry, Eberhard Karls University Tübingen, Tübingen, Germany.
4) Central Regulation of Metabolism, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany.
5) Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA.
6) Modern Diet and Physiology Research Center, Yale University, New Haven, CT, USA
7) Department of Pharmacy and Biochemistry, Interfaculty Centre for Pharmacogenomics and Pharma Research, University of Tubingen, Tubingen, Germany
8) Institute for Diabetes and Obesity, Helmholtz Diabetes Center, Helmholtz Center Munich, German Research Center for Environmental Health, Neuherberg, Germany

Summary

Insulin acts on the central nervous system to modulate behavior and systemic metabolism. Disturbance in brain insulin action is a potential link between metabolic and cognitive health. Current findings in human research suggests that boosting central insulin action in the brain modulates peripheral metabolism enhancing whole-body insulin sensitivity and suppressing endogenous glucose production. Moreover, central insulin action curbs food intake by reducing the salience of highly palatable food cues and increasing cognitive control. Animal models show that the mesocorticolimbic circuitry is finely tuned in response to insulin driven mainly by the dopamine system. These mechanisms are impaired in persons with obesity, which may increase the risk to develop type 2 diabetes and associated diseases. Overall, current findings highlight the role of insulin action in the brain and its consequences on peripheral metabolism and cognition. Hence, improving central insulin action could represent a therapeutic option for persons at increased risk for metabolic and cognitive diseases.

Introduction

Several lines of research provide evidence that there is a bidirectional relationship between metabolic and cognitive impairments. Diabetes increases the risk of dementia about 2-fold and neurocognitive disorders are linked to an increased risk of metabolic diseases [1]. Insulin resistance, a state of an absent or inadequate response to the hormone insulin, is considered a hallmark feature of type 2 diabetes (T2D) and is associated with metabolic disorders. Decrements in insulin action, however, do not only pertain to metabolic diseases. Many of the metabolic disturbances found in T2D can also be observed in neurodegenerative and psychiatric diseases. For example, patients with Alzheimer disease (AD) and schizophrenia display reduced peripheral insulin sensitivity [2]. As the central nervous system does not depend on insulin to utilize glucose, brain function was long assumed insulin independent. However, after identifying an abundance of insulin receptors in the brain [3], it was quickly appreciated that insulin signaling specifically modulates brain function with diverse metabolic or cognitive outcomes ranging from memory, olfactory perception, emotion regulation, eating behavior and peripheral metabolism [4]. Since then evidence is unfolding in clinical research that insulin resistance of the brain may accelerate the development of T2D and the deleterious effect on the metabolic health in patients with neurodegenerative and psychiatric diseases [2,5].

The aim of this review is to highlight the impact of insulin action in the human CNS in health and disease - with a special focus on peripheral metabolism.

Figure 1. Expression of the insulin receptor (IR) in the human brain. Box plots are shown as median, 25th and 75th percentiles. The graph shows gene expression of the IR in the human brain based on postmortem human brain samples (sample size ranged between 139 – 255 for the different regions) of the cortex, cerebellum and different available specific brain regions as the frontal cortex (Brodmann Area 9: which includes the dorsolateral prefrontal cortex), the midbrain (i.e. the substantia nigra), the striatum (including the nucleus accumbens, caudate, and putamen) and the hippocampus and amygdala. The human brain data described in this manuscript were obtained from the GTEx Portal on the 13th of December 2019 (https://gtexportal.org/home/gene/INSR#geneExpression).

EFFECTS OF INSULIN IN THE BRAIN

Insulin receptors (IR) are ubiquitously expressed throughout the brain and have been identified so far on neurons and glial cells [6,7]. Animal studies, particularly in the rodent model, show the highest expression levels in the olfactory bulb, followed by cortex, hippocampus, hypothalamus, cerebellum, striatum and midbrain [8]. Similarly, postmortem human brain samples show the highest IR expression in the hypothalamus, cerebellum as well as cortical and subcortical regions [see Figure 1 for IR expression levels in humans].

MECHANISMS OF INSULIN ACTION IN THE BRAIN

Insulin binds to its numerous receptors after being transported into the brain's interstitial fluid by receptor mediated transcytosis. Specifically, pancreas-derived insulin enters the brain via the blood stream using a saturable, insulin receptor mediated pathway and engages mainly two distinct signaling cascades. The phosphoinositide 3-kinase predominantly controls metabolism and the mitogen-activated protein-kinase pathway regulates mitochondrial function, proliferation and growth. Alterations of these signaling cascades hamper insulin sensitivity resulting in brain insulin resistance.

EVIDENCE OF BRAIN INSULIN RESISTANCE

When administered to the brain, insulin acts in an anorexigenic fashion. In rodent models, infusing insulin into the lateral ventricle reduces food intake [9], while decreasing insulin receptors results in hyperphagia [10]. Moreover, selective disruption of neuronal insulin receptors induces a diet-induced obese phenotype with increased body fat and peripheral insulin resistance [11-13]. This occurs rapidly in response to overfeeding [14]. The restoration of brain insulin receptor function, on the other hand, prevents diabetes [15]. The IR deficiency affects different neuronal populations including agouti-related protein, neuropeptide and dopaminergic neurons. These neurons are partly gamma-Aminobutyric acid (GABA) positive [16-18] and play a prominent role in the metabolic effects of central insulin action via the inhibitory GABAergic system [12,19]. As these neurons are present in various neuronal circuitries suggests that insulin´s effect on the regulation of peripheral metabolism depends on alterations of various brain regions and their interplay. Meanwhile, numerous studies corroborate that the disruption of insulin action in the brain leads to a manifold of alterations in neural and glial cell function [20] directly influencing the pathology and behavioral characteristics of metabolic diseases but also psychiatric and neurodegenerative diseases. These alterations include for example changes in dopamine signaling [6,21], blood-brain-barrier function [22], hippocampal synaptic plasticity [23], mitochondrial function [14,21] and beta-amyloid [24] and microtubule-associated tau protein [25].

In humans, the role of insulin in the brain was long unknown. Recent advances in brain imaging revealed an altered neural responsiveness to insulin in persons with obesity and patients with T2D. Preissl and colleagues [26] first showed that exogenous insulin administration leads to a prominent

neural response in normal weight but not individuals with obesity, proposing brain insulin resistance as part of the obese phenotype.

DETECTING BRAIN INSULIN RESISTANCE IN HUMANS

In response to a hyperinsulinemic clamp, obesity is associated with a failure to show insulin-stimulated cortical activation, evaluated by magnetoencephalography (MEG) [26] and abnormal insulin-induced brain glucose metabolism using ^{18}Fluordesoxyglucose (FDG) - positron emission tomography (PET) [27]. Both findings are highly linked to peripheral insulin resistance and impaired glucose tolerance. How extreme underweight or cachexia affects insulin sensitivity of the human brain is still unclear. To pinpoint the specific regions affected by brain insulin resistance, functional magnetic resonance imaging (fMRI) has emerged as a valuable tool with superior spatial resolution compared to PET and MEG [see panel 1 on imaging methods]. Recent fMRI findings illuminated the role of central acting insulin in the hypothalamus and predominantly in brain regions of the mesocorticolimbic (MCL) circuitry [4].

INSULIN STIMULATION TECHNIQUES

HYPERINSULINEMIC EUGLYCEMIC GLUCOSE CLAMP

During a hyperinsulinemic euglycemic glucose clamp, insulin is continuously infused into the venous bloodstream, while glucose is kept constant at normal fasting level. This technique is considered the "gold-standard" for the quantification of peripheral insulin sensitivity[28]. Plasma insulin levels optimal to stimulate insulin effects in the tissue of interest are achieved by using different insulin doses. During the clamp, insulin reaches the brain continuously. However, insulin effects are not limited to the brain, but occur in most tissues throughout the body, making it difficult to distinguish between peripheral and central effects. In animals, this can be solved, for example, by injecting specific blockers into the brain; an approach that is not available in humans. With the clamp technique, it is possible to evaluate insulin stimulated brain activation and inhibition and simultaneously whole-body insulin sensitivity. When an experiment is performed using labeled glucose, it is also possible to measure insulin-induced suppression of endogenous glucose production and stimulation of glucose uptake.

INTRANASAL INSULIN ADMINISTRATION

Intranasal insulin is a non-invasive method for the selective detection of central insulin actions. When administered as a nasal spray, insulin is rapidly delivered from the nasal cavity to the brain: insulin enters the nasal mucosa and is then transported to the CNS via olfactory and trigeminal pathways, bypassing the blood brain barrier [29]. By the olfactory pathway, insulin is transported extracellularly through intercellular clefts of the olfactory epithelium to the olfactory bulb, where it significantly modulates olfactory perception [30,31]. Subsequently, insulin is transported to the brain stem,

hypothalamus and eventually spreads throughout the brain (including cortical and subcortical regions). This can be observed by using fluorescent tracers in animal models [29]. In humans, a biologically relevant cerebrospinal fluid increase in insulin levels is detected 30 minutes after 40U intranasal insulin application [32]. Only very small amounts of the intranasally administered insulin are absorbed into the circulation (e.g., around 0.1U after intranasal application of 160U insulin) [33-35] and minor effects on peripheral glucose levels are usually observed [34]. Using the intranasal approach, it is possible to evaluate selective central insulin stimulation of brain activation and inhibition and evaluate central insulin-induced modulation of peripheral metabolism.

Panel 1. Brain imaging methods for the investigation of insulin action in the brain
Functional magnetic resonance imaging (fMRI)
fMRI measures **blood flow** related to neural activity, which is termed **neurovascular coupling**. It is possible to measure **cerebral blood flow (CBF)** directly using arterial spin labelling or to use the **BOLD** (blood oxygenation level dependent) contrast, which measures increased blood flow that is coupled with neural activity. The BOLD signal is based on the different magnetic susceptibilies of oxygenated to deoxygenated blood. Based on BOLD time course correlations, it is also possible to evaluate brain **functional connectivity**. The measurement of CBF with MRI is based on arterial blood water flowing into the brain after being marked (magnetically 'labeled') by a radiofrequency pulse. The decay of that signal is then measured as a proxy for neural activity. Additionally, the direct change in **CBF** provides absolute **quantification** of the neural signal, thus resulting in a well-characterized physiological parameter (ml/100g brain tissue/min). A major limitation of fMRI is the low temporal resolution based on the hemodynamic response time (approx. 3 seconds), which is much slower than the underlying neural processes. Using fMRI, **insulin induced neural activity** and **insulin-induced functional connectivity** changes can be detected non-invasively at high spatial resolution (typically 2-3 millimeter isotropic at 3 Tesla).
Position emission tomography (PET)
PET measures **metabolic processes** and binding potential using **radioactive tracers** and ligands of particular molecules of interest. PET typically uses isotopes with a short half-life such as the radionuclides carbon-11, oxygen-15 and fluorine-18. These are either incorporated into compounds normally used by the body as glucose or water, or into molecules that bind to receptors. Hence, PET is used to directly investigate the synthesis and receptor binding of **specific neurotransmitters**, as for example dopamine. Due to the travel distance of the positron, the temporal (tens of seconds to minutes) and the spatial resolution of these methods (approx. 4 mm) is rather limited, making them applicable in specific research questions only. To increase the spatial resolution, PET was recently combined with MRI to investigate specific neurotransmitters at higher resolution. Using PET, **insulin induced specific metabolic processes** of the brain are evaluated, as for example changes in dopamine levels (by using [^{11}C] Raclopride or [^{18}F] fallypride) or regional glucose uptake (by using [^{18}F] fluorodeoxyglucose).
Electroencephalography (EEG) /Magnetoencephalography (MEG)
EEG and MEG are non-invasive methods for directly measuring the **electric activity** of simultaneously activated neurons with high temporal resolution (range of milliseconds). While EEG measures the electric signal using electrodes attached to the head, MEG measures the magnetic field generated by the electric activity by superconducting sensors distributed in a helmet over the whole head. The major advantage of EEG and MEG is that they operate on a timescale on which neuronal activity actually takes place (i.e. milliseconds). In both cases, brain activity can be analyzed in the time or frequency domain. EEG and MEG have limited sensitivity for processes in deep brain structures such as the hypothalamus and striatum, and are mainly used to **investigate cortical processes**. Using EEG and MEG, **insulin induced cortical activity** is detected in specific frequency bands.

EFFECTS OF INSULIN ACTION IN THE HYPOTHALAMUS

The hypothalamus is the main brain area controlling whole-body energy homeostasis. Early lesion studies in animals demonstrated the seminal role of different nuclei in the hypothalamus in the maintenance of energy homeostasis [36] and subsequent work identified insulin receptors on neurons within these various nuclei (e.g. agouti-related protein, neuropeptide, proopiomelanocortin) [37]. Human imaging studies on the hypothalamic control of metabolism and insulin action are still scarce; largely owing to methodological challenges of imaging this region of the brain. Due to the small size of the hypothalamus and its position on the walls of the floor of the third ventricle, it is challenging to detect BOLD hypothalamic response by fMRI. The spatial resolution of most fMRI studies is 2-3 mm while the human hypothalamus measures around 700 mm^3 in total volume with many specialized cell groups [38]. Nonetheless, a handful of studies have been undertaken, showing changes in hypothalamic activity in response to hypoglycemia [39] and glucose ingestion [40,41]. In response to hypoglycemia, the hypothalamus shows a persistent increase in cerebral blood flow, which is most likely mediated by a drop in local gamma-aminobutyric acid (GABA) as identified by an ultra-high field magnetic resonance imaging study at 7 Tesla [42]. Increasing central insulin levels, on the other hand, results in a decrease in the fMRI signal here. This hypothalamic-inhibition has been shown in recent studies in response to intranasal insulin. In the fasting state, intranasal insulin administration produces a decrease in regional cerebral blood flow- and BOLD signal in the hypothalamus- starting 15 minutes after application [41,43-47]. This effect is also observed in the postprandial state (i.e. after glucose ingestion), suggesting that intranasal insulin enhances the inhibitory effects of nutrient consumption [48]. However, and in line with animal studies [49], the effects of intranasal insulin on hypothalamic activity is blunted in obesity and the magnitude of blunting correlates with the amount of visceral adipose tissue [50]. In the periphery, a recent animal study showed that insulin resistance leads to inflammation rather than the other way around [51]. Whether enlarged visceral fat mass is cause or consequence of hypothalamic insulin resistance (or both) is still unclear. Recent evidence suggests that impaired modulation of peripheral tissues in hypothalamic insulin resistance leads to altered postprandial energy fluxes that ultimately results in fat accumulation in the visceral compartment [44,52-54] (see Figure 2). Hence, we postulate that there is a specific obese phenotype with highly inflamed visceral adipose tissue and brain insulin resistance, who are at increased risk to develop T2D and maybe even neurodegenerative [4] and psychiatric diseases [2].
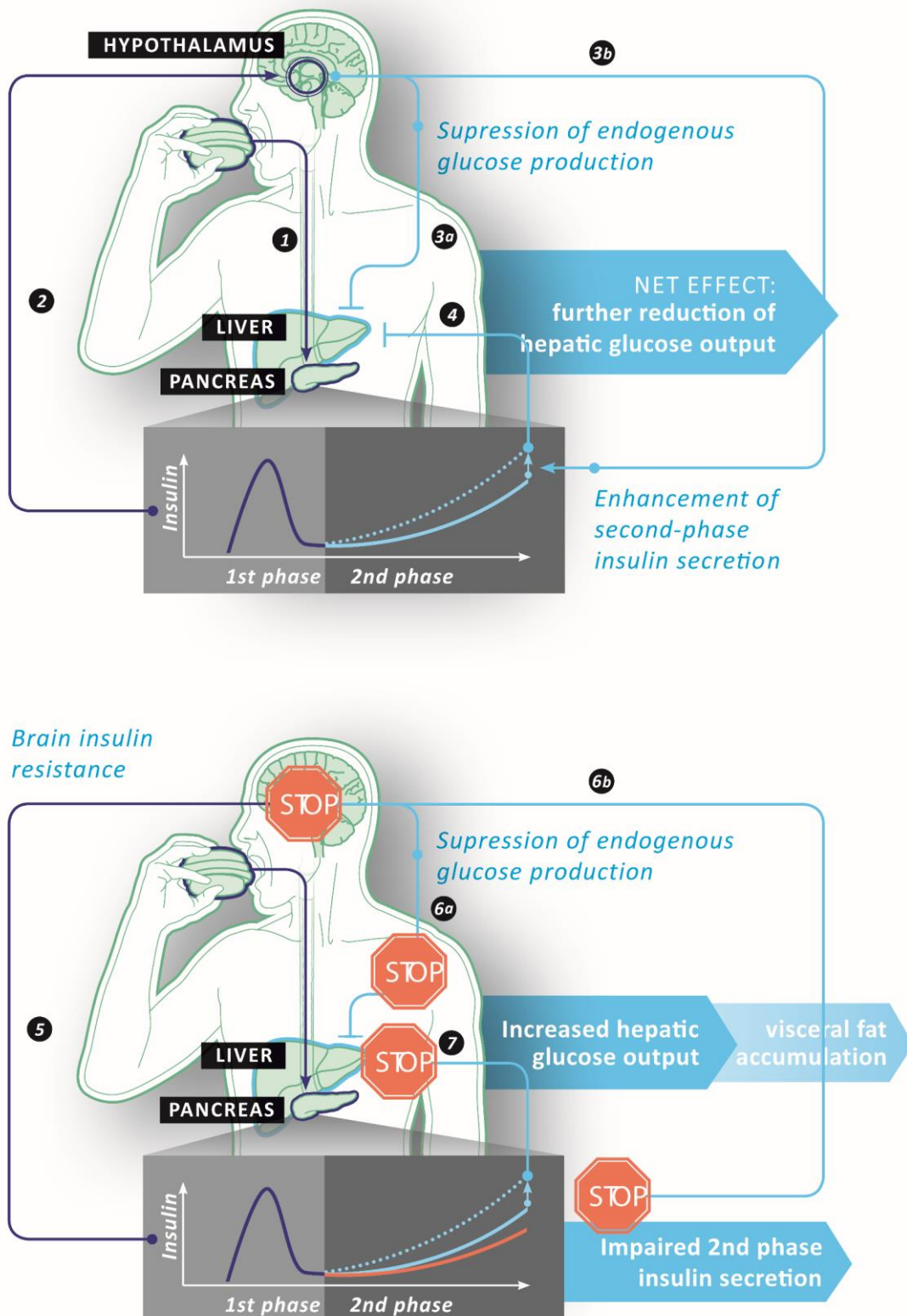
Figure 2. Schematic overview of the hypothesized effect of brain insulin action and brain insulin resistance on peripheral metabolism. **A) Brain insulin sensitive state (1)** In response to food intake, insulin secretion is initiated from the pancreatic beta cells. An initial peak of insulin

is observed during the first phase of insulin secretion. **(2)** Insulin reaches the brain via the bloodstream. Specific neurons sense insulin and trigger peripheral effects presumably via the parasympathetic nervous system. **(3a)** Brain-derived signals reach the liver to suppress endogenous glucose production. **(3b)** Projections to the pancreas enhance second phase insulin secretion into the portal vein. As portal insulin is the strongest suppressor of hepatic glucose production, **(4)** enhanced insulin secretion will further suppress endogenous glucose production. Thus, brain-derived signals that are activated by initial insulin secretion help to reduce hepatic glucose output in the later postprandial state. **B) Brain insulin resistant state (5)** In the case of hypothalamic insulin resistance, meal-induced pancreatic insulin cannot activate specialized neurons in the brain. **(6)** Therefore, outflows to the liver are compromised and can no longer sufficiently suppress endogenous glucose production. **(7)** Second phase insulin secretion is not adequately stimulated. As a result, postprandial portal insulin concentrations are lower and will thus not suppress endogenous glucose production appropriately. This will ultimately result in increased hepatic glucose output. First results suggest that the excess energy might be stored subsequently in the unfavorable visceral fat compartment.
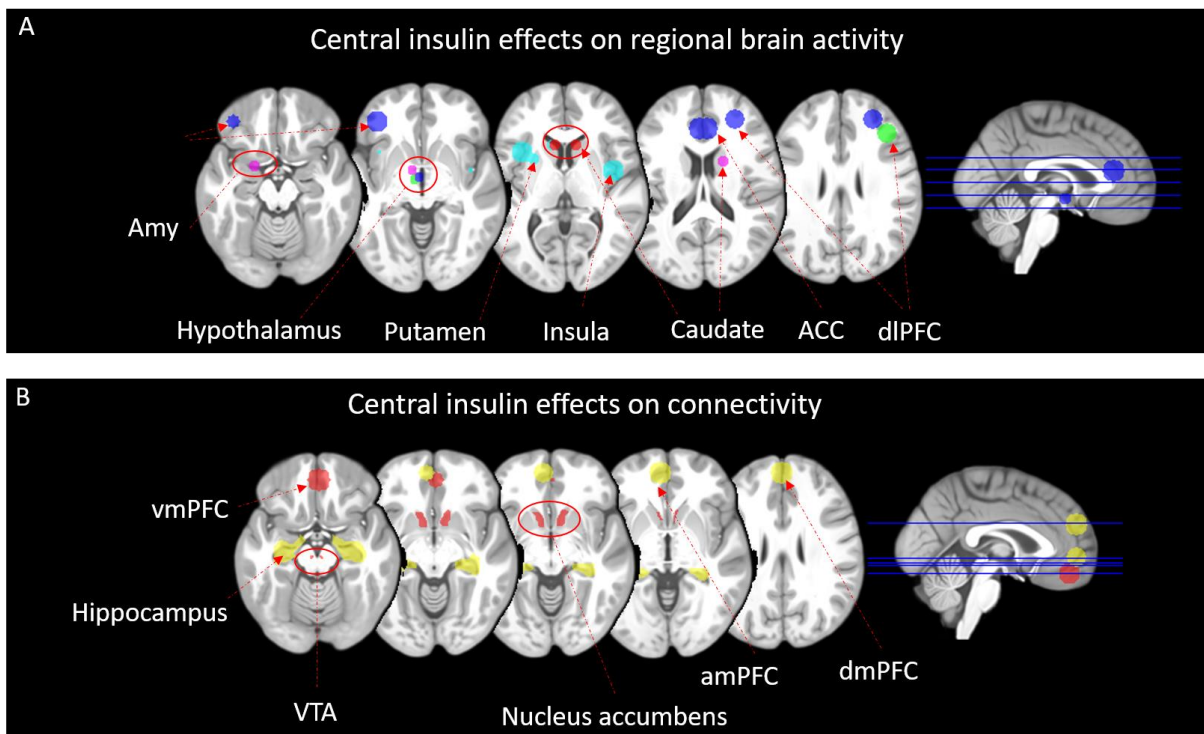

Figure 3. Central insulin action in humans. Brain sections show regions identified in human fMRI studies that respond to intranasal insulin application. (A) The top part of the figure shows brain regions showing regional changes in BOLD and CBF after intranasal insulin, color-coded by study. These regions include the prefrontal cortex (i.e. the OFC, ACC and dorsolateral PFC), insula, striatum (putamen and caudate), amygdala and hypothalamus [study color coding: blue[45], cyan[55], green[50], red[52], and violet[35]]. (B) The bottom part of the figure shows regions in the brain exemplifying connectivity changes in response to central insulin. Regions color-coded in red are part of the dopaminergic MCL network, including the nucleus accumbens, VTA and ventromedial PFC. Functional connections between the midbrain (i.e. VTA), nucleus accumbens and ventromedial PFC significantly respond to central insulin[56,57]. Regions in yellow include the hippocampus, anterior medial and dorsal medial PFC and are part of the default-mode network. Functional connections between the hippocampus and the PFC are significantly enhanced by intranasal insulin[58,59]. [Abbreviations: ACC, anterior cingulate cortex; Amy, amygdala; amPFC, anterior medial prefrontal cortex; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; vmPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area. Color-coded spheres are based on studies providing normalized coordinates]

BRAIN INSULIN ACTION IN THE MESOCORTICOLIMBIC CIRCUITRY

INSULIN-DOPAMINE INTERACTION- EVIDENCE FROM HUMAN IMAGING STUDIES

Human imaging studies show that regions within the mesocorticolimbic (MCL) circuitry react to peripheral changes in insulin with a decrease in spontaneous activity and lower responsiveness to food cues [47,60-62]. Moreover, central insulin modulates, besides the hypothalamus, regional activity and connections of the MCL circuitry [35,45,46,55-57,63]. This includes parts of the prefrontal cortex, insula, striatum (including caudate, putamen and nucleus accumbens (NAc), amygdala, hippocampus, and ventral tegmental area (VTA) (see figure 3). Specifically, studies using intranasal insulin demonstrate that insulin inhibits connectivity from the VTA to the NAc [56] and modulates regional activity of the MCL circuitry [35,45,46,63]. Functional connectivity to parts of the prefrontal cortex is enhanced by intranasal insulin [57,59], and correlates with measures of food craving and hunger [50,59]. Hence, boosting insulin action in the brain may have beneficial effects on eating behavior by reducing food craving. In a similar vein, Tiedemann et al. [56] report that persons with a strong insulin-induced inhibition of the VTA-NAc connection show a more pronounced decrease in food palatability ratings in response to intranasal insulin, suggesting a role for central insulin action in the regulation of food reward in response to food intake. Accordingly, in insulin resistant persons, central insulin action of the MCL circuitry is disturbed [46,50,57,64] and this is associated with higher preference for palatable food [50,56]. Specifically, the strength of the insulin-induced change in connectivity from the VTA to the NAc is weakened in insulin resistant persons [56]. Hence, central insulin action may influences food reward behavior via the MCL circuitry in healthy individuals. In line with these findings, acute doses of intranasal insulin reduced caloric intake and food preference in the fasted state, however only in men [50,65]. Interestingly, when administered after lunch intake, intranasal insulin reduces food craving and snacking in women [66]. These findings corroborate the concept that central nervous insulin is a pivotal negative feedback signal in the regulation of the reward-related aspects of food intake, possibly in a sex-dependent manner.

INSULIN-DOPAMINE INTERACTIONS- EVIDENCE FROM RODENT STUDIES

Work in animals suggest that these MCL effects observed in imaging studies in humans rely on insulin action on dopamine signaling [67-69]. IRs are expressed on dopaminergic neurons in the midbrain (i.e. VTA and substantia nigra) and on GABAergic medium spiny neurons, cholinergic interneurons and on astrocytes in the nucleus accumbens (NAc). Insulin action in the VTA and NAc results in differential effects on dopamine signaling [70]. Insulin action in the VTA decreases dopamine, specifically by decreasing excitatory transmission [71] and increasing the activity of dopamine reuptake transporter [72]. In the NAc, insulin increases dopamine by excitatory synaptic transmission [73] onto striatal medium

spiny projection neurons and by increasing the firing of cholinergic interneurons and terminal dopamine release [67,70]. A possible explanation for this differential effect of central insulin action in the VTA and NAc is a time dependent response. Early in the feeding period, when the animal is still fasted, lower insulin leads to an increase in NAc dopamine to drive food intake followed by a suppression of dopamine concentration 30 to 60 min into the meal when insulin levels are rising. The latter results in decreased food intake and food approach behavior [70]. Thus the effect of dopamine on food intake may be time-dependent.

Insulin resistance impairs dopamine response in the VTA and NAc in response to a meal resulting in enhanced food consumption [70]. It is even postulated that when IRs on dopaminergic neurons are desensitized the effect of insulin in the VTA and NAc is abolished [70]. Normalization of dopamine function can be achieved by using insulin sensitizers, i.e. selective inhibitors of protein tyrosine phosphatase 1B, thereby enhancing insulin action [74]. In support of these findings, recent evidence in human research suggest that boosting central insulin action in the striatum enhances peripheral metabolism in persons of normal weight [44,52]. Hence, the MCL circuitry may well act as a link between central insulin and peripheral metabolism.

BRAIN INSULIN ACTION IN THE PREFRONTAL CORTEX AND HIPPOCAMPUS

The hippocampus is known for its prominent role in learning and memory and hippocampal IRs regulate structural and functional plasticity to enhance cognition [75]. Recent efforts in improving cognitive functions in patients with T2D and early AD revealed that hippocampal-memory processes benefit from central acting intranasal insulin [58,76-81]. Interestingly, there is evidence that hippocampal insulin resistance may occur independently of peripheral insulin resistance and glycemic control [75]. Rats with hippocampal-specific insulin resistance, by selectively downregulating IR expression, show no changes in body weight and peripheral insulin sensitivity, however changes in neural plasticity and impaired spatial learning [82] (for a recent review on hippocampal insulin resistance and cognitive dysfunctions see [23]). However, the hippocampus can detect interoceptive signals of hunger and satiety [83,84] and forms memory of a meal to inhibit subsequent food intake [84,85]. These observations are complemented by the findings in humans that central insulin, by intranasal administration, decreases hunger through the hippocampal-prefrontal cortex connection [59]. Similarly, improvements in cognition in T2D are modulated by intranasal insulin induced enhancement of the connection between the hippocampus and the prefrontal cortex (PFC) [58] (Figure 3).

The PFC plays a prominent role in human behavior, as in the control over food intake and food choice. Moreover, human imaging studies revealed that the parts of the PFC are particularly sensitive to hormonal changes [45,46,57,60-62]. Persons with obesity-associated insulin resistance and increased

susceptibility to uncontrolled eating and food craving show insulin resistance of the prefrontal cortex [50,57,59]. These findings are complemented by gene expression studies in post-mortem brain tissue linking insulin-signaling expression genes with dopamine-expression genes in the dorsolateral PFC. In people with obesity, significantly lower expressions were detected [86]. Hence, the insulin-dopamine interaction extends to the prefrontal cortex, further shaping the concept of insulin as an important player in cognitive functions.

EFFECT OF BRAIN INSULIN ACTION ON PERIPHERAL METABOLISM

Central insulin action does not only affect brain activity but also stimulates signals to the periphery. Initial findings from rodents, genetically lacking the IR in the brain, suggest that pituitary function depends on insulin signaling [12]. However, these findings did not directly translate to humans, as intranasal insulin administration has no effect on the pituitary endocrine axes [35,46,87]. There is accumulating evidence, however, that brain insulin action shifts the autonomic nervous system towards the parasympathetic tone [35,44,88] and might thereby modulate peripheral metabolism. This is well in line with recent concepts on the integrative function of the brain in the control of whole body energy balance that are mainly based on findings from rodents [89].

EFFECT OF BRAIN INSULIN ACTION ON PERIPHERAL INSULIN SENSITIVITY

In humans, effects of central insulin action on peripheral metabolism is tested either by intranasal insulin administration [33,53,90,91] or by pharmacologically blocking specific potassium channels that are among others expressed in neurons located in insulin sensitive brain areas [92,93]. Most studies indicate that stimulating brain-derived signals improve peripheral insulin sensitivity. Initially, this was investigated using an indirect index of insulin sensitivity, HOMA-IR [46,94], and later confirmed by the hyperinsulinemic-euglycemic glucose clamp procedure, which is the gold standard for investigating whole-body insulin sensitivity [44,52,90]. Specifically, Heni et al. showed that intranasal insulin administration improved peripheral insulin sensitivity in lean men [44,46]. Insulin action in the hypothalamus and striatum appear to be involved in this process. In obese men, who are not responsive to central insulin in these regions, intranasal insulin failed to improve peripheral insulin sensitivity investigated during the hyperinsulinemic-euglycemic glucose clamp [44,52,54]. This suggests an altered brain-derived modulation of peripheral glucose metabolism in obesity-associated insulin resistance. Importantly, it is unclear whether intranasal insulin administration constitutes a suitable means of overcoming central nervous insulin resistance. A proof-of-concept study showed that eight weeks of intranasal insulin treatment significantly reduced body weight and body fat. However, this beneficial effect was only observed in lean men and not in women or obese men [95]. Accordingly, in animal experiments, male rats decreased their food intake after intracerebroventricular insulin

infusion and lost weight after 24h of treatment, whereas female rats remained unaffected [96]. While the underlying cause is still unknown, animal data point to estrogen signaling playing a pivotal role [97]. However, this has not been confirmed in human studies [98].

EFFECT OF INSULIN ACTION ON THE 'BRAIN-LIVER AXIS'

Peripheral insulin sensitivity is well known to be dependent upon a number of different peripheral tissues and mechanism. Recent evidence points to the existence of a 'brain-liver axis', indicating that insulin action in the brain affects peripheral glucose metabolism, such as endogenous glucose production (EGP). This is of special interest, as altered insulin-induced EGP suppression is an important facet of T2D. Intranasal insulin administration during systemic hyperinsulinemia suppresses endogenous glucose production (measured by tracer-dilution techniques) [52,90] and enhances glucose uptake into the periphery [52]. Thus, brain-derived outflow most likely targets multiple tissues, such as the liver, skeletal muscle and adipose tissue. Obese men failed to show this central insulin effect on EGP suppression [52,54]. Interestingly, the metabolic reaction in lean individuals depended on elevated circulating insulin levels and might therefore be limited to the postprandial state, when insulin levels physiologically rise in the periphery and the brain [53]. Concomitantly, Gancheva et al.[33] found no suppression of EGP in response to intranasal insulin in the fasting state. Nevertheless, intranasal insulin administration improved hepatic energy metabolism and reduced liver fat content in lean healthy persons but not in patients with T2D [33]. Research in animals furthermore suggests a role of brain insulin in the control of lipolysis in adipose tissue [99]. In humans, results on this topic are conflicting [4]. Only one study thus far reported reduced lipolysis after nasal insulin administration [100]. Other studies, however, could not confirm this finding [33,90,101], presumably due to different study designs. Hence, further research is needed to clarify potential effects of brain insulin on systemic lipolysis in humans.

Another approach used to investigate associations between EGP and the brain's response to insulin is by increasing insulin (hyperinsulinemic clamp) systemically [27,102]. Insulin-stimulated brain glucose uptake measured by PET seems to be linked to insulin resistance and failed EGP suppression in morbid obesity [27,102]. Furthermore, chronic administration of intranasal insulin over four weeks reduced secretion of branched chain amino acids from the liver in healthy men [103]. This is of potential importance for metabolism, as branched chain amino acids are proposed to be involved in the pathogenesis of T2D and obesity [104]. However, as the response to chronic intranasal insulin was not associated with any improvements in body weight or insulin sensitivity [103,105], the metabolic relevance of this finding remains to be determined.

EFFECT OF BRAIN INSULIN ACTION ON INSULIN SECRETION

Human glucose metabolism not only depends on peripheral insulin sensitivity, but is crucially regulated by insulin secretion from pancreatic beta cells. Knock down of the IR in in a specific region of the hypothalamus known for glucose-sensing impaired insulin secretion and caused glucose intolerance in rodents [106]. First correlative findings suggest that there might be a connection between insulin responsiveness of the hypothalamus and pancreatic insulin secretion [107]. A recent study [108] experimentally addressed this question using the hyperglycemic clamp, which is considered the gold standard for the quantification of pancreatic insulin release. Thereby, intranasal insulin administration enhanced the second phase insulin secretion only in persons with strong hypothalamic insulin responsiveness, while other pancreatic hormones glucagon and somatostatin remained unaltered [108]. As pancreatic insulin drains into the portal vein and thereby reaches the liver at high concentration, brain derived enhancement of postprandial insulin secretion could contribute to the suppression of endogenous glucose production and might represent an additional pathway that allows the brain to modulate postprandial glucose metabolism. Failure of this mechanism could contribute to altered postprandial energy fluxes and unfavorable body fat distribution (see Figure 2) [44,52-54].

LINKING PERIPHERAL AND CENTRAL INSULIN ACTION- POTENTIAL ROLE OF DOPAMINE

Evidence is accumulating that the connection between central and peripheral insulin and glucose metabolism may depend on dopamine function. Obesity is associated with a dysfunctional brain dopamine system [109] and reduced peripheral insulin sensitivity as well as beta cell function are related to low dopamine levels in the brain [110,111]. The central insulin-dopamine interaction seems to contribute to these findings. Diminished central insulin action in the striatum is observed in persons who are genetically prone to obesity and have lower dopamine-receptor availability due to their specific genotype [63]. With this genetic background, carriers are at increased risk for abdominal adiposity and insulin resistance [64].

Thus, insulin signaling in the hypothalamus, the striatum and presumably additional dopaminergic brain areas contributes to the modulation of peripheral metabolism in lean humans. These mechanisms appear to be impaired in obesity and brain insulin resistance and could thereby contribute to the pathogenesis of metabolic diseases like T2D. As insulin action in the brain modulates the parasympathetic tone [35,44,88], the reported insulin-dopamine interaction could in part be mediated via the vagus nerve.

BRAIN INSULIN RESISTANCE AND ITS TREATMENTS

DEVELOPMENT OF BRAIN INSULIN RESISTANCE

It is well established that noncommunicable diseases including T2D, cardiovascular disease, and mental health diagnoses in adulthood can be in part caused by periconceptional and in-utero adverse conditions, including parental obesity. This effect is referred to as the developmental origin of health and diseases [112]. For peripheral insulin resistance several studies showed that impaired insulin signaling during different gestational periods lead to impairment of peripheral insulin action and glucose metabolism in the offspring [113,114]. Moreover, evidence is emerging that central insulin resistance can develop prior to birth. In seminal human fetal imaging studies, impaired maternal metabolism, due to obesity associated insulin resistance and gestational diabetes, affects fetal brain activity and autonomic nervous system function [115,116]. Specifically, these alterations in the fetus are observed only in response to a glucose challenge. Page et al. [117] recently showed that these alterations persist into childhood. Children exposed to maternal obesity or gestational diabetes failed to show hypothalamic inhibition after a glucose challenge at the age of 7-11 years [117]. These studies clearly show that brain insulin action is already affected during development even starting in the periconceptional state; however, the developmental trajectory and possible sensitive periods for interventions are only partially known.

TREATING BRAIN INSULIN RESISTANCE THROUGH WEIGHT LOSS

While brain-imaging studies after weight-loss interventions have increased over the last years, less is known about the impact of weight loss on brain insulin action. Tschritter et al.[118] were the first to show the weight loss success correlated with insulin-stimulated cortical activity prior to the intervention measured using MEG. This response was diminished in obese insulin resistant persons [26]. Using a hyperinsulinemic clamp, insulin significantly stimulated activity in cortical theta activity, which is vital for synaptic plasticity in the hippocampus- a potential cellular mechanism of learning and memory known to be significantly modulated by insulin. Furthermore, the greater the cortical responsiveness to insulin prior to the intervention, the more metabolically unhealthy visceral fat was lost 2 years after the intervention [118] and less fat mass was regained during a nine year follow-up [119]. It is currently not clear, however, whether enhancing central insulin action after weight loss (by using intranasal insulin for example) will help maintain the reduced body weight. Studies in animals show that central insulin decreases food intake to maintain body weight; however only when animals are at their basal weight[120]. This could explain why no study thus far was able to show significant weight reduction by enhancing brain insulin action in persons with obesity and peripheral insulin resistance [105]. More recently, Rebelos et al.[102] showed that marked weight loss after bariatric surgery was not sufficient to eliminate aberrant central insulin action. In response to a hyperinsulinemic clamp, insulin-stimulated brain glucose uptake (BGU) was measured by ^{18}FDG-PET. BGU is a known predictor for T2D and is associated with worse glycemic control [102]. Insulin-stimulated BGU was associated with EGP in morbid

obese but not lean individuals. The association persisted even after substantial weight loss. This could be in part due to inflammation, as aberrant central insulin action positively relates with systemic inflammation and highly inflamed visceral adipose tissue [50,102].

CONCLUDING REMARKS AND FUTURE DIRECTIONS

Recent findings show that insulin impinges on the hypothalamus and the MCL circuitry to influence metabolism, eating behavior as well as motivation, reward and cognition. In this review, we highlighted particularly the role of central insulin on metabolism. Using intranasal insulin, central insulin action enhances peripheral metabolism and acutely curbs food intake. Brain imaging studies attribute these central insulin effects mainly to the dopaminergic system of the brain, which is in part mediated by the parasympathetic nervous system. Therefore, insulin acts on the MCL circuitry to either reinforce palatable energy-rich foods or post-prandially reduce the rewarding properties of food cues. However, these effects were predominantly identified in men but not in women. Hence, future studies are needed to identify other circulating factors that interact with central insulin action, such as estrogen. We also reviewed evidence that disturbances in brain insulin action may develop in utero to impact the trajectory of diabetes later in life. We hypothesize that brain insulin resistance promotes the development of a metabolically unhealthy phenotype thereby increasing the risk to develop T2D, pointing to brain insulin resistance as a possible "culprit" of diabetes and associated complications. In line with this conceptualization, the response to insulin in the brain seems to be predictive for the outcome of weight-loss programs. Whether overcoming brain insulin resistance constitutes a suitable means of treating and preventing obesity and diabetes is at present unclear. Evidence is rapidly accumulating that insulin resistance plays a prominent role in psychiatric and neurodegenerative diseases [2]. Furthermore, brain regions affected by obesity-associated insulin resistance overlap with brain networks that are sensitive to cognitive decline later in life [4]. Consequently, insulin resistance is currently discussed as a shared pathological feature between metabolic and cognitive dysfunctions [2,4]. Targeting insulin resistance in the brain may have therapeutic potential to treat and prevent a number of noncommunicable diseases.

Search strategy and selection criteria
We searched PubMed for articles published from database inception up to Aug 16, 2019, using the search terms "insulin action & brain", "intranasal insulin", "hyperinsulinemic clamp", "obesity", "diabetes", and "neuroimaging (fMRI, PET, EEG, MEG)". Publications were selected on the basis of relevance, with priority given to publications from human research on brain insulin action in obesity from the past 10 years. We also searched the reference lists of articles identified by this search strategy and selected those that we judged to relevant. We supplemented the search with records of relevant publications from our personal files.

Contributors

SK and AK performed the literature search, review and extraction. MH and SK conceptualized and designed the review. All authors interpreted the findings and were involved in drafting the article. All authors read and approved the final version of the article.

Declaration of interests

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