Behavioural Brain Research 282 (2015) 209–217

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Review

Mechanisms of insulin resistance in the amygdala: Influences on food intake

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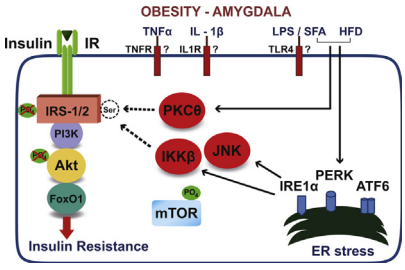
HIGHLIGHTS

- Studies showing the amygdala regulating feeding behavior were reviewed.
- The insulin signaling in the amygdala is similar to what occurs in the hypothalamus.
- Obese animals have dysregulation of amygdala including insulin resistance.
- ER stress, inflammation and PKCθ induce insulin resistance in the amygdala.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 10 September 2014
Received in revised form
31 December 2014
Accepted 5 January 2015
Available online 16 January 2015

Keywords:
Amygdala
Insulin signaling
Food intake
Obesity
ER stress
Protein kinase C theta

ABSTRACT

Obesity is increasing worldwide and is triggered, at least in part, by enhanced caloric intake. Food intake is regulated by a complex mechanism involving the hypothalamus and hindbrain circuitries. However, evidences have showing that reward systems are also important in regulating feeding behavior. In this context, amygdala is considered a key extra-hypothalamic area regulating feeding behavior in human beings and rodents. This review focuses on the regulation of food intake by amygdala and the mechanisms of insulin resistance in this brain area. Similar to the hypothalamus the anorexigenic effect of insulin is mediated via PI3K (phosphoinositide 3-kinase)/Akt (protein kinase B) pathway in the amygdala. Insulin decreases NPY (neuropeptide Y) and increases oxytocin mRNA levels in the amygdala. High fat diet and saturated fatty acids induce inflammation, ER (endoplasmic reticulum) stress and the activation of serine kinases such as PKCθ (protein kinase C theta), JNK (c-Jun N-terminal kinase) and IKKβ (inhibitor of nuclear factor kappa-B kinase beta) in the amygdala, which have an important role in insulin resistance in this brain region. Overexpressed PKCθ in the CeA (central nucleus of amygdala) of rats increases weight gain, food intake, insulin resistance and hepatic triglycerides content. The inhibition of ER stress ameliorates insulin action/signaling, increases oxytocin and decreases NPY gene expression in the amygdala of high fat feeding rodents. Those data suggest that PKCθ and ER stress are main mechanisms of insulin resistance in the amygdala of obese rats and play an important role regulating feeding behavior.

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http://dx.doi.org/10.1016/j.bbr.2015.01.003
0166-4328/

Contents

1. Introduction

Obesity is recognized as the most prevalent metabolic disease worldwide, reaching epidemic proportions in both, developed and developing countries, affecting not only adults but also children and adolescents. The increasing prevalence of obesity and associated comorbidities such as cardiovascular disease, hypertension, type 2 diabetes, dyslipidemia, certain types of cancers and arteriosclerosis constitute a major jeopardy to public health [1].

Therefore, the study of molecular mechanisms related to the development of obesity is very important nowadays. Epidemiologic data suggest that increased caloric intake including fatty and fructose diets, as well as more frequent consumption of fast foods enhanced the risk of obesity [2,3]. Food intake is regulated by a complex mechanism involving nutrients, hormones and neural signals. Most of the studies focus on the investigation of food intake control by the hypothalamus and hindbrain circuitries [4–8]. Over the past 20 years, several studies have demonstrated the importance of activation of hypothalamic insulin signaling in the control of energy homeostasis. This hormone has significant effects on transcriptional and electrical events in neurons [9–11]. Insulin receptors (IR) are abundantly expressed in hypothalamic neurons. The insulin signaling is initiated by binding of the hormone to its receptor. This undergoes a conformational change, activating a catalytic site located in the β subunit of the receptor. Once active, the site catalyzes the tyrosine phosphorylation of proteins such as IRS-1 and IRS-2 (insulin receptor substrates). Phosphorylation of IRSs promotes the binding and activation of PI3K (phosphatidylinositol-3-kinase). Once active, the PI3K induces the phosphorylation of Akt (protein kinase B). The phosphorylated Akt migrates to the cell nucleus, which phosphorylates the transcription factor FoxO1 (forkhead transcription factor O1) that is excluded from the nucleus. FoxO1 controls the transcription of target genes, including neuropeptides related to the energy balance. In neurons that express POMC (proopiomelanocortin), deletion of FoxO1 increases the transcription of POMC. The product of metabolism of POMC is αMSH (alpha-melanocyte stimulating hormone) that has anorexigenic actions. The αMSH increases the release of other anorexigenic neuropeptides such as TRH (thyrotropin releasing hormone) and CRF (corticotropin releasing factor) by PVN (paraventricular nucleus). In AgRP (agouti related peptide) neurons, which also express NPY (neuropeptide Y), the FoxO1 and STAT3 (signal transducer and activator of transcription 3), compete for binding to DNA. When FoxO1 is in the nucleus, it activates the transcription of AgRP and NPY, which are orexigenic neuropeptides. The nuclear exclusion of FoxO1 due to insulin stimulation allows STAT3 to bind to the DNA, inhibiting the transcription of these neuropeptides. Therefore, the action of insulin signaling promotes an increase in the expression of POMC, TRH and CRF and a reduction in AgRP and NPY expression [12] (Fig. 1).

Recently, evidences have shown that reward systems are also important in regulating feeding behavior. Brain reward systems regulate learning and memory regarding the hedonic food properties increasing the motivation and seeking toward obtaining food rewards. Cortex, basal ganglia and the limbic system including amygdala are considered key extra-hypothalamic areas regulating feeding behavior [13–16].

Herein, evidences from recent studies that highlight the contribution of amygdala in the control of food intake were reviewed. Amygdala participates in a neurocircuitry that integrates sensory and hormonal stimuli with other regions of the central nervous system such as cortex and hypothalamus important for feeding behavior (Fig. 2). In human beings, the activation of amygdala was investigated in obese subjects by using noninvasive functional neuroimaging methods. In addition, to gain insight into the molecular mechanisms by which the amygdala contributes to the control of feeding, we review several studies in which animal models were used.

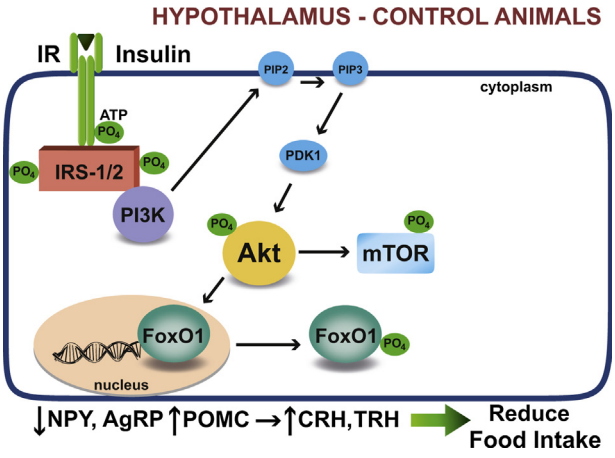

Fig. 1. Insulin Signaling in the Hypothalamus of Control Animals. In the hypothalamus, the insulin signaling is initiated by binding to the hormone and activating its receptor (IR). Once active, catalyzes the tyrosine phosphorylation of proteins such as IRS-1 and IRS-2 (insulin receptor substrate 1 and 2). Phosphorylation of IRSs promotes the binding and activation of PI3K (phosphatidylinositol-3-kinase). PI3K phosphorylates the lipid PIP2 (phosphatidylinositol 4,5-bisphosphate), reaction that yields PIP3 (phosphatidylinositol 3,4,5-trisphosphate) which actives PDK1 (3-phosphoinositide-dependent kinase-1). Once active, PDK1 catalyzes the phosphorylation of Akt (protein kinase B). Akt phosphorylation increases mTOR (mammalian target of rapamycin) phosphorylation and activation leading to reduced food intake. In addition, the activated Akt migrates to the cell nucleus, which phosphorylates the transcription factor FoxO1 (forkhead transcription factor O1) that is excluded from the nucleus. FoxO1 in the nucleus increases the transcription of the orexigenic NPY (neuropeptide Y) and AgRP (agouti-related peptide) and reduces the transcription of the anorexigenic POMC (pro-opiomelanocortin). Increased POMC gene expression induces the release of CRH (corticotrophin releasing hormone) and TRH (thyrotropin-releasing hormone) from the paraventricular nucleus of the hypothalamus. CRH and TRH are also anorexigenic neuropeptides. PO4: phosphate; ATP: adenosine triphosphate.