Neuroscience and Biobehavioral Reviews 72 (2017) 43–49

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review article

Selfish brain and selfish immune system interplay: A theoretical framework for metabolic comorbidities of mood disorders

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ARTICLE INFO

Article history:
Received 29 August 2016
Received in revised form 6 October 2016
Accepted 16 November 2016
Available online 18 November 2016

Keywords:
Bipolar disorder
Major depressive disorder
Brain energy metabolism
Immune system energy metabolism
Metabolic syndrome
Inflammation

ABSTRACT

According to the "selfish brain" theory, the brain regulates its own energy supply influencing the peripheral metabolism and food intake according to its needs. The immune system has been likewise "selfish" due to independent energy consumption; and it may compete with the brain (another high energy-consumer) for glucose. In mood disorders, stress in mood episodes or physiological stress activate homeostasis mechanisms from the brain and the immune system to solve the imbalance. The interaction between the selfish brain and the selfish immune system may explain various conditions of medical impairment in mood disorders, such as Metabolic Syndrome (MetS), obesity, type 2 diabetes mellitus (T2DM) and immune dysregulation. The objective of this study is to comprehensively review the literature regarding the competition between the brain and the immune system for energy substrate. Targeting the energetic regulation of the brain and the immune system and their cross-talk open alternative treatments and a different approach in the study of general medical comorbidities in mood disorders, although more investigation is needed.

Contents

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http://dx.doi.org/10.1016/j.neubiorev.2016.11.010
0149-7634/

1. Introduction

There has been a major paradigmatic shift in the conception of mood disorders (Insel and Quirion, 2005; McIntyre and Carvalho, 2016). Although their behavioral and emotional symptoms remain considered as manifestation of structural or functional impairments in the brain, robust evidence has indicated that this underlying brain dysfunctions are in interplay with multi-systemic dysregulations (Mansur et al., 2015; Rosenblat et al., 2015). As a result, the prevalence of comorbid medical conditions is significantly higher in individuals with mood disorders, relative to the general population. Conversely, mood disorders have been reliably associated with premature mortality, insofar as individuals with mood disorders die, on average 10 years earlier than the rest of the population. Although suicide is an important cause, cardiovascular events that actually account for most of this excessive deaths (Weiner et al., 2011). A myriad of systemic changes have been implicated in mood disorders including but not being restricted to chronic low grade inflammation, thyroid dysfunction, Hypothalamus-Pituitary-Adrenal (HPA) axis reprogramming and metabolic syndrome (MetS) (Czepielewski et al., 2013; Liu et al., 2014; Taylor and MacQueen, 2006).

Metabolic syndrome is defined as a set of risk factors for cardiovascular mortality, including central obesity, diabetes, hypertension and dyslipidemia (i.e. elevated triglycerides and low HDL) (Lawlor et al., 2006). In fact, in both major depressive disorder (MDD) and bipolar disorder (BD), MetS, obesity and type 2 diabetes mellitus (T2DM) are more frequent compared to the general population (Czepielewski et al., 2013; Vancampfort et al., 2015; McIntyre et al., 2005; Gurpegui et al., 2012; Fagiolini et al., 2008; Hung et al., 2014; Sicras et al., 2008). Obesity is also a marker of poor prognosis in mood disorders with high body mass index (BMI) being correlated with severity of depressive symptoms and impaired cognition including attention and psychomotor skills in BD (McIntyre et al., 2008; Yim et al., 2012; Brietzke et al., 2011; Grande et al., 2012). Individuals with BD and T2DM are more likely to present a chronic course and rapid cycling, with increased disability and worse overall functioning, when compared to euglycaemic BD patients (Hajek et al., 2005; Calkin et al., 2015; Ruzickova et al., 2003). In addition, in MDD, impaired glucose metabolism and insulin resistance are associated with suicidal behavior and impaired executive functioning (Koponen et al., 2015).

Metabolic abnormalities are associated with chronic low-grade inflammation (Lee and Pratley, 2005), which is well documented in MDD and BD (Noto et al., 2014). There is increased interleukin 6 (IL-6), IL-1β and C-reactive protein (CRP) in MDD (Raison et al., 2006) and increased IL-6, IL-2, IL-4, IL-10 and TNF-α in BD (Modabbernia et al., 2013) (Cunha et al., 2008; Dickerson et al., 2007). Also, inflammation has been associated with disease severity and neuronal damage in mood disorders (Alesci et al., 2005; Thomas et al., 2005; Lindqvist et al., 2009; Aktas et al., 2007). Different theoretical explanations for immune-inflammatory activation were proposed in the literature including genetic vulnerability, childhood maltreatment, chronic stress and iatrogenic effects, although all of them have limitations in understanding the multiplicity of factors involved in the cross-talk between the brain and the immune system (Marco et al., 2015; Jaramillo et al., 2013).

The "selfish brain" theory, proposed by (Peters et al., 2004), was an advance in the understanding of metabolic abnormalities in mood disorders. They argue that the brain uses several mechanisms to control the allocation of glucose availability and food intake in order to supply its own energetic needs prior to others organs. As the brain consumes up to 65% of the circulating glucose (Reinmuth et al., 1965), this control has a highly significant impact on the metabolism of the body as a whole. Recently, (Straub, 2014a, 2014b) defended the immune system as "selfish" and integrated it as a potential competitor to the brain for energy resources. Like the brain, the immune cells do not depend on any organ to obtain energy and its energetic demand is prioritized (Straub, 2014a, 2014b). Its "selfishness" is critical for survival, since immune activation corresponds to an increase in approximately 25% of the basal metabolic rate (Tsigos et al., 1997; Fong et al., 1990; Straub et al., 2010).

The body responds to psychological or immune stress through many orchestrated mechanisms to retrieve homeostasis. All these changes are energy consumptive; and an unsuccessful response could be involved in pathophysiology of brain and systemic changes characteristics of mood disorders. Indeed, these assumptions are in line with the pioneers studies from Raison and Miller which suggested that inflammation due to insufficient cortisol signaling may be implicated in mood disorders (Raison and Miller, 2003). In 2004, Robert Dantzer proposed that stimuli like stress or chronic inflammation would elicit production of pro-inflammatory cytokines in the brain and result in mood manifestations in sickness behavior and depression (Dantzer, 2004, 2006). Afterwards, Capuron et al. (2008), comparing twins, found an association between metabolic syndrome (MetS) and depressive symptoms, which were associated with inflammatory biomarkers (Capuron et al., 2008). In the last few years, the role and specific mechanisms explaining inflammation and MetS in mood disorders has been increasingly been studied.

The objective of this study was to comprehensively review the literature regarding the competition between the brain and the immune system for energy substrate and the implications of this theoretical framework for the understanding of mood disorders biology as well as their general medical comorbidities.

2. Methods

The journal articles found in PubMed mentioning "selfish brain" and "selfish immune system" were selected and read throughout. The seminal papers that proposed the "selfish brain" and the "selfish immune system" theories and the articles about the "selfish brain" in mood disorders were set as conceptual base to guide our investigation in the literature published in PubMed and google scholar. Secondary subjects that derived from the rationale, including oxidative stress, MetS, obesity and IR were also searched for further details.

3. Results and discussion

3.1. The "selfish brain" theory

The energy required for a well-functioning brain is very high and energy supply for the brain is different from other organs since it uses almost exclusively glucose as an ATP substrate and the glucose transport into the brain is insulin-independent (Peters et al., 2011; Hitze et al., 2010). The highest hierarchical position of the brain in energy obtainment is of extreme importance for survival in acute life-threatening situations. In such cases, the mechanisms activated to provide more energy to the brain are called "brain pull" (Peters and Langemann, 2009).

The "brain pull" begins with glutamate release via sympathoadrenal system, in response to decrease in ATP in the hypothalamus, to decrease insulin secretion and its downstream effects (Ahren, 2000; Mulder et al., 2005; Chan et al., 2007; Tong et al., 2007), while astrocytes increase its glucose uptake via insulin-independent glucose transporter 1 (GLUT1) (Pellerin and Magistretti, 1997). Low astrocyte integrity was found in melancholic depression (Rothermundt et al., 2001) and BD during both manic and depressive episodes (Schroeter and Steiner, 2009;