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INSULIN–LEPTIN SIGNALING IN THE BRAIN

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Abstract: Energy homeostasis, a term used to designate the physiological processes that regulate the metabolic state, is controlled by different organs, including the brain. Leptin and insulin play a key role in the central control of feeding and body weight, with interconnected signaling pathways at various levels. In addition, central resistance to their actions has a primary role in the pathogenesis of obesity and type 2 diabetes. Studies performed in knockout mice for insulin targets show that the impairment of insulin signaling is related to changes in learning and memory. Moreover, circadian neurological alterations induce metabolic processes that lead to obesity and insulin resistance in patients with mental disorders. Thus, leptin and insulin signaling may be a link between the pathophysiological states affecting energy homeostasis and the appearance of mental illnesses. Pharmacological targeting for these signaling pathways could lead to important medical benefits in these diseases.

4.1 INTRODUCTION

This chapter first reviews the central regulation of food intake and energy balance. Brain insulin-leptin signaling mechanisms and the cross-talk between these hormones are described. Finally, some situations where metabolic disorders and neurodegenerative diseases associated with disturbances in leptin and/or insulin signaling are illustrated.

Current evidence indicates that the central nervous system (CNS) plays a key role in the control of food consumption and energy homeostasis. The regulation of body weight is the result of the combination of peripheral signals and central mechanisms where a negative feedback mechanism between other control systems seems to be implicated. According to this idea, peripheral signals related to energy homeostasis are sensed by central structures to induce physiological outputs that modulate feeding and energy expenditure. In addition, behavioral outputs are also involved in this response. Thus, the availability of nutrients via leptin and insulin signaling is detected and regulated not only in hypothalamic nuclei, but also in other brain regions, such as the hippocampus, a critical brain area for learning and memory functions, which plays a key role in the regulation of energy balance [1].

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Data show that obesity could be a risk factor for neurodegenerative disorders, especially Alzheimer disease (AD). Initial studies revealed that being obese when middle aged increases the risk of developing dementia in the future [2] and that inflammatory processes and hyperglycemia establish a relationship between fat mass and serum β-amyloid (Aβ) content [3]. Recently, a link between obesity and AD has been proposed to occur through several hormones that participate in the regulation of food intake and energy homeostasis, in particular, leptin and insulin [4]. Leptin signaling is involved in the central adaptation mechanisms to the changes in energy availability, with a direct association of plasma levels with body fat content [5] and the development of resistance to its action in situations of excess energy storage. Interestingly, the transport of leptin across the blood-brain barrier is impaired in obesity, whereas its central administration to AD-transgenic rodents decreases the brain Aβ load [6].

Insulin is an important modulator of the metabolic functions of the central nervous system, controlling food intake, glucose homeostasis, and metabolism [7,8]. Impairment of insulin signaling seems to play a key role in the onset of AD through its influence on the synthesis and degradation of Aβ peptides [9]. Insulin resistance, associated with type 2 diabetes mellitus (T2DM), is related to cognitive disorders in the CNS. In fact, hyperinsulinemia could be associated with reduced insulin transport across the blood–brain barrier [10]. Nevertheless, the neuroprotective effect of insulin is controversial, as recent data suggest that insulin accelerates Alzheimer-related pathology [11].

4.2 LEPTIN- AND INSULIN-RELATED SIGNALING IN THE CENTRAL REGULATION OF ENERGY HOMEOSTASIS

Control of energy balance requires the CNS to sense and act in response to changes in peripheral energy stores and glucose levels. Leptin and insulin are key hormones involved in the modulation of energy balance and glucose homeostasis involving the regulation of hypothalamic neurons, although other brain areas also modulate food intake and body weight [12].

Leptin is a hormone produced by adipose tissue and other tissues, including the brain [13], and it acts in the CNS to inhibit feeding behavior. In the hypothalamus, leptin reduces food intake and body weight by regulating the synthesis of both orexigenic and anorectic peptides produced mainly by neurons of the arcuate nucleus [14]. The mechanism involves the binding of leptin to the long-form of its receptor (Ob-Rb) and the subsequent autophosphorylation of Janus kinase 2 (JAK2) and the activation of signal transducer and activator of transcription 3 (STAT3) [15]. The phosphorylation of STAT3 at Tyr705 is a prerequisite for its dimerization and nuclear translocation, whereas Ser727 phosphorylation is required for DNA binding and activation of transcription. After the translocation of STAT3 to the nucleus, suppressor of cytokine signaling 3 (SOCS3) is activated, exerting feedback inhibition on JAK2 and insulin receptor substrate (IRS) (Fig. 4.1). Thus, an increase of SOCS3, as may occur in obesity and states of leptin resistance, can negatively modulate insulin signaling and leptin receptors. In addition, leptin can activate the IRS-phosphatidylinositol 3-kinase (PI3K) cascade, due to stimulation of tyrosine phosphorylation of IRS proteins by JAK2. Activation of the PI3K/protein kinase B (Akt) pathway may restrict food intake through the modulation of extracellular regulated kinases (ERKs) [16]. These kinases may exert their anorexigenic effects through inhibition of hypothalamic AMP-activated protein kinase (AMPK) that enhances food intake [17].

Insulin receptor activation induces tyrosine kinase activity, resulting in receptor autophosphorylation and subsequent phosphorylation of IRS proteins. This event activates PI3K that phosphorylates phosphatidylinositol-4',5'-biphosphatate (PIP2) on position 3', producing PIP3, which stimulates phosphoinositide-dependent protein kinase (PDK). This kinase phosphorylates Akt that enters the nucleus (Fig. 4.1), where it phosphorylates forkhead-O transcription factor (FOXO1). This results in FOXO1 exiting the nucleus and its inactivation, reducing its stimulatory actions on the transcription of orexigenic neuropeptides and its negative effect on anorexigenic peptides in the hypothalamus. In this way, it has been recently reported that overexpression of FOXO1 in the hypothalamus accounts for the development of two hallmarks of the metabolic syndrome, obesity and glucose intolerance [18]. Thus, due to this precise modulation of FOXO1, among

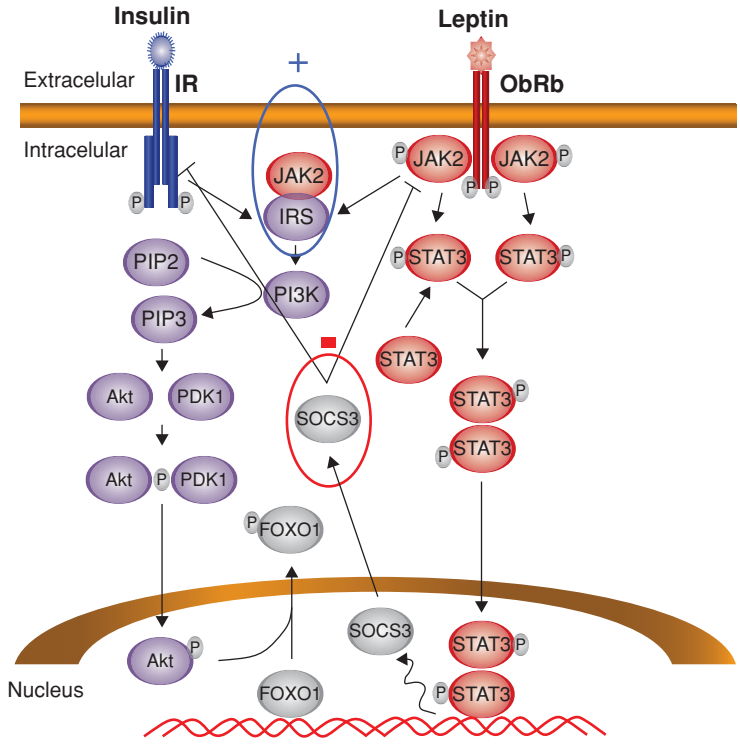

Fig. 4.1 Insulin and leptin signaling in the hypothalamus. Overlap (+, positive; −, negative) of insulin and leptin signaling are marked with a circle. Abbreviations: Akt, protein kinase B; FOXO1, forkhead-O transcription factor; IR, insulin receptor; IRS, insulin receptor substrate; ObRb, long-form of the leptin receptor; PI3K, phosphatidylinositol 3-kinase; JAK2, Janus kinase-2; PDK, phosphoinositide-dependent protein kinase; PIP2, phosphatidylinositol-4',5'-biphosphatate; SOCS3, suppressor of cytokine signaling-3; STAT3, signal transducer and activator of transcription-3. For a color version of this figure, please refer to the color plate.

other factors, one of the main central insulin actions is to reduce food intake.

Leptin and insulin receptors are also expressed in regions not classically associated with modulation of energy homeostasis including the hippocampus, the cerebral cortex, and the cerebellum [19, 20]. However, these areas may participate in the regulation of food consumption, which is closely related to cognitive functions [21]. Alterations of nutritional status are linked to changes in the expression of proteins, some of them regulated by leptin and insulin and involved in energy metabolism in the hippocampus [22]. On the other hand, leptin resistance is associated with changes in the affective state and cognitive function, both related to the impairment of hippocampal synaptic potential [23]. Moreover, amnesic patients with hippocampal damage are unable to inhibit the consumption of a second meal after having already eaten because they cannot remember their last meal [24]. Hippocampal damage in rats has been linked to increased appetite, leading to an increase in body weight [25], and the intake of a saturated-fat-rich diet has a negative effect on hippocampal oxidative stress and cognitive processes related to energy homeostasis [26].

Several studies provide further evidence that other brain areas are involved in eating behavior and control of energy balance. The cerebral cortex is important for metabolic control as selective lesions on this area alter feeding behavior [27]. Furthermore, some cytokines exert modulatory effects on homeostatic regulation in this area and activation of JAK2 and STAT3 has been described in neurons of the cerebral cortex [28] with decreased activity in the cortex of obese rats in the presence of food [29]. As obese rats are hyperleptinemic and may have high serum insulin

levels, modulation of the JAK/STAT pathway by both hormones could be involved in the decrease of cortical activity. Leptin and insulin promote changes in neuronal morphology through the ERK pathway, as well as modulation of the activities of certain neurotransmitters, and also participate in synaptic plasticity in this region [30, 31].

The cerebellum is a key area for the control of locomotor activity [32] and cerebellar insulin receptor levels have been shown to be reduced in experimental ataxia [33]. We reported an increase in p-Tyr705-STAT3 levels in the cerebellum after central leptin administration [34] and activation of STAT3 in hypothalamic AgRP neurons promotes locomotor activity in the cerebellum, whereas leptin-deficient rodents display reduced mobility [35]. There is evidence indicating that this area is involved in goal-oriented eating and animals with cerebellar lesions have reduced food-seeking behavior [36]. Finally, experimental cerebellar damage reduces body weight [37]. Thus, these hormones appear to be involved in cerebellar control of motor activity through activation of STAT3.

4.3 CROSS-TALK BETWEEN INSULIN AND LEPTIN SIGNALING IN THE BRAIN

As previously mentioned, leptin and insulin are key signals in modulating energy balance and body weight in the hypothalamus; however, other brain regions with structural and functional co-localization of leptin and insulin receptors also play a relevant role in modulating energy homeostasis [38]. During the last years, the molecular bases of the overlapping actions of these hormones in the modulation of energy balance have been partially elucidated. Among them, it is noteworthy that insulin induces the phosphorylation of JAK2, increasing activation of STAT3 [39]. Moreover, metformin, an antidiabetic drug, exerts its anorexigenic effects, at least in part, by enhancing central Ob-Rb expression [40]. Leptin increases levels of the catalytic subunit of PI3K and activates this kinase through JAK2 phosphorylation [41] and both hormones additively suppress food intake, acting in the same hypothalamic areas with significant cross-talk among their signaling pathways [42].

Development of resistance to the action of both hormones has a major role in the pathogenesis of obesity and T2DM. The interrelationship between these diseases and central signaling has been widely studied, emphasizing the impairment of PI3K pathway stimulation by leptin with no change in STAT3 pathway activation during the development of diet-induced obesity [43]. Chronic central leptin infusion may have a dual effect on insulin signaling, decreasing the central response to insulin by increasing SOCS3 association with the insulin receptor, which inhibits insulin signaling at the level of interaction of its receptor with IRS2 and the PI3K signaling pathway in the hypothalamus by enhancing the association between JAK2 and IRS2 [8]. Finally, leptin may reduce central and peripheral insulin signaling [44] by decreasing insulin receptor expression and reducing the association of IRS proteins with the regulatory subunit of PI3K [45]. Weight gain during diet-induced obesity also results in hypothalamic insulin resistance by reducing phosphorylation of protein kinase B, a marker of PI3K activity [46]. Insulin also induces SOCS3, which then inhibits the insulin receptor and inactivates leptin signaling by desphosphorylating Ob-Rb [47].

The parallel effects of leptin and insulin are unified on the proopiomelanocortin (POMC) neurons, with each hormone stimulating the PI3K pathway in the absence of synaptic inputs in POMC neurons [48]. In addition, intracerebroventricular injection of PI3K inhibitors blocks the capacity of both hormones [49], but not other anorexigenic peptides, to reduce food consumption, supporting the idea that the PI3K pathway is implicated in leptin and insulin metabolic actions in the brain. SOCS proteins have been reported as a negative regulator of intracellular cytokine signaling. Several members of this family, and in particular SOCS3, contribute to the development of leptin and insulin resistance due to their ability to reduce signaling of these anorexigenic hormones, mainly in the hypothalamus [50]. Finally, increased endoplasmic reticulum (ER) stress causes central leptin and insulin resistance; hence, central injection of the ER stress inducer thapsigargin modifies leptin and insulin signaling and inhibits the anorexigenic and weight-reducing effects of both hormones [51].

4.4 CENTRAL LEPTIN AND INSULIN RESISTANCE: CLINICAL IMPLICATIONS

4.4.1 Defective Intracellular Signaling and Metabolic Alterations

Abnormalities in neuronal leptin-insulin signaling have been reported to play a role in metabolic syndrome and neurodegenerative diseases. Leptin can modify learning and memory in the hippocampus by increasing long-term potentiation [52], and leptin signaling deficiency may affect neuronal plasticity, as has been described in the leptin receptor deficient db/db mouse. These mice present impairment similar to that described in rats with streptozotocin-induced diabetes [53]. Central insulin signaling has important effects in maintaining normal glucose homeostasis and, interestingly, leptin can improve or normalize glycemia in states of insulin-deficiency by mimicking the actions of insulin [54].

Brain leptin concentrations depend on local synthesis and transport to the brain and obesity may also affect the amount of leptin reaching the CNS. Leptin crosses the blood-brain barrier through a saturable transport system and obese patients, with hyperleptinemia, have lower cerebrospinal fluid leptin concentrations than lean subjects [55]. Several data support the hypothesis that brain resistance to leptin in obese subjects with peripheral hyperleptinemia is due to diminished efficacy of leptin transport to the brain and not to intra-hypothalamic insensitivity [56]. Decreased activation of leptin signaling increases the expression of orexigenic neuropeptides and appears to be related to sudden onset diabetes in knockout models of diabetic mice. In addition, disruption of leptin signaling to the interactive hypothalamic network of orexigenic neuropeptides contributes to metabolic derangements related to the metabolic syndrome [57].

On the contrary, increased leptin availability in the hypothalamus reduces glycemia and attenuates the response to a central insulin bolus [8] and central leptin infusion maintains euglycemia in leptin deficient ob/ob mice, as well as in animals receiving a high-fat diet [58]. Moreover, the concomitant activation of hypothalamic leptin and insulin pathways seems to be linked to a nondiabetic phenotype and exerts a protective effect against hypothalamic deregulation of appetite [59].

It has been reported that experimental obesity/hyperleptinemia damages hippocampal synaptic transmission and that the deficit is closely related to the impairment of leptin activity in the hippocampus, whereas food restriction attenuates these symptoms [26]. Hyperleptinemia is associated with an increased onset of depressive symptoms, especially in the presence of abdominal obesity, suggesting that underlying leptin resistance may play a deleterious role [60]. On the other hand, leptin infusion has been shown to induce antidepressive behavior in a forced swimming test [61]. Nevertheless, leptin also has adverse effects, as central infusion increases several acute-phase proteins and cytokines promoting a systemic inflammatory profile compatible with metabolic alterations [62].

The brain insulin/PI3K pathway is essential for glucose and energy homoeostasis. Interventions that reduce insulin receptors or insulin-dependent activation of this pathway lead to acute hyperglycemia, reduced fat mass, and lower insulin sensitivity to inhibit endogenous glucose synthesis [63]. The amount of insulin reaching the brain, central insulin biosynthesis, and intracellular signaling are modulated by nutritional status, with a disruption of these mechanisms in response to high-fat feeding [64]. Likewise, deregulation of insulin transport to the brain and central insulin resistance to this hormone has been reported in post mortem studies of obesity, diabetes, and degenerative disorders, as well as in experimental models of these diseases [65,66]. Additionally, inflammation and metabolic disturbances increase with aging due to alterations in this pathway [67].

Several studies in models of food restriction and diet-induced obesity demonstrate abnormal insulin action in the CNS [68, 69]. These reports show that starvation or access to high-fat diets for short- and medium-time periods alter central insulin actions on food consumption, as well as glucose and energy homeostasis.

4.4.2 Leptin, Insulin, and Neurodegenerative Diseases

Leptin, in addition to having a hypothalamic role in energy homeostasis, also has extra-hypothalamic functions, modifying hippocampus, midbrain, and

hindbrain through the increase of neurogenesis, axonal growth, and synaptogenesis [70]. Leptin-deficient patients have reduced brain weight, myelination, and synaptogenesis, whereas a positive effect of leptin therapy on homeostatic, reward, and food-related brain areas has been described, possibly due to these stimulatory leptin effects [71]. In addition, leptin is a potent neurogenic factor in the cortex, not only inducing structural changes, but also modifying neuronal excitability [72], suggesting a cognitive role of leptin in this area.

This hormone also reduces cell death caused by serum or neurotrophin withdrawal in hippocampal cell cultures through the activation of JAK2/STAT3 pathway [73]. These neuroprotective effects of leptin have also been demonstrated *in vivo*, reversing dopaminergic neuron loss in an experimental model of Parkinson disease (PD). Leptin decreases caspase activation levels through a mechanism involving the phosphorylation of JAK2 and ERKs, with a positive effect of leptin on brain-derived neurotrophic factor also being involved, as this factor is a survival molecule for dopaminergic neurons reduced in PD [74]. In AD, leptin attenuates β-secretase processing of amyloid precursor protein (APP) in neurons and can reduce Aβ load levels, probably through processes that change the composition of membrane lipid rafts [6]. Nevertheless, high leptin levels, as well as other adipokines, may have adverse effects in other degenerative diseases, such as multiple sclerosis (MS) and other inflammatory disorders. Leptin production is enhanced both in serum and cerebrospinal fluid of patients with multiple sclerosis [75]. In addition, it has been demonstrated that leptin can promote experimental autoimmune encephalomyelitis in an animal model of MS [76].

Neuronal insulin receptor signaling has a key role in energy homeostasis status and the development of neurodegenerative diseases. Hence, the coincidence of metabolic disturbances where central insulin sensitivity is affected, such as obesity, insulin resistance, or diabetes with neuropsychiatric diseases, particularly AD, has been reported in humans and in experimental models [77, 78]. Particularly, eating disorders are serious mental illnesses where dysfunctions in insulin signaling pathways [79] and in the insulin-like growth factor (IGF) axis [80] have been implicated in the pathophysiological mechanisms.

In the CNS, insulin, together with members of the IGF axis, regulates cognitive functions after binding to its receptors and activation of intracellular signaling through interaction of the phosphorylated receptor and IRSs, promoting inhibition of apoptosis and stimulation of metabolism and plasticity in a mechanism mediated by phosphorylation of Akt [81] and inhibition of GSK3β. These processes are altered in an experimental model of AD [82] and activation of PI3K/Akt mediates neuroprotection in AD and PD models [83, 84].

Although the molecular mechanism linking AD and type 2 diabetes remains partially undetermined, several reports show a link between impaired PI3K signaling and aberrant Aβ production [85] or hyperphosphorylation of tau due to lower activation of Akt and increased GSK3β levels [86]. Insulin accelerates βAPP/Aβ trafficking to the plasma membrane and metformin reduces neuropathology related to Alzheimer disease in obese mice [87], whereas lower activation of the IRS/PI3K pathway disrupts the processing of Aβ, increasing AD-related symptoms [66].

4.5 CONCLUSION

Evidence is accumulating to indicate that leptin and insulin interact to play an essential role in regulating brain functions related to the modulation of food intake and energy balance. Receptors for both hormones are ubiquitously present in the brain and regulate not only glucose homeostasis, but also several CNS functions, such as reward, cognition, and memory. Disruption of central leptin- and insulin-signaling mechanisms causes adverse changes in energy homeostasis closely related to the appearance of metabolic disorders. The relationship between obesity, leptin-insulin resistance, and type 2 diabetes and neurodegenerative disorders has been demonstrated in the last years and several studies indicate that some degenerative diseases may be hypothesized to be metabolic diseases with progressive impairment in the use of glucose. Thus, pharmacological targeting of leptin- and insulin-signaling pathways could be favorable for the normalization of brain related-metabolic functions.

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