Neuroscience and Biobehavioral Reviews xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

Refining and integrating schizophrenia pathophysiology – Relevance of the allostatic load concept

Błażej Misiak[a,b,*,1], Dorota Frydecka[a,1], Marcin Zawadzki[c], Maja Krefft[a], Andrzej Kiejna[a]

[a] Department of Psychiatry, Wroclaw Medical University, 10 Pasteur Street, 50-367 Wroclaw, Poland
[b] Department of Genetics, Wroclaw Medical University, 1 Marcinkowski Street, 50-368 Wroclaw, Poland
[c] Department of Forensic Medicine, Wroclaw Medical University, 4 J. Mikulicz-Radecki Street, 50-345 Wroclaw, Poland

ARTICLE INFO

Article history:
Received 14 October 2013
Received in revised form 2 April 2014
Accepted 9 June 2014

Keywords:
Allostatic load
Mediators of allostasis
Stress
Schizophrenia
Pathophysiology

ABSTRACT

Adaptation to stress leads to the activation of several biological systems that maintain homeostasis and enable effective coping with challenges. These adaptive processes have been designated as 'allostasis'. However, overactivation or aberrant performance of allostatic mechanisms due to chronic stress exposure may exert systemic deleterious effects. This condition has been called 'allostatic load' (AL). The AL concept is a useful framework allowing to understand the mulitisystem physiological dysregulation due to cumulative stressful demands over the lifespan. In the recent years, the AL paradigm has emerged as a novel concept explaining the morbidity and mortality with respect to several mental disorders. In this article, we suggest that AL provides a useful framework to describe schizophrenia – its etiology, course, outcome and comorbidities. Schizophrenia is a severe mental illness that is characterized by multidimensional psychopathology including positive and negative symptoms, affective symptoms and cognitive impairment with several known risk factors and accompanying pathophysiological correlates. However, there is a great need to refine and integrate the plethora of findings reported from various research perspectives. We propose that AL is a meaningful concept integrating findings on pathophysiological underpinnings, factors influencing course of the disorder and the development co-occurring physical health impairments as well as substance use disorders in schizophrenia. Furthermore, there is an urgent necessity to investigate AL and its correlates in schizophrenia as no studies in this field have been performed so far.

Contents

* Corresponding author at: Department of Psychiatry, Wroclaw Medical University, 10 Pasteur Street, 50-367 Wroclaw, Poland. Tel.: +48 71 784 16 50/12 56; fax: +48 71 784 16 02/00 63.
E-mail address: mblazej@interia.eu (B. Misiak).
[1] These authors have contributed equally.

http://dx.doi.org/10.1016/j.neubiorev.2014.06.004
0149-7634/

1. Introduction

Schizophrenia is a severe mental illness that is characterized by multidimensional psychopathology including positive and negative symptoms, cognitive dysfunction, as well as affective symptoms. In addition, schizophrenia is associated with high prevalence and incidence rates of physical health problems and reduced life expectancy up to 25–30 years due to medical morbidity and suicide risk (Casey et al., 2011; de Almeida et al., 2012). Notably, cardiovascular mortality is the core contributor of natural causes of death in this group of patients (Auquier et al., 2007) and the prevalence of metabolic syndrome in schizophrenia has been estimated at 37–63% (Correll, 2007). Finally, evidence is accumulating that psychosocial stress may trigger the onset of schizophrenia and worsen its course and outcome. There are studies showing high prevalence rates of comorbid posttraumatic stress disorder (PTSD) in schizophrenia patients (Grubaugh et al., 2011). Moreover, the comorbid PTSD positively correlates with poor functional status and low self-rated quality of life, worse cognitive performance in attention and memory domains (Fan et al., 2008), higher rates of homelessness and unemployment (Mueser et al., 2004), higher rates of suicidality (Alvarez et al., 2012), more distressing auditory hallucinations (Steel et al., 2011), as well as worse psychopathological manifestation of schizophrenia (Duke et al., 2010; Strauss et al., 2011). Although a great progress has been made in recognizing putative markers of schizophrenia, the majority of studies investigate single biological pathways. Therefore, there is a need for refining and integrating different views on schizophrenia pathophysiology. In this article, we propose that schizophrenia psychopathology might be described and integrated using the allostatic load (AL) concept.

The term 'allostasis' refers to biological processes that are activated in response to homeostasis alterations to meet the demands of a new situation (McEwen and Stellar, 1993). Therefore, this adaptive process has been also alternatively designated as 'stability through change' (Sterling and Eyer, 1988). These adaptive mechanisms act via various mediators including hormones, neurotransmitters, neurotrophins, oxidative stress indices, immune and inflammatory response markers. Mechanisms of allostasis are adaptive in a short-term perspective; however, chronic activation of allostasis processes exerts systemic deleterious effects. This state was defined as allostatic load (McEwen, 2006). Disease outcomes associated with prolonged or persistent AL have been defined as allostatic overload (AO) (McEwen and Wingfield, 2003). There are four types of AL delineated by McEwen (1998). The first type refers to repeated hits representing exposure to frequent stressors. The second type of AL addresses lack of adaptation in response to stress. The third type represents inability to shut off AL mechanisms after terminated stress exposure. Finally, the fourth type represents a cross-talk between AL mechanisms. In this type, inadequate response of one biological systems evokes compensatory response of another system.

The AL paradigm is recognized as the explanation of the development of physical illness in response to long-term stress stimuli. For instance, chronic overproduction of mediators of allostasis may lead to the development of hypertension, visceral obesity, type 2 diabetes and cardiovascular disease (Hamer and Malan, 2010). Notably, AL is not only a theoretical model describing reciprocal links between stress and various diseases as there are biomarker panels enabling the measurement of AL index. The first operationalization of AL concept was performed in Mac Arthur Studies of Successful Aging and included 10 following biomarkers: 12-h urinary cortisol, epinephrine, norepinephrine output, serum dehydroepiandrosteron-sulphate (DHEA-S), total cholesterol, high and low density lipoproteins (HDL and LDL), plasma glycosylated hemoglobin, blood pressure and waist-to-hip ratio (WHR) (Seeman et al., 1997). Subsequently, more complex panels including up to 16 biomarkers have been implemented (reviewed in detail by Juster et al. (2010)). Furthermore, McEwen and Seeman (1999) elaborated the conceptualization of AL delineating primary mediators (glucocorticoids and catecholamines), primary effects (cellular mechanisms that are influenced by primary mediators e.g. oxidative stress, inflammatory response or neurotrophins), secondary outcomes (integrated processes reflecting the cumulative outcome of primary effects in tissues (e.g. waist-to-hip ratio, blood pressure, glycosylated hemoglobin) and tertiary outcomes (various diseases and disorders resulting from AL).

Emerging evidence indicates that the AL concept can serve as the model explaining the course of various mental disorders including bipolar disorder (Grande et al., 2012; Kapczinski et al., 2008; Vieta et al., 2013), major depression (McEwen, 2003, 2004), Alzheimer's disease (von Kanel et al., 2003), PTSD (McFarlane, 2010) and substance use disorders (George et al., 2012), as well as the occurrence of comorbid physical illnesses (McIntyre et al., 2007). In the recent years, a particular attention has been paid to understanding bipolar disorder in the frame of AL paradigm. It has been found that some AL mediators including indices of oxidative damage of proteins and lipids, neurotrophin-3 (NT-3), interleukin (IL)-10 and tumor necrosis factor-α (TNF-α) may discriminate between distinct bipolar mood states (Kapczinski et al., 2011). Additionally, Kapczinski et al. (2010) elaborated a systemic toxicity index (STI) that was based on the shared variance of several AL mediators including neurotrophins, cytokines and oxidative stress markers. STI was found to differentiate euthymic, manic and depressive patients, while there was no significant difference in STI between euthymic patients and healthy controls. Finally, the AL concept has been also incorporated to explain neuroprogression in bipolar disorder (Berk et al., 2011; Fries et al., 2012). These findings raise the question as to whether AL progresses throughout illness duration and whether mediators of allostasis may differentiate various subgroups of schizophrenia patients including first-episode psychosis subjects, acutely relapsed individuals, stable and chronic patients.

Here, we present evidence that schizophrenia constitutes another mental disorder that can be described using assumptions underlying the AL concept. In this article, we review the contribution of various mediators of AL to the etiology, course and outcome of schizophrenia with particular attention on comorbid physical health conditions and cognitive dysfunction.

2. Allostatic load mediators in schizophrenia

Following the above mentioned conceptualization of AL proposed by McEwen and Seeman (1999) mediators of allostasis in schizophrenia might be divided into primary mediators (catecholamines and glucocorticoids), primary effects (e.g. oxidative stress markers, immune and inflammatory mediators, neurotrophins), secondary outcomes (biochemical and anthropometric parameters that are easy to measure and reflect the cumulative outcome of primary effects in tissues) and tertiary outcomes (schizophrenia and comorbidities) (Fig. 1). Of note, there is a complex interaction between AL mediators creating a cross-talk response to stress between key biological systems including brain, endocrine system and immune system. Here, we provide an overview of core AL mediators with respect to schizophrenia pathophysiology.

2.1. The hypothalamic–pituitary–adrenal (HPA) axis

The HPA axis is recognized as a main neural system that is responsible for biological response to stress stimuli. In brief, it acts via feedback interactions between three hormones:

Please cite this article in press as: Misiak, B., et al., Refining and integrating schizophrenia pathophysiology – Relevance of the allostatic load concept. Neurosci. Biobehav. Rev. (2014), http://dx.doi.org/10.1016/j.neubiorev.2014.06.004