Title: Hippocampal insulin resistance and altered food decision-making as players on obesity risk

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Abstract: There are increasing evidences that hippocampus can modulate the decision of what, when and how much to eat, in addition to its already recognized role in learning and memory processes. Insulin also has been linked to brain functions such as feeding behavior and the imbalance of its mechanism of action on hippocampus is being related to cognitive dysfunction. The discussion here is whether changes in insulin action could contribute to intake dysregulation and obesogenic behavior as a primary consequence of impairing hippocampal functioning, aside from the role of this hormone on obesity development through peripheral metabolic pathways. Excess intake of high-fat and high-sugar diets leads to insulin resistance, which disrupts hippocampal function. Hippocampal physiology is sensitive to signals of hunger and satiety, inhibiting the ability of food cues to evoke appetite and eating, therefore alterations in hippocampal integrity could affect food inhibitory control leading to increased intake and obesity.

Key- words: Feeding behavior; cognitive decline; metabolic syndrome.

1. Obesity: a growing concern

Obesity is considered pandemic as it occurs in a wide geographical area affecting an exceptionally high proportion of the population (Wylie-Rosett, 2004). The higher frequency of obesity was first observed in the United States but has spread to other industrialized countries and also occurs in developing countries such as Brazil (Caballero, 2007). In 2014, 39% of the adults worldwide were overweight, and 13% were obese; rates that were twice as big as observed since 1980 (WHO, 2016)..

Obesity is characterized by body mass index of >30 kg per m^2, which is mainly the result of an increase in fat mass. This condition occurs when there is an unbalance between calories that are consumed as compared to what is wasted and it can negatively affect health and decrease longevity (Flegal et al., 2013; Mitchell et al., 2011). The reasons why excessive intake occurs and how it leads to obesity are not fully understood, but it is known to involve genetic, physiological, metabolic, behavioral and cultural factors.

The concern about obesity relies on the fact that it is considered the fifth largest risk factor for disease worldwide, being a major risk factor for non-communicable diseases (Dulloo et al., 2010; Keller and Lemberg, 2003; WHO, 2016). Excess fat, especially in the central region of the body, is related to the most prevalent and costly current medical problems such as type 2 diabetes, coronary artery disease, gastrointestinal problems, respiratory complications, osteoarthritis and various types of cancer (Haslam and James, 2005; WHO, 2016). Furthermore, obesity is closely associated with metabolic syndrome, which is characterized by hyperinsulinemia, insulin resistance, glucose intolerance, atherogenic dyslipidemia, hypertension, and increased expression of pro-thrombotic and pro-inflammatory markers (Olufadi and Byrne, 2008).

Obesity is also related to brain vulnerability and cognitive disorders, both in humans (Bruce-Keller et al., 2009; Galioto et al., 2013; Whitmer et al., 2005; Wolf et al., 2007) and in

rodents (Bruce-Keller et al., 2009; Greenwood and Winocur, 2001; Winocur and Greenwood, 2005). As showed in many studies, obese humans (Benito-Leon et al., 2013) and rodents (Goldbart et al., 2006; Jurdak et al., 2008; Molteni et al., 2002; Park et al., 2010; Winocur and Greenwood, 1999) that consume hyperlipidemic and hypercaloric diets perform worse on learning and memory tests as compared to those with normal weight and to those who eat more healthy diets. In addition, clinical studies in humans show that abdominal fat and high body mass index are associated with reduced brain volume (Debette et al., 2010) and specific cortical thinning (Medic et al., 2016).

According to Sethi and Vidal-Puig (2007), there is an increased uptake of nutrients from the circulation to the periphery, particularly in insulin sensitive tissues shortly after food intake. During periods of fasting, the movement of molecules takes place in the opposite direction. In obesity, however, this bidirectional energy flow is altered due to endocrine dysfunction of adipose tissue and therefore decreases the effectiveness of endocrine mechanisms in the tissues (Caimari et al., 2010; Kahn et al., 2006; Lopez et al., 2003). Adipose tissue has humoral and hormonal regulation, and numerous functions, for example, insulation, physical barrier to trauma, energy storage and protein secretion with autocrine, paracrine and endocrine action. Secreted proteins, also called adipokines, can impact on biological aspects, including energy homeostasis, immune, cardiovascular, reproductive and neurological functions (Bruce-Keller et al., 2009; Sethi and Vidal-Puig, 2007). The extra supply of glucose and free fatty acids through exaggerated food intake with consequent increase in adipokines secretion (such as leptin and others) by adipose tissue growth, contributes to the onset of insulin resistance. This condition is characterized by reduced biological action of insulin on target cells, with dysfunctions on uptake, metabolism and glucose storage at physiological concentrations of insulin (Kahn and Flier, 2000; Zeyda and Stulnig, 2009).

Many researchers are nowadays focusing in the association between insulin and the neurophysiology of hippocampus, an important region for learning and memory development and also eating behavior (Biessels and Reagan, 2015). Aside from the peripheral role of insulin on obesity development, we aim to discuss here a different way by which this hormone may, by acting centrally, influence obesogenic behavior and lead to excessive calorie intake. It is important to understand how metabolic and neural signals interact with each other on eating behavior. Thus, in this review we will focus on insulin action in the hippocampus and its consequent impaired memory related to food intake as well as the association between eating inhibition and insulin resistance.

2. Regulation of eating behavior

Animals must get enough food from its environment for its energy expenditure as an essential requirement for survival. The physiological state that makes an animal or a man seek food is called hunger. However, feeding behavior is not only an event that occurs to satiate hunger and that ends when hunger is finished throughout a metabolic feedback. A better way to describe feeding behavior is that it is controlled by homeostatic (bottom-up) but also hedonic (top-down) mechanisms, involving emotional, reward and cognitive factors.

Although the arcuate nucleus of the hypothalamus is one of the main areas of the central nervous system (CNS) responsible for the control of intake and energy homeostasis, feeding behavior is also modulated by the predicted reward values processed predominantly by the cortico-limbic structures (Berthoud, 2011). Deregulation of these systems leads to changes in consumption and predicts weight gain and obesity (Davis et al., 2011; Levitan et al., 2004; Silveira et al., 2016).

2.1. Memory of eating and obesity

In addition to the vast evidence that impulsive eating can result from an over-activation or a faulty signaling in the reward system components (Hebebrand et al., 2014; Johnson and Kenny, 2010; Luo et al., 2013; Volkow et al., 2011), some studies show that uncontrolled eating behavior can also be a result of a failure in cognitive inhibitory control related to food (Batterink et al., 2010; Bruce et al., 2010; He et al., 2014; Rangel, 2013). Food and its stimuli are cues that may evoke vigorous appetitive and consummatory responding on some occasions and little or no responding at other times. Thus, animals engage in appetitive and eating behavior until they become satiated and then refrain from making these responses until satiety wanes (Davidson et al., 2007; Davidson and Martin, 2014). Therefore, under conditions of negative energy balance,

114 appetitive behaviors and food intake produce the rewarding effects of returning to homeostasis;
115 however, once homeostasis is achieved, these behaviors no longer produce rewarding
116 postingestive outcomes and could instead be followed by unpleasant consequences. According to
117 some authors (Davidson et al., 2005), animals learn to anticipate both of these outcomes, and
118 based on these associations, the food cues should excite or activate the stored representation of
119 that reward (i.e., its memory) on subsequent occasions.

120 It has been shown that increasing awareness of food as it is eaten (Higgs and Woodward,
121 2009; Wansink and Payne, 2007), as well as simple recall of foods eaten at the last eating
122 occasion decrease food intake in the following meal (Higgs, 2002). Robinson and colleagues
123 (Robinson et al., 2013) suggest that these processes enhance episodic memory representation of
124 the food consumed, and this information is used to process subsequent decisions about how
125 much to eat (Brunstrom et al., 2012; Higgs, 2002; Higgs et al., 2012). Distraction exerts a greater
126 influence on later intake than it does on immediate consumption, suggesting a larger effect as the
127 memory of that eating episode fades (Robinson et al., 2013). In addition, it was shown that
128 overweight adolescents have a memory bias in the recollection of high caloric food cues (that
129 was not associated with better memory in general), suggesting a more elaborative encoding of
130 this type of information or a bias at the retrieval stage of memory processing (Soetens and Braet,
131 2007).

132 Satiety regulation is a dynamic interaction process of peripheral signals such as hormones
133 and different brain structures and neurotransmitter systems also involving the hippocampus. The
134 hippocampus, classically associated with memory, is also recognized as a feeding behavior
135 modulator (Parent et al., 2014) once it has many receptors for pre and post-prandial signals, such
136 as insulin, leptin, ghrelin, glucose, cholecystokinin, glucocorticoids, NPY, galanin and bombesin
137 (Lathe, 2001). In addition, the hippocampus receives neural signals related to food stimuli from
138 different brain regions, such as the arcuate nucleus, nucleus of the solitary tract, insula and

orbitofrontal cortex (Wang et al., 2006) and sends efferent projections to other regions that can influence ingestive behavior, such as the hypothalamus, stria terminalis, and nucleus accumbens (Hsu et al., 2015; Kahn and Shohamy, 2013).

Hippocampal connectivity with striatum and neocortex throughout projections of parahippocampal region can also contribute directly to value assignment and decision-making in general, even without conscious awareness, dynamically modulating value representations during learning itself, allowing value to spread and biasing decisions without effortful retrieval at the time of decision (Wimmer and Shohamy, 2012). These properties could well influence food intake as the hippocampus has been suggested to be a discriminatory retention region for food cues. It is involved in the learned anticipatory response to environmental cues associated with eating (Davidson et al., 2007) and the inhibitory control of food intake and appetitive behavior depends on its structural integrity (Hebben et al., 1985; Rozin et al., 1998).

The influence of the hippocampus on food intake is mediated by adiposity signals, being related to the connection to the hypothalamus, and playing a role in body weight changes (Davidson et al., 2007), as shown in several rodent studies (Davidson et al., 2010; Forloni et al., 1986). Interestingly, overeating impairs hippocampal functioning, which contributes to the development and/or maintenance of diet-induced obesity in rodents (Davidson et al., 2013; Kanoski and Davidson, 2011). Hippocampal dysfunction increases meal frequency, total energy intake, and weight gain in rats (Davidson et al., 2010; Davidson et al., 2005). In humans, the famous H.M. case illustrates the importance of the hippocampus to integrate the information of internal metabolic states and willingness to eat; H. M., a patient that became amnesic after a bilateral resection in the medial temporal lobe region for epilepsy, had altered perception of internal states and would eat a second full dinner 1 min after he had completed the first one (Hebben et al., 1985).

Given that a host of life events that can impair hippocampal function, including excess intake of sugars and fats as shown in animal studies (Davidson et al., 2013; Freeman et al., 2011; Goldbart et al., 2006; Kanoski and Davidson, 2011; Kanoski et al., 2010; McNay et al., 2010; Molteni et al., 2002; Morris et al., 2016; Park et al., 2010; Tozuka et al., 2009) it is possible that diet-induced obesity is caused, at least in part, by impaired hippocampal inhibition of meal onset (Parent et al., 2014). Eating high-fat and high-sugar diets may impair hippocampal inhibitory control of eating behavior, perhaps because it becomes insensitive to satiety states and does not properly store information related to previous meal. The so called “western” diet seems to reduce hippocampus’ ability to resist the environmental food cues (Davidson et al., 2007; Davidson and Martin, 2014) and increases the chance of overeating, excess weight gain, and more severe forms of cognitive impairment.

3. Physiological role of insulin

Insulin, a molecule composed by two polypeptide chains of 21 and 30 amino acids (Reid et al., 1968), is produced by pancreatic islets beta cells and is secreted into circulation with anabolic functions. This hormone promotes the deposition of substrates in the form of nutrients in tissues and, on the other hand, inhibits catabolism. Insulin promotes the transport of mainly glucose (but also amino acids and free fatty acids) from the extracellular compartment to inside the cells with consequent decrease in their circulating levels (Dimitriadis et al., 2011). Moreover, it can regulate the rate of carbohydrates used by most cells. Immediately after a high carbohydrate meal, the glucose absorbed into the blood may induce a rapid secretion of insulin (Aronoff et al., 2004) that promotes glucose uptake, storage and utilization by almost all body tissues, especially skeletal muscle, adipose tissue and liver (Pansuria et al., 2012). Also, insulin is responsible for inhibiting liver, kidney and small intestine glucose production in order to maintain glucose homeostasis (Wilcox, 2005).

Once released into the blood, insulin binds to a specific plasma membrane glycoprotein receptors on its target cells. Insulin receptor (IR) activation induces autophosphorylation of the tyrosine residues of the docking protein known as insulin receptor substrate (IRS), and leads to activation of several signaling cascades including phosphoinositide 3 kinase (PI3K)/Akt (at the metabolic tissue) and the mitogen-activated protein kinase (MAPK) pathways (Dimitriadis et al., 2011), that may increase or decrease the expression and the activity of IR. IR stimulates rapid glucose uptake in muscle, adipocytes, pancreatic and hepatic cells via translocation of glucose transporter type 4 (GLUT4) vesicles (Saltiel and Kahn, 2001) and also controls glycogen/lipid/protein synthesis, specific gene expression and energy metabolism (Pansuria et al., 2012). The MAPK pathway transmits a signal surface to the nucleus, controlling different biological responses such as cell growth, proliferation, differentiation, and cell death (Zhang et

al., 2011). Of the six IRS families described, IRS-1 and IRS-2 are involved in most of the effects of insulin in these two signaling pathways.

3.1. Insulin in the central nervous system

For a long time, it was believed that the brain was not insulin-dependent, but insulin and its receptors are found in abundance in the olfactory bulb, hypothalamus, and hippocampus, among other regions, both in humans and in rodents (Havrankova et al., 1978; Hill et al., 1986; Schulingkamp et al., 2000). Insulin is actively transported across the blood-brain barrier and it may even be produced locally in the brain, although most brain insulin is thought to be originated from the systemic circulation (Bingham et al., 2002; Ghasemi et al., 2013). Elevations in circulating insulin can alter brain function, augmenting the counter regulatory response to hypoglycemia (Fruehwald-Schultes et al., 1999). Physiologically relevant increases in plasma insulin levels also stimulate the translocation of GLUT4 to the plasma membrane in many CNS areas (McEwen and Reagan, 2004), even if the carrier is not as abundant in the CNS as GLUT1 and GLUT3 (Blazquez et al., 2014).

Many studies have shown a relationship between IR signaling and ion channels and receptors expression at synapses in various regions of the CNS, suggesting that insulin and IR can regulate synaptic plasticity and cognitive functions (Biessels and Reagan, 2015; Gispen and Biessels, 2000). Their location on hippocampal glutamatergic synapses indicates a role of insulin in the transmission and synaptic plasticity and modulation of learning and memory (Irvine et al., 2011; Muller et al., 2011; Skeberdis et al., 2001). In addition, IRS-1 inhibition is described in Alzheimer's disease and related animal models (Bomfim et al., 2012; Moloney et al., 2010), and the reversion of this inhibition improves cognitive outcomes in mice (Bomfim et al., 2012). It is also recognized the trophic function of insulin referred to proliferation, differentiation, and neurite growth (Lee et al., 2011; Xu et al., 2004).

Astrocytes are also known to express both IR and insulin signaling pathway proteins (Stern et al., 2014). Neurons from CNS depend on astrocytes for energy metabolism, maintenance of the blood-brain barrier, vascular reactivity, regulation of extracellular glutamate levels, protection from reactive oxygen species, amyloid-beta peptides, and spread of inflammatory cells (Koistinaho et al., 2004; Zonta et al., 2003). Diabetes-related disturbances in the brain are associated with changes in astrocytes activity and can be prevented with insulin treatment (Coleman et al., 2010).

Moreover, insulin receptor signaling controls vessel dilation and contraction and regulates monocyte differentiation into macrophages (Baron, 1994; Laakso and Kuusisto, 2014; Pansuria et al., 2012), explaining why people with type II diabetes mellitus (T2DM) are more susceptible to central lesions, white matter hyperintensities, and brain atrophy than people without T2DM (de Bresser et al., 2010). Patients with T2DM also have increased levels of amyloid polypeptide deposits in and around blood vessels, which may be involved with their risk to develop vascular and neurological pathologies (Oskarsson et al., 2015). Insulin has also been shown to be important in maintaining the integrity and permeability of the blood-brain barrier (Hawkins et al., 2007; Sartorius et al., 2015).

Figure 1 - Insulin receptor activation on central nervous system (more specifically, in the hippocampus). Pancreas-derived insulin binds to receptors on endothelial cells of the blood-brain barrier, where it is transported into the brain interstitial fluid by a saturable process of receptor-mediated transcytosis. As soon as insulin binds its receptors (distributed throughout the cerebral cortex, hippocampus, hypothalamus, amygdala, olfactory bulb and septum) they become activated as a tyrosine kinase, leading to autophosphorylation of the IR subunits and phosphorylation of the tyrosine residues of its docking protein (insulin receptor substrate). This activates both the phosphoinositide 3 kinase (PI3K)/Akt and the mitogen-activated protein

kinase (MAPK) pathways. The PI3K/Akt pathway seems to be associated with metabolic signaling, including an increase of glucose transporter from the GLUT4 translocation and subsequent conversion to ATP, while the MAPK pathway is associated with mitogenic signaling. Both these pathways of insulin signaling and glucose utilization are recognized to be important for neuronal function and required for neuronal synaptic plasticity and for learning and memory. Impaired insulin signaling leads to synaptic dysfunction and altered glucose homeostasis that impacts energy metabolism, osmolarity, redox balance and could contribute to increased depots of amyloid precursor protein (APP), Aβ accumulation and tau hyperphosphorylation. These alterations lead to cognitive impairment and are accompanied by astrogliosis and possibly by neuroinflamation. Insulin receptor substrate (IRS); Phosphoinositide-dependent kinase-1 (PDK1); Protein kinase B (AKT); Phosphatidylinositol 3 kinase (PI3K); Growth factor receptor-bound protein 2 (GRB2); Son of Sevenless (SOS); Mitogen-activated protein kinase kinase (MEK); Extracellular signal-regulated kinase (ERK); Mitogen-activated protein kinase (MAPK); Forkhead box protein O1 (FOXO1). Adapted from (Verdile et al., 2015) and (Duarte, 2015).

3.1.1. Insulin in the hypothalamus and mesocorticolimbic system

Insulin functions as a body adiposity signal, as it is secreted in proportion to body fat mass, and thus provides information about the status of long-term energy stores (Woods and D'Alessio, 2008). It acts by moderating satiety signals generated by a meal in the brain tissue (Schwartz et al., 2000; Woods et al., 1998), influencing the amount of food consumed in a meal and also contributing to body weight regulation and reproduction (Bruning et al., 2000; Rodin et al., 1985).

Insulin is involved in feeding control and energy balance by regulating orexigenic and anorexigenic neurons (Palou et al., 2009). The IR is expressed by neurons in the arcuate nucleus and found both in POMC and AgRP neurons. In general, NPY/AgRP neurons are directly

inhibited by insulin (as by leptin), while POMC/CART neurons are stimulated by these hormones (Mayer and Belsham, 2009). During the cephalic phase of eating behavior, peripheral changes in the insulin to glucose ratio are detected by these hypothalamic neurons, stimulating appetite by increasing the expression of both NPY and AgRP and decreasing POMC and CART expression (Berthoud and Jeanrenaud, 1982; Palou et al., 2009). During the gastric phase, insulin secretion is stimulated by gastrointestinal hormones such as CCK, but the release of insulin is higher when food is absorbed in the intestine (intestinal phase) and glucose levels rise. This increase in insulin due to increased glycemia during postprandial state has an anorexigenic effect by acting on the same NPY and POMC hypothalamic neurons (Langhans et al., 2001; Palou et al., 2009). On the other hand, animals that lack or are insensitive to insulin are known to be hyperphagic and to gain weight, thus central administration of this hormone can reduce food intake and body weight (Gomez-Pinilla, 2008; Schwartz et al., 2000; Stockhorst et al., 2004).

Moreover, food intake is regulated via insulin in the mesolimbic system (Figlewicz, 2003; Figlewicz and Benoit, 2009), since there are IRs in the ventral tegmental area (VTA) and ventral striatum (Li et al., 2009; Mebel et al., 2012; Woods et al., 2016) as shown in experimental studies. Insulin suppresses dopamine release in the VTA, which decreases food "wanting" (Mebel et al., 2012). The decreased sensitivity to insulin in CNS limbic regions results in increased food consumption and in inaccurate valuation of foods, contributing to impulsive eating and obesity (Figlewicz et al., 2004; Woods et al., 2016). Another way by which insulin influences feeding behavior is modifying the sensory properties of food, by acting on olfactory mucosa and decreasing olfactory perception in rodents (Savigner et al., 2009) and humans (Ketterer et al., 2011).

Recent fMRI studies in humans suggest the existence of functional connections between the hypothalamus and different parts of the fronto-striatal circuitry of the brain (Kullmann et al., 2014). In addition, glucose ingestion increases the functional connectivity between the

hypothalamus and the striatum, possibly via insulin (Page et al., 2013). Activity in the putamen, orbitofrontal cortex and insula correlate positively with enhanced peripheral insulin sensitivity via intranasal insulin application in humans (Heni et al., 2012; Kullmann et al., 2013a).

Finally, the prefrontal cortex plays an important role modulating feeding behavior and choices in humans, being involved in inhibitory control (lateral prefrontal cortex) (Hare et al., 2009) and reward-based decision-making (orbito-frontal cortex and anterior cingulate) (Rolls, 2004). All prefrontal regions are responsive to insulin (Guthoff et al., 2010; Heni et al., 2014a; Heni et al., 2012; Karczewska-Kupczewska et al., 2013; Kroemer et al., 2013; Page et al., 2013; Page et al., 2011). Exogenous intranasal insulin administration causes a decrease in the response of the prefrontal cortex to food pictures (Guthoff et al., 2010), and insulin increases after a glucose load are associated with reduced activation in frontal and limbic regions (Kroemer et al., 2013). Therefore, brain insulin signaling in the striatal-frontal regions seems to act on value attribution and decision making negatively modulating food intake.

3.1.2. Insulin on the hippocampus

Insulin improves cognitive performance in humans and animals, including young healthy adults (Kern et al., 2001) and individuals with Alzheimer's disease (Chen et al., 2016; Freiherr et al., 2013), young rats (Haj-ali et al., 2009), aged rodents (Haas et al., 2016; Maimaiti et al., 2016) and animal experimental models with insulin resistance (Greenwood and Winocur, 2001; McNay et al., 2010). Studies using intranasal insulin administration show that this hormone is involved in cognition and particularly memory development (for a review, see (Ott et al., 2012)). Intracerebroventricular injection of insulin immediately after inhibitory avoidance training leads to memory enhancement 24h after training in rodents (Park et al., 2000). Intracerebroventricular or hippocampal injection of insulin also enhances spatial working memory and water maze memory dependent of PI-3K, increasing local glycolytic metabolism (Haj-ali et al., 2009;

McNay et al., 2010; Stern et al., 2014). Furthermore, this hormone promotes neural growth in the hippocampus and the impairment of central insulin receptors is associated with learning and memory deficits (Stockhorst et al., 2004). Additionally, hippocampal-dependent spatial learning tasks, such as the Morris water maze, increase the hippocampal IR signaling in rodents (Zhao et al., 1999). These data highlight that IR cascade activation in the hippocampus is associated with cognitive performance (Cholerton et al., 2013).

The hippocampal development is particularly sensitive to changes in glucose homeostasis (Amin et al., 2013). As in the periphery, central insulin action results in translocation of the neuronal insulin-sensitive GLUT4 to the plasma membrane of hippocampal neurons (Grillo et al., 2009), which increases their glucose uptake. It also decreases glucose extracellular levels, and increases lactate levels in the extracellular space, indicating an increase in local glycolytic metabolism (McNay et al., 2010). Hippocampal cell culture experiments suggest that the dendritic distribution of insulin receptors is in accordance with a synaptic localization (De Felice et al., 2009; Zhao et al., 2008). Insulin also induces synaptogenesis, modulates the synaptic function, and regulates dendritic spine formation and excitatory synapse development in hippocampal neurons through the activation of PI3K/mTOR pathway (Lee et al., 2011; Lee et al., 2005) and upregulation of tau protein (Nemoto et al., 2011).

N-Methyl-D-Aspartate receptors (NMDARs) are part of the ionotropic glutamate receptors family and glutamate is known as the major excitatory neurotransmitter of the nervous system (Paoletti et al., 2013). The specific patterns of neuronal activity occurring by calcium flow through these receptors are converted into long-term changes in synapse structure and function, essential for memory, behavioral inhibition and other cognitive functions (Baker and Kim, 2002; Taylor et al., 2014). In hippocampal synapses, the NMDARs complex in the post-synaptic density (PSD) is a structure intimately involved in the regulation of synaptic plasticity (Gardoni et al., 2002). The impairment of synaptic plasticity in streptozotocin (STZ)-induced diabetic rats

is associated to an inappropriate level of NMDARs stimulation required for the induction phase of long-term potentiation. In fact, insulin can potentiate current flow through NMDA, and the Tyr-phosphorylation of the subunits GluN2A and GluN2B of the NMDARs, an important component of signal transduction mechanisms occurring in PSD, is mediated by insulin in hippocampal slices (Christie et al., 1999). Additionally, IR and the insulin receptor substrate-1, 2 and p58/p53 (IRS-1, 2, and p58/p53) are components of PSD (Abbott et al., 1999). In mice that lack IRS-2, there is a deficit in NMDA receptor-dependent synaptic plasticity in the hippocampus, with concomitant deficits in the modulation of synaptic plasticity, and these changes are associated with reduced basal phosphorylation of the NMDA receptor subunit GluN1 as well as downstream targets of the PI3K pathway (Costello et al., 2012). This suggests that insulin modulates synapse plasticity by stimulating long-term depression and potentiation, which are involved in memory representation (Feldman, 2009) reviewed in (Moult and Harvey, 2008).

The expression and concentration of GluN2B are significantly reduced in hippocampal PSD in STZ-treated rats (Di Luca et al., 1999; Muller et al., 2011) (Di Luca et al., 1999; Muller et al., 2011), but insulin can prevent the decreased Tyr-phosphorylation in hippocampal pyramidal cells of these animals (Gardoni et al., 2002). The disturbances of the NMDARs on STZ-diabetes are the result of a slowly progressive process, rather than an acute insult caused by hyperglycaemia, and at least part of the learning and plasticity deficits in STZ-rats may be a direct consequence of disturbances at the level of the NMDARs complex.

Interestingly, human fMRI studies show a significant positive correlation between fasting plasma insulin levels and hippocampal activity after stimulation with high-caloric food images strongly suggesting a link between insulin signaling pathways, hippocampal activation, and craving behavior to food cues in humans (Avena et al., 2008; Hargrave et al., 2016; Pelchat et al., 2004; Wallner-Liebmann et al., 2010). Hippocampal neighboring gyri (parahippocampal and

fusiform gyri) are linked to neural pathways of visual recognition, especially visual food cues (Kullmann et al., 2013b; van der Laan et al., 2011), being particularly sensitive to insulin. These findings corroborate the idea that the hippocampus participates in the identification of external signs of food and that insulin is closely linked with that role of the hippocampus in feeding behavior, possibly reducing the attention to food cues (Kullmann et al., 2016).

4. Implications of insulin resistance

There are many factors that can explain the mechanisms of insulin resistance, including obesity, inflammation, mitochondrial dysfunction, hyperinsulinemia, lipotoxicity/ hyperlipidemia, genetic background, endoplasmic reticulum stress, aging, oxidative stress, fatty liver, hypoxia, lipodystrophy, and pregnancy (Ye, 2013). In obesity, the increase in glucose and free fatty acids by high food intake, as well as by adipose tissue growth products including hormones such as leptin and cytokines, contribute to the onset of insulin resistance (Kahn et al., 2006). In obese individuals, adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines, and other factors that are involved in the development of insulin resistance (Hotamisligil, 2003).

This dysfunction occurs when insulin-sensitive tissues progressively become less responsive to insulin and, consequently, insulin-induced glucose uptake is impaired. The failure may be the result of changing insulin signaling in target tissues (reduced concentration and kinase activity of IR, limited concentration and phosphorylation of IRS-1 and 2 of PI activity 3-kinase, low GLUT4 translocation and diminished activity of intracellular enzymes). In addition there is a down-regulation of GLUT4 in adipocytes (Petersen and Shulman, 2006). Thus, there is a dysfunction in glucose uptake, metabolism and storage under physiological concentrations of insulin and, therefore, increased production of this hormone by the pancreas (Kahn and Flier, 2000). In many progressive cases, the lipids deposits into pancreatic islet cells impair the ability of beta cells to maintain enhanced insulin secretion, leading to glucose intolerance and type 2 diabetes (Cerf, 2013; Haslam and James, 2005).

4.1. Central implications of insulin resistance

In humans, one of the first studies to show that, the brain was unresponsive to insulin in situations of obesity was published in 2006 (Tschritter et al., 2006). The benefits promoted by insulin centrally are not found in situations of resistance of this hormone (Biessels and Reagan, 2015; Kullmann et al., 2016; Lee et al., 2016; Stoeckel et al., 2016). In this condition, glucose metabolism and insulin signaling are impaired in many brain regions, including those involved in learning and memory, such as the hippocampus (Biessels and Reagan, 2015; Pearce et al., 2012). Patients with type II diabetes have impaired performance in almost all neuropsychological tests, especially in memory, information processing speed and executive function (Moheet et al., 2015). In obesity and Alzheimer's disease, and aging itself, there is a change in the ratio of central and peripheral levels of insulin, wherein the concentration of the hormone in the periphery is higher as compared to healthy and younger individuals (Rani et al., 2016; Stockhorst et al., 2004). It is also known that there is lower transport of peripheral insulin to the brain under these conditions, although some studies show that the reduction of insulin signaling is not generalized to all brain regions and for all existing signaling pathways at the same time (Steculorum et al., 2014).

In human neuroimaging studies, patients with obesity or type II diabetes exhibit reduction in gray matter volume and in cortical thickness, as well as loss of white matter integrity (Bischof and Park, 2015; Brundel et al., 2014), particularly in limbic structures such as the hippocampus and amygdala (den Heijer et al., 2003; Hajek et al., 2014; Manschot et al., 2006). They also have altered brain activation and functional connectivity in different brain networks, including areas involved with working memory (Qiu et al., 2016; Zhang et al., 2016). Reduction in the volume of the hippocampal formation is seen in individuals with impaired glucose tolerance and insulin resistance (Convit et al., 2003; Ursache et al., 2012), and deficits in hippocampal-based memory performance and preservation of other cognitive domains are observed in these patients (Gold et

al., 2007). Obese adolescents with type II diabetes have worse cognitive performance in verbal memory and psychomotor efficiency, accompanied by reduced white matter volume and increased ventricles observed on MRI (Yau et al., 2010). In postmenopausal women, it was found a negative correlation between insulin resistance indexes such as HOMA-IR (Homeostasis Model of Assessment - Insulin Resistance) and hippocampal volume, as well as cognitive performance in tests of declarative and non-declarative memory (Rasgon et al., 2011). Patients with type II diabetes (Hoogenboom et al., 2014; Musen et al., 2012) and obese individuals (Kullmann et al., 2012) show diminished connectivity in the default mode network (DMN), a network including the precuneus, prefrontal cortex, lateral temporal cortex and hippocampus, that is essential for higher cognitive processes such as memory and cognitive function. Interestingly, the use of insulin in type II diabetes patients increases the functional connectivity between the hippocampus and frontal regions (Gottschalk and Ellger, 2015; Zhang et al., 2015), and this enhanced functional connectivity correlates with better performance in cognitive tests (Zhang et al., 2015).

Insulin resistance reduces peripheral insulin transport and its uptake into the brain (Plum et al., 2005; Stockhorst et al., 2004), turning the neurons less able to use glucose. In animal studies, this cell disorder is associated to impairment in normal neural transmission and electrophysiology, as well as to learning and memory due to hippocampus damage (Amin et al., 2013; Gardoni et al., 2002; Grillo et al., 2009). This is in accordance to other studies using the consumption of high-fat and/or high-sugar diets in animal models of obesity and insulin resistance (Davidson et al., 2012; Dinel et al., 2011; Jurdak et al., 2008; Kanoski et al., 2010; Kohjima et al., 2010; Molteni et al., 2002; Stranahan et al., 2008; Winocur and Greenwood, 2005). Insulin-induced long-term depression is attenuated in these animals (Mielke et al., 2005), especially in the hippocampus (Pratchayasakul et al., 2011), suggesting that brain insulin resistance contributes to cognitive impairment.

The combination of impaired insulin receptor signaling and decreased insulin transport across the blood-brain barrier (Davidson et al., 2012; Kanoski et al., 2010) can lead to hippocampal insulin resistance (Biessels and Reagan, 2015), which includes decreases in insulin-stimulated phosphorylation of IR and Akt, less insulin-stimulated translocation of GLUT4, as well as increased serine phosphorylation of IRS-1, a marker of insulin resistance (Arnold et al., 2014; Mielke et al., 2005). Experimental studies in rodents show that this imbalance of insulin mechanism of action on the hippocampus can be explained by mitochondrial dysfunction, increased reactive oxygen species production, caspases inhibition, disturbances in the expression of apoptosis regulator genes, impairments in hypothalamic–pituitary–adrenal axis function, and neuroinflammation (Boitard et al., 2014; Dinel et al., 2011; Morrison et al., 2010; Pipatpiboon et al., 2013; Piroli et al., 2007; Sadeghi et al., 2016). However, these factors may also act independently of IR, causing hippocampal neuroplasticity deficits and neuronal apoptosis in obesity and elderly (Tucsek et al., 2014). Together, these phenomena increase neuronal damage and collaborate for the low cognitive performance in obese individuals.

Additionally, it was found that obesity and insulin resistance result in reduced hippocampal expression and signaling of the brain derived neurotrophic factor (BDNF) in several studies (Molteni et al., 2002; Park et al., 2010; Tozuka et al., 2009), which is known to play important roles in proliferation, differentiation and survival of neurons during development, as well as in the synaptic activity and plasticity in many groups of mature neurons, being also anorexigenic (Lebrun et al., 2006). On the other hand, treatment with hypoglycemic agents and insulin sensitizers, as peroxisome proliferator-activated receptor-γ (PPARγ) agonist, metformin, and inhibitors of dipeptidyl peptidase 4 (DPP-4), reduces brain mitochondrial dysfunction and reverses memory impairments in high-fat induced insulin resistant rats (Pintana et al., 2012; Pipatpiboon et al., 2013; Pipatpiboon et al., 2012).

5. Network hubs and modulators

As reviewed in the previous sections, a decreased connectivity within the default mode network, including the hippocampus, posterior cingulate cortex/precuneus and prefrontal regions in seen in patients with type II diabetes (Hoogenboom et al., 2014; Musen et al., 2012) and could explain the cognitive deficits associated with this condition. This core network has a functional connection to both lateral and medial hypothalamus (Kullmann et al., 2014), and this may constitute the link between the peripheral metabolism and higher cognitive function and its effects on food choices and feeding behavior.

Another possible link between peripheral metabolism and eating behavior central control relies on the mesocorticolimbic pathways, as the VTA dopaminergic neurons have insulin receptors (Figlewicz, 2003; Li et al., 2009), and activity in the striatum correlates with enhanced peripheral insulin sensitivity (Heni et al., 2012). Insulin acting on these neurons could modulate feeding preferences as suggested in experimental studies (Portella et al., 2015).

Elevated proinflammatory cytokines, such as TNF alfa, interfere with insulin signaling and contribute to insulin resistance (Ferreira et al., 2014). Peripheral chronic low-grade inflammation is a feature of obesity and type II diabetes, being associated with hypothalamic gliosis (Thaler et al., 2012), loss of hypothalamic structural integrity (Cazettes et al., 2011; Puig et al., 2015), and impaired cognitive performance (Puig et al., 2015). Therefore, inflammation is an important modulator of insulin action and a possible link between metabolic disorders and cognitive decline.

Impaired brain insulin action could also result from insulin resistance at the blood-brain barrier (Verdile et al., 2015), or changes in the transport ratio of insulin across the blood-brain barrier (Heni et al., 2014b; Sartorius et al., 2015). These processes are seen during aging (Shah and Mooradian, 1997). In animal models, exposure to high-fat diets leads to increased blood-brain barrier permeability and cognitive dysfunction (Davidson et al., 2012; Pallebage-

Gamarallage et al., 2012), suggesting that blood-brain barrier injury is another contributing factor to the development and progression of cognitive impairment in insulin resistant states.

6. Hippocampal insulin resistance and altered food decision-making – role on obesity risk

In this review, we propose to approximate two sets of evidence that appeared to have a very reasonable association. On the one hand, the contribution of the hippocampus on food decision-making and, on the other, the role of insulin in the healthy functioning of the hippocampus. Both phenomena collaborate to balance food intake and body dimension. However, a disruption of the equilibrium that occurs in insulin resistant states may lead to a vicious cycle of obesity (Davidson et al., 2005; Davidson and Martin, 2014; Kanoski and Davidson, 2011): diets rich in fat and sugar induce an increase in adipose tissue; this leads progressively to insulin resistance, at least in some regions of the CNS; hippocampus is affected by the imbalance in insulin receptor signaling; the memory related to food is altered; there is no further inhibition to food stimuli, even when already satiated; hyperphagia leads to obesity in a feed forward process.

We reviewed evidence showing that hippocampal damage can disrupt interoceptive state signals ability to modulate eating behavior, leading to increased appetitive responding. Findings that satiety neuropeptides such as insulin play a role in the performance of hippocampal-dependent learning and memory processes encourage speculation that the effects of these neuropeptides on food intake might be based in part on their effects on behavioral inhibition processes that are mediated by the hippocampus (Benoit et al., 2010; Wimmer and Shohamy, 2012). Additionally, there are evidences that insulin resistance can be strongly involved with hippocampal damage.

Individuals vulnerable to uncontrolled eating show insulin resistance in the prefrontal cortex (Kullmann et al., 2015) and hippocampus (Convit et al., 2003) and altered measures of

cognition related to eating behavior, such as disinhibition and food craving. The homeostatic control of food intake works in close interaction to regions involved in decision-making and value attribution (Berthoud, 2012). Therefore, in agreement with Biessels & Reagan (Biessels and Reagan, 2015), we can suggest that memory impairment for a consumed meal, which can harm the stability of feeding patterns (Epstein et al., 2010), is an early sign associated with hippocampal insulin resistance. This specific cognitive deficit may contribute to increased food intake, leading to overeating, obesity and higher insulin resistance in long term, as a "vicious cycle" model proposed by Martin and Davidson (Davidson and Martin, 2014; Martin and Davidson, 2014). The development of tools and protocols to detect subtle behavioral characteristics associated with increased risk for developing obesity and related metabolic disturbances (e.g. behavioral tasks and cognitive testing that could lead to a better comprehension of the role of memory on food patterns) can be of interest for target prevention and counseling.

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Glucose Utilization and ATP Production

Insulin Signalling

Glucose

Insulin

Insulin Receptor

P

SHC

GRB2

SOS

P

IRS

PI3K

RAS

PDK1

CRAF

MEK1 or MEK2

P

Akt

ERK

Pyruvate

ATP

GLUT 4

Glucose Transport

PI3K/Akt pathway

MAPK pathway

Synaptic Plasticity

Normal Neuronal Homeostasis

MEMORY

Glucose Metabolism

Glycogen/Lipid/Protein Synthesis

Specific Gene Expression

METABOLIC SIGNAL

General Gene Expression

Cell Growth

Proliferation

Differentiation

MITOGENIC SIGNAL

FOXO1

Nucleus

DNA

Impaired energy metabolism

Altered glucose homeostasis

Osmolarity deregulation

Impaired Insulin Signalling

Impaired redox regulation

Oxidative stress

Synaptic dysfunction

Synaptic degeneration

+APP, +Aß

+ Tau phosphorylation

COGNITIVE IMPAIRMENT

Insulin influences feeding behavior and cognition.

Central insulin resistance can disrupt hippocampal function.

Changes in hippocampal integrity can affect food inhibitory control.

Hippocampal insulin resistance can lead to increased intake and obesity.