The Effects of Insulin on the Central Nervous System – Focus on Appetite Regulation

R. U. Pliquett[1]
D. Führer[1]
S. Falk[1]
S. Zysset[2]
D. Y. von Cramon[2]
M. Stumvoll[1]

Abstract

Appetite and satiety are subject to complex regulation, with neuroendocrine mechanisms playing an important role. The central nervous system is attracting increasing attention as a target tissue for many hormones such as leptin, PYY3-36, ghrelin, glucagon-like-peptide 1 and many others. Among its many well-known functions, insulin is also a potent anorexigenic hormone, and insulin receptors are widely distributed throughout the central nervous system. One way to advance our understanding of central nervous regulation of hunger and satiety in humans is to develop suitable neuroimaging techniques for use in various clinical and experimental conditions. Several studies have been performed using functional magnetic resonance imaging and positron emission tomography to identify areas of the brain that are differentially activated by alteration of the feeding state. These preliminary data are taking shape as a complex neuronal network involving the hypothalamus, thalamus, limbic and paralimbic areas including the insular cortex and the anterior cingulate gyrus and the orbitofrontal cortex. Continuous efforts to understand hormonal effects on these pathways may advance our understanding of human obesity.

Key words
Insulin · central nervous system · appetite and satiety · neuroimaging

Introduction

Insulin is the main glucose regulatory hormone; however, with the insulin receptor being expressed in virtually all tissues, insulin can contribute to the regulation of many processes unrelated to glucose metabolism. The target tissues most immediately related to plasma glucose are muscle, liver and adipose tissue (Table 1). In the brain, on the other hand, glucose metabolism is not thought to be regulated by insulin. In humans, for example, positron emission tomography (PET) studies have repeatedly failed to reveal any effects of hyperinsulinemia on brain glucose uptake [7,10,14]. Although a permissive role of basal insulin concentrations for global brain glucose uptake can not be excluded [2], the human brain has been traditionally regarded as an insulin-insensitive organ.

Nevertheless, studies on animals and humans have shown the insulin receptor to be expressed throughout the brain, with particularly high concentrations in the hypothalamus, hippocampus and cortex [15,16]. Moreover, all key components in the insulin-signaling cascade (insulin receptor, insulin receptor substrate 1, phosphatidyl inositol-3 (PI3) kinase) have been identified in cortical neurons [15,16]. Glucose transport is probably not an important downstream effector of insulin in neurons since this is largely facilitated by GLUT3 (an insulin-independent glucose transporter) and, to a minor extent, GLUT1 [26]. Nevertheless, an effect on neuronal glucose oxidation or glial glycogen metabolism can not be excluded.

The most relevant neuronal insulin effect at the cellular level seems to be the inhibition of norepinephrine re-uptake [4]. The

Affiliation
[1] University of Leipzig, Faculty of Medicine, III. Medical Department, Leipzig, Germany
[2] Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Correspondence
Michael Stumvoll · MD · Professor of Medicine · University of Leipzig · III. Medical Department · Philipp-Rosenthal-Str. 27 · 04103 Leipzig · Germany · Tel.: +49/341/971 33 80 · Fax: +49/341/971 33 89 · E-mail: michael.stumvoll@medizin.uni-leipzig.de

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Table 1 Important physiological non-CNS effects of insulin

Target Tissue	*Insulin effect*
Muscle	Glucose uptake increase
Liver	Gluconeogenesis decrease
Adipocyte	Lipolysis decrease
Hepatocyte/Adipocyte	HDL increase, LDL decrease, VLDL decrease
Platelets	Aggregation decrease
Renale tubule	Sodium-Reabsorption increase
Endothelium	Vasodilatation

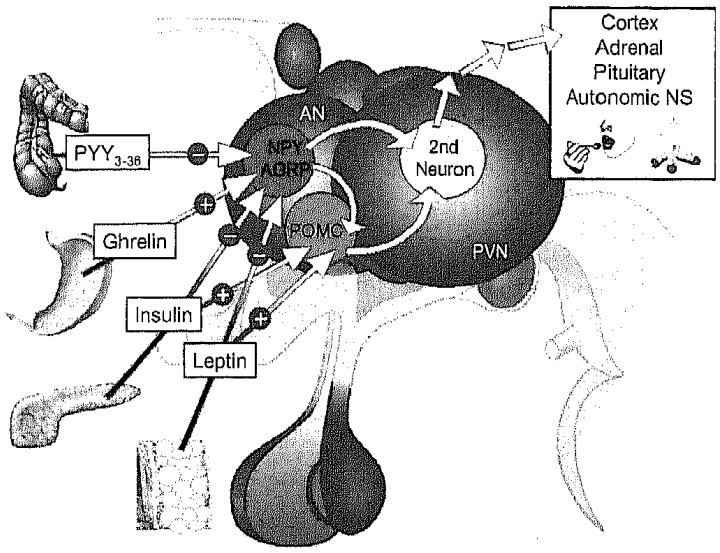

Fig. 1 Humoral stimuli for appetite regulation in the CNS including gut-derived PYY 3–36 (peptide YY 3–36), insulin, leptin, and the mainly stomach-derived ghrelin, affecting orexigenic neurons, i.e. neurons co-expressing NPY (neuropeptide Y) and AgRP (Agouti-related peptide), or anorexigenic, i.e. POMC (proopiomelanocortin) or CART (cocaine- and amphetamine-regulated transcript) containing neurons within the arcuate nucleus (AN) of the hypothalamus. Projections to other hypothalamic nuclei such as the paraventricular nucleus (PVN), dorsomedial hypothalamic nucleus, and lateral hypothalamic areas exist, and are crucial to body-weight control in terms of food-intake behavior and energy expenditure.

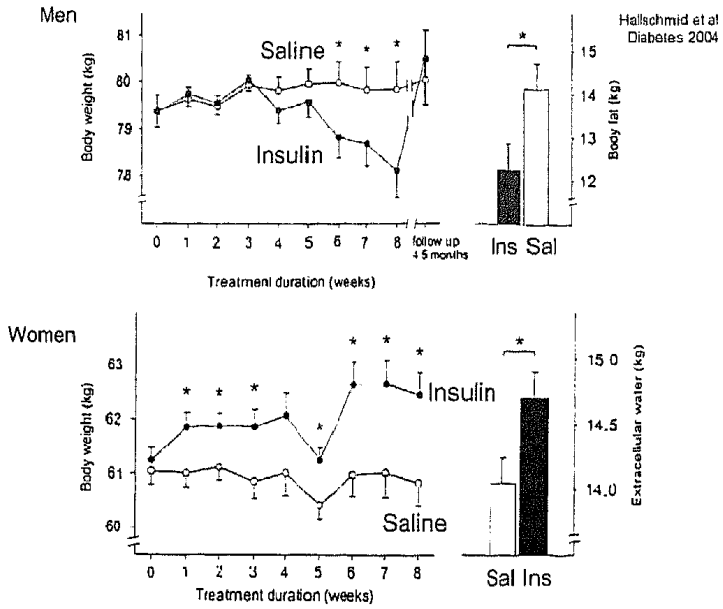

Fig. 2 Data from Hallschmid et al. [12, 17] showing that intranasal insulin reduces body weight and fat in men (left panel: time course of body weight ± SE in males during eight weeks of intranasal insulin administration and in a follow-up examination eighteen weeks after cessation of treatment; right panel: kg of body fat ± SE in the same participants after eight weeks of treatment. (INS = Insulin, SAL = Saline). Significant differences are highlighted with asterisk ($p < 0.05$), n = 12 for each group.

resulting increase in synaptic cleft norepinephrine may present a variety of secondary effects, not only on the post synaptic neuron but also on adjacent astrocytes (glial cells) via beta-adrenoceptor activation. In addition, neuronal insulin signaling may cross-talk with neurotransmitter signaling or signaling involving other hormones. For example, hypothalamic insulin signaling has been proposed to converge with leptin signaling at the level of phosphatidylinositol-3 kinase [21]. Thus, insulin clearly has every potential to modulate central nervous system (CNS) activity.

Control of Appetite by Insulin

Although insulin has been found to be associated with improvement of cognitive function in rodents [1] and patients with Alzheimer's disease [6] while affecting several neurophysiological parameters in healthy volunteers [13, 18, 25, 34], more robust evidence exists for its role in appetite regulation. Early work on animals has suggested that insulin inhibits appetite at the CNS level [35]. Subsequently, evidence has become available that insulin crosses the blood-brain barrier [27]. When given directly into the brain, the CNS effects of insulin include the suppression of food intake [23, 28] and inhibition of gluconeogenesis in the liver brought on by hypothalamic insulin signaling [22]. Finally, brain selective deletion of the insulin receptor resulted in hyperphagia, obesity and metabolic insulin resistance in mice [5]. Thus, the understanding of insulin regulation of appetite and its potential dysregulation in obesity should be of great relevance. Fig. 1 demonstrates the integrative position of insulin in the neuroendocrine network of appetite control.

CNS Effects of Insulin in Humans

Limited experimental access presents a major obstacle to studying insulin effects in the human CNS – especially in those regions involved in appetite regulation. A number of neuroimaging techniques are available and can also be used for metabolic studies, which include PET, whole-head magnetic encephalography (MEG) and functional magnetic resonance imaging (fMRI). Another problem is superimposition of any neurophysiological parameter by hypoglycemia with intravenous administration of insulin. In this respect, it is important that insulin can also be administered intranasally, which results in increased CSF insulin concentrations [3] and favorable effects on selected EEG parameters (reduction of the N1 and P3 component of auditory evoked potentials) [17] without affecting systemic insulin or glucose concentrations.

Given that insulin negatively regulates appetite in the CNS, the impact of CNS insulin on body weight regulation still remains

widely unclear. In normal-weight males, insulin administered intranasally over eight weeks resulted in a weight loss of 1.3 kg and a loss of 1.4 kg of body fat according to the standard body impedance technique. Waist circumference decreased by 1.6 cm, while plasma leptin levels dropped by an average of 27 %. However, the same intervention in normal-weight females yielded an increase in body weight by one kg, mainly due to increased extracellular water [12] (Fig. 2). Gender or sex-hormonal effects – all women were on contraceptives – may attenuate CNS effects of insulin. Likewise, differences in fat distribution between men and women may explain the differences in body-weight regulation. The authors' explanation for this sex-specific effect also implicated differential leptin regulation observed in rodents.

Insulin's effect on obesity in the CNS

Another way to study the role of insulin in human obesity is to compare its effect in lean and obese study participants. Preliminary evidence has been provided from a MEG study in lean and overweight participants [31]. MEG provides information of cerebrocortical activity similar to electroencephalography, but with a greater temporospatial resolution. Theta activity has been used as a parameter for CNS insulin sensitivity. In this study, the insulin's stimulatory effect (expressed as the difference from the placebo experiment) on theta activity was significantly smaller in obese than in lean subjects. Moreover, the attenuation of insulin induced changes in theta activity was inversely correlated with body-mass index in multivariate analysis and positively with insulin-stimulated glucose disposal, that is, metabolic insulin sensitivity in univariate analysis. These preliminary data may suggest that obesity is associated with reduced cerebrocortical insulin sensitivity.

Neuroimaging and Appetite

The proposed CNS effects of insulin and other anorexigenic *vs.* orexigenic stimuli primarily affect appetite and satiety, the principal regulators of caloric intake. Functional neuroimaging techniques such as PET and fMRI may serve to unravel the neuroanatomical location of CNS regions involved in these processes. PET imaging uses positron-emitting radiotracers such as ^{15}O water, which readily crosses the blood barrier after intravenous injection and can be used to detect changes in cerebral blood flow. Such changes accompany altered neuronal activity upon exposure to a defined stimulus. Superimposition of functional onto an anatomical MRI allows the mapping of the CNS regions with changes in CBF/neuronal activity. A downside of PET technology is its limited spatial resolution (5 mm), which can be critical for hypothalamic imaging.

Functional MRI scanning uses the blood oxygen level-dependent (BOLD) signal as a measure for neuronal activity, and is based on uncoupling of oxygen consumption and supply (decreased levels of deoxygenated hemoglobin and increased blood flow) with increased neuronal activity. The spatial resolution of fMRI is as low as 1 mm. Another advantage is the high temporal resolution of fMRI, which makes the technique suitable for monitoring processes of appetite regulation and satiation over time.

Table 2 Peripheral Hormones with central effects on appetite

Hormone	*Source*	*Effect on appetite*
Insulin	Pancreatic beta cell	Decrease
Amylin	Pancreatic beta cell	Decrease
Leptin	Adipocytes	Decrease
Ghrelin	Gastric K-cell, gut	Increase
CCK	Mucosal cells of duodenum, jejunum	Decrease
PYY 3-36	Ileum, colon	Decrease
PP	Pancreas	Increase
GLP-1	Duodenal L cells	Decrease
OXM	Duodenal L cells	Decrease
GIP	Duodenal K cells	Increase

CCK, cholecystokinin; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; PP, pancreatic polypeptide PYY 3-36, peptide YY 3-36; OXM, oxyntomodulin

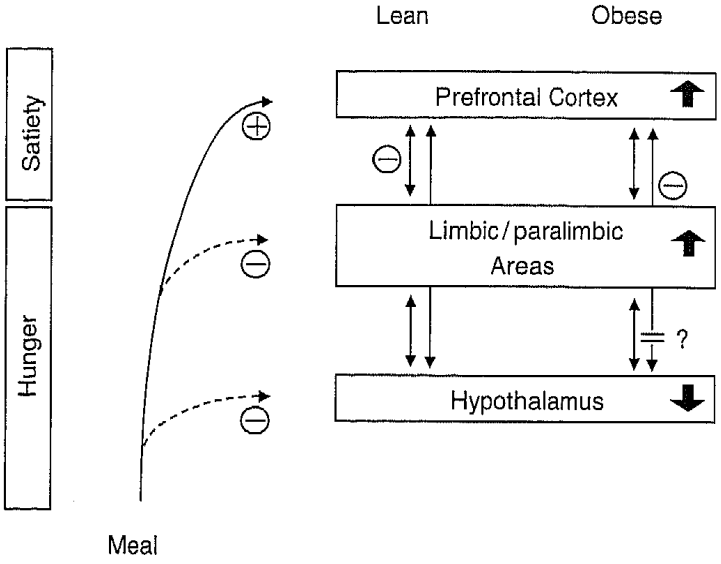

Fig. 3 Model of differences in brain activation in response to meal in lean and obese individuals as proposed by Tataranni and Del Parigi [28] based on PET studies. According to this model, the prefrontal cortex signals satiation by sending inhibitory inputs to limbic and paralimbic areas (cingulate gyrus, frontal insula) and possibly the hypothalamus to suppress hunger. In obesity, prefrontal cortex activity may increase to suppress chronically hyperactive orexigenic areas. In addition, resistance of the hypothalamus to the inhibitory inputs of the prefrontal cortex may play a role.

Besides technology, the most crucial prerequisite for neuroanatomical dissection of appetite is probably experimental design. States of increased or decreased appetite such as hunger and satiety are relative terms that are affected by a variety of mechanisms in the CNS such as predictive reward mechanisms [11, 20], as well as by adipocyte and gastrointestinal-tract stimuli (Table 2). Thus, imaging results will likely vary with the kind of food presented (such as favorite or non-favorite food, which may vary intra-individually; low *vs.* high caloric food, low *vs.* high carbohydrate or fatty food), how the food is presented (such as by images, talk, smell, taste), and the circumstances under which food presentation takes place (such as fasting, non-fasting, euglycemia, hypoglycemia or hyperglycemia) [8, 24, 29, 33]. In addition to food-related issues, problems central to neuroimaging studies in general also need to be taken into account (such as gender,

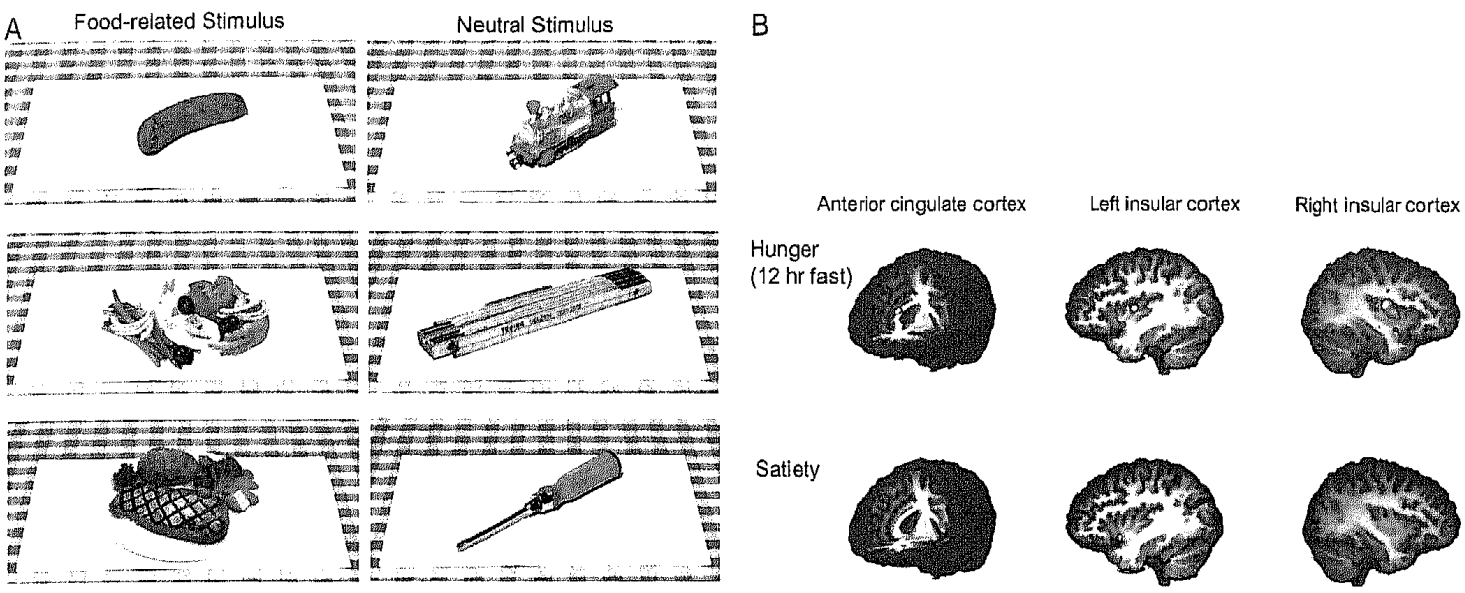

Fig. 4 Food-related or food-neutral objects (Fig. **4A**) presented as visual stimuli to participants either in the condition of hunger or satiety using fMRI. Fig. **4B** demonstrates the resulting regional brain activation pattern in the state of hunger and satiety averaged for twelve participants. Yellow and red denote different statistical degrees of increased activation (red indicates $p < 0.005$) for food-related objects in contrast to food-neutral objects.

body weight & fat mass, left-handedness, anxiety state, tiredness, physical fitness). Controlling for these parameters when selecting the study population and designing the study is absolutely essential.

For these reasons, a direct comparison of the available neuroimaging studies addressing appetite and satiety is difficult at present. Nevertheless, PET imaging suggests hunger to correlate with activation of a complex neuronal network, including hypothalamic and thalamic regions as well as limbic and paralimbic areas such as the insular cortex, anterior cingulate cortex and orbitofrontal cortex. In satiety, the activation pattern is somewhat shifted with prominent neuronal activity within the prefrontal cortex and decreased activity of the before mentioned "hunger" areas. Since the prefrontal cortex is known to have inhibitory projections to these areas, Del Parigi and Tataranni have suggested that inhibitory effects on termination of eating might be exerted by the "anorexigenic" prefrontal cortex by downregulating neuronal activity in the orexigenic CNS regions [9,30] (Fig. **3**). Similar results have been obtained when comparing low and high-calorie diet in an fMRI setting [19]. Furthermore, a recent study using PET methodology and gastric distention as a mechanic visceral stimulus demonstrated inferior frontal gyrus activation. This suggests a pivotal role of this region as a convergence zone for processing food-related/visceral stimuli and for a coordination of states of appetite and satiety [32].

We have developed an fMRI paradigm to image the hunger *vs.* satiety state using visual stimuli in healthy subjects. Fifty pairs of food-neutral and food-related objects were presented in a blocked design using a head-mounted display. The images were matched for proportionality and graspability (Fig. **4A**). A subtractive analysis of BOLD activity was performed to identify areas of the brain activated differentially by food-related *vs.* food-neutral visual stimuli. This paradigm was presented once after a 14 h fast and once one hour after *ad libitum* ingestion of a mixed meal (standard pizza). We found that activation of the anterior cingulate gyrus and the inferior and posterior insula after the fasting period was significantly greater than in the fed state (Fig. **4B**, upper row). In contrast, the satiety period revealed anterior medial frontal (superior frontal gyrus) activation. Apart from that, the inferior insula's activation lasted. This activation pattern is largely in agreement with the above mentioned PET data from other groups.

Once this paradigm has been further substantiated with data, it can be used to study the cerebral correlates of insulin and other hormones in the regulation of hunger and satiety in various clinical conditions.

Conclusions

Appetite and satiety are subject to complex regulations, with many other factors and neuroendocrine mechanisms playing an important role. The central nervous system is attracting increasing attention as a target tissue for many hormones, including insulin. Neuroimaging techniques may open novel exciting avenues for studying appetite and satiety regulation in the CNS. Exaggerated responses to food stimuli or decreased post-meal hunger attenuation may represent mechanisms for hyperphagia gradually leading to obesity, which we need to understand in more detail. With tools for imaging appetite and satiety becoming increasingly available, we may yet be able to stratify human obesity according to individual brain activation in the fed *vs.* hungry state, which may advance our understanding of human obesity and facilitate the development of specific pharmacological therapies.

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