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Review article

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.

Contents

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

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

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