Neuroscience and Biobehavioral Reviews 92 (2018) 7–15

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review article

A review of brain insulin signaling in mood disorders: From biomarker to clinical target

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ARTICLE INFO

Keywords:
Mood disorder
Insulin signaling
Metabolism
Homeostasis
Stress
HPA axis
Neuroinflammation
Allostatic load

ABSTRACT

Patients with mood disorders are at increased risk for metabolic dysfunction. Co-occurrence of the two conditions is typically associated with a more severe disease course and poorer treatment outcomes. The specific pathophysiological mechanisms underlying this bidirectional relationship between mood and metabolic dysfunction remains poorly understood. However, it is likely that impairment of metabolic processes within the brain play a critical role. The insulin signaling pathway mediates metabolic homeostasis and is important in the regulation of neurotrophic and synaptic plasticity processes, including those involved in neurodegenerative diseases like Alzheimer's. Thus, insulin signaling in the brain may serve to link metabolic function and mood. Central insulin signaling is mediated through locally secreted insulin and widespread insulin receptor expression. Here we review the preclinical and clinical data addressing the relationships between central insulin signaling, cellular metabolism, neurotrophic processes, and mood regulation, including key points of mechanistic overlap. These relationships have important implications for developing biomarker-based diagnostics and precision medicine approaches to treat severe mood disorders.

1. Introduction

Adding to the already heavy burden of morbidity and functional disability, individuals with major depressive disorder have a 1.5 fold greater chance of developing insulin resistance, compared to those without depression (Pan et al., 2012). In fact, there is now substantial evidence for a bidirectional link between insulin resistance and depression (Pan et al., 2012). Moreover, this co-morbidity is associated with persistent depressive symptoms, primarily as a result of poor treatment outcomes (Lin et al., 2015; Rasgon et al., 2010). Despite this clear relationship, there is a significant gap in our understanding of the mechanistic link between insulin resistance (IR) and depression, particularly in the case of IR occurring in the brain, known as central IR. Contrary to the long-held belief that brain function is insulin independent, recent human neuroimaging studies indicate that acute insulin stimulation can rapidly regulate corticolimbic glucose metabolism (Anthony et al., 2006; Bingham et al., 2002) and neural connectivity (Kullmann et al., 2015; Zhang et al., 2015). In rodents, central insulin signaling facilitates neurotrophic processes (Haas et al., 2016) and glucose uptake (Garcia-Caceres et al., 2016). Here we review current knowledge of the relationship between mood disorders and metabolic function, focusing on emerging ideas about the role of insulin signaling in the brain.

2. Relationship between insulin resistance and depressive illness

Depression increases one's chance of developing IR by approximately 50% (Pan et al., 2012). Patients diagnosed with both depression and IR often experience age-related health problems and are at increased risk of developing additional comorbidities, including cardiovascular disease and dementia (Dunbar et al., 2008; Pan et al., 2012; Rasgon et al., 2001; Rasgon and Jarvik, 2004; Rasgon and Kenna, 2005; Rasgon and McEwen, 2016). Decades of data from clinical and epidemiological studies attest to a bi-directional link between mood and

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https://doi.org/10.1016/j.neubiorev.2018.05.014
Received 1 December 2017; Received in revised form 8 April 2018; Accepted 8 May 2018

metabolic dysfunction (Dunbar et al., 2008; Lloyd et al., 2012; Pan et al., 2012). Some have proposed a pathogenic relationship, mediated by IR, with important long-term implications for disease course over the lifespan (Rasgon et al., 2001; Rasgon and Jarvik, 2004; Rasgon and Kenna, 2005; Rasgon and McEwen, 2016).

Validation of this mechanistic link would have significant implications for the way we conceptualize, diagnose, and treat depression (Rasgon and Jarvik, 2004; Rasgon and Kenna, 2005). For example, biological indicators of metabolic dysregulation have been directly associated with a more chronic depressive illness course over a two year period, resulting primarily from reduced antidepressant treatment response (Vogelzangs et al., 2014). Thus, patients with underlying metabolic pathophysiology may benefit from specific alternative or augmentive therapies. In line with this, recent studies using insulin sensitizing compounds in conjunction with antidepressants report significantly increased response rates when compared to conventional treatment (Lin et al., 2015; Rasgon et al., 2010; Sepanjnia et al., 2012).

Understanding why, when, and how metabolic and psychiatric pathologies co-occur is critical to advancing new and better therapeutic options and ultimately improving patient outcomes. This is because comorbid metabolic and mood disorders come with serious consequences, including increased diabetic retinopathy, nephropathy, neuropathy, macrovascular complications, sexual dysfunction (de Groot et al., 2001), poorer glycemic control (Lustman et al., 2000), 50–70% increase in health services cost (Simon et al., 2005), two-fold increase in cardiac risk factors (Katon et al., 2004), and increased risk of depressive symptom recurrence (Fagiolini et al., 2003).

The precise causal relationship between these two types of pathologies is unknown. However, there are numerous points at which metabolic signaling pathways and the processes that regulate neuronal structure and function overlap. On a mechanistic level, elevated glucocorticoid levels, inflammatory cytokines, and disruptions to the gut microbiome can contribute to both metabolic and mood disorders (Duman et al., 2016). In addition, we now know that insulin signaling occurs within the brain and that it can significantly impact the structure and function of the central nervous system through neurotrophic effects and regulation of synaptic plasticity (Blázquez et al., 2014). These interactions could underlie the link between metabolic and neuropsychiatric disease (Kaidanovich-Beilin et al., 2012).

Shifting therapeutic strategies to instead target points of overlap between metabolic and neurotrophic processes could significantly improve the effectiveness and safety of treatment for those suffering from comorbid conditions. Many first-line antidepressant drugs have side effects, such as weight gain, that are particularly dangerous for those with pre-existing metabolic conditions (Himmerich et al., 2015; Serretti and Mandelli, 2010). Brain insulin signaling in particular has the potential to serve both as a target of future therapeutic innovation and as a biomarker to identify those patients for whom metabolic factors may be contributing to neuropsychiatric pathology.

3. Insulin's role in the central nervous system

The majority of the body's insulin is produced by beta cells in the pancreas and secreted into the bloodstream. Long believed to be insulin-independent, we now know that the brain is sensitive to insulin. Not only can insulin effectively cross the blood brain barrier *via* active transport (Woods et al., 1985), it is also produced and secreted locally throughout the central nervous system (CNS) (Blázquez et al., 2014; de la Monte and Wands, 2005; Devaskar et al., 1994; Rivera et al., 2005; Rulifson et al., 2002; Steen et al., 2005; Wozniak et al., 1993). Insulin receptors are expressed abundantly in brain areas responsible for food intake and cognition, such as the hypothalamus, hippocampus, and olfactory bulbm (Unger et al., 1991; Zhao and Alkon, 2001). Furthermore, concentrations of brain insulin and insulin receptors appear to be regulated independently of peripheral insulin activity (Havrankova et al., 1979). These observations point to a significant role for insulin signaling in regulating key functions of the CNS.

Within the CNS, Insulin serves as a neuropeptide signaling molecule, co-regulating cellular functions *via* direct interaction with insulin receptors throughout the CNS (Havrankova et al., 1978). This positions it optimally to link behavioral and neuronal functions with metabolic states. For example, insulin acts within the hypothalamus to regulate feeding behavior and energy homeostasis (Baskin et al., 1987; Brief and Davis, 1984; Ikeda et al., 1986; Woods et al., 1979), including suppression of hepatic glucose production (Buettner and Camacho, 2008; Obici et al., 2002a; Obici et al., 2002b) and regulation of peripheral fat metabolism (Koch et al., 2008; Scherer and Buettner, 2011; Scherer et al., 2011). Conversely, targeted disruption of central insulin signaling in rodents leads to hyperphagia, insulin resistance (central and peripheral), and a diabetic phenotype (Bruning et al., 2000; Obici et al., 2002b; Plum et al., 2005). Thus, there is significant bidirectionality between insulin signaling in the brain and metabolic processes throughout the body. Disruptions to either can lead to pathology.

3.1. Points of molecular overlap between metabolic and neurotrophic pathways

At the molecular level, insulin signaling pathways overlap with neurotrophic pathways. Insulin in the CNS supports neuronal growth, survival, and differentiation, including neural outgrowth and migration, increases in neuronal cytoskeletal protein expression, and nascent synapse formation (Chiu et al., 2008; Dou et al., 2005; Skeberdis et al., 2001; Valenciano et al., 2006; Wan et al., 1997; Zhao et al., 1999). Specific mechanisms include insulin-sensitive modulation of synaptic maintenance (Dou et al., 2005; Zhao et al., 1999) and cellular excitability *via* alteration of potassium ion channel ($K_v1.3$) expression levels (Plum et al., 2005). In addition, insulin signaling modulates protein kinase C, mitogen activated protein kinase (MAPK), Casitas B-lineage Lymphoma (CBL), and phosphoinositide 3-kinase (PI3K) pathways implicated in memory storage and neuronal repair (Nelson et al., 2008). These insulin-sensitive molecular mechanisms can play a critical role in learning and memory (McNay and Recknagel, 2011; Sherwin, 2008).

3.1.1. The IRS/PI3K pathway

The insulin receptor substrate (IRS)/PI3K pathway plays an important role in the regulation of food intake. However, several molecules involved in the pathway also serve a neuromodulatory function. Insulin binding to insulin receptors initiates receptor autophosphorylation that in turn triggers the recruitment of the regulatory subunit p85 of PI3K, phosphorylation of phosphoinositylinositol-4, 5-bisphosphate, generating phosphatidylinositol-3,4,5-triphosphate (PIP_3), and activation of phosphoinositide-dependent protein kinase 1 (PDK1). Active PDK1 then phosphorylates and activates protein kinase B (Akt) that then phosphorylates numerous downstream proteins, including glycogen synthase kinase-3 (GSK3; important for both metabolic regulation and neuromodulation), forkhead box protein O1 (FOXO1; regulation of food intake), or mammalian target of rapamycin (mTOR; involved in neurotrophic processes) (See Fig. 1).

Food intake regulation *via* the IRS/PI3K pathway takes place for the most part within the arcuate nucleus (ARC) and the ventromedial nucleus (VMH) of the hypothalamus. On a cellular level, there are two key neuronal populations within the ARC: the proopiomelanocortin (POMC)-expressing neurons and the agouti-related peptide (AgRP)/neuropeptide Y (NPY)-co-expressing neurons. AgRP and NPY act both as body energy homeostasis sensors and as messengers between the brain and periphery. After Akt phosphorylates and inactivates FOXO1, POMC expression is increased (Plum et al., 2006), leading to activated melanocortin receptors (MCR) that results in decrease food intake and increase energy expenditure (Kleinridders et al., 2009; Vogt and Bruning, 2013). On the other hand, AgRP/NPY neuron activation results in increased food intake and decreased energy expenditure (Gropp et al., 2005; Luquet et al., 2005; Mesaros et al., 2008).