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Guest Editorial / Misafir Editoryal

Revisiting Allostasis and Allostatic Load in Bipolar Disorder

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The term "allostasis" defines the process of adaptation and management of changing physiological and emotional demands. The need for a normally functioning system to change bodily parameters in response not only to physiological changes, but also to other environmental challenges such as diseases, noise etc. is called allostasis. Allostasis is normally a protective process. However, the system may face a chronically forced (overactive or inactive) process while coping with the changes. This "wear and tear of the body and brain" is called "allostatic load" (1). Aging and acute and chronically repeating stress are among the most notable processes where "allostatic load" is evident (2). In such events, either it is not possible to shut off the physiological stress response when the stress is over or the stress response is inadequate. In either case, the allostatic load increases and results in pathological conditions (2,3). In follow-up studies, allostatic load, as a cumulative measure of dysregulation across multiple physiological systems, was reported to be an independent predictor of decline in physical and cognitive functionality in the elderly population (4). Also the risk of all-cause mortality and frailty were shown to increase together with each unit increment in the allostatic load (5,6).

A good example of allostasis is the mobilization of energetic pathways through glucocorticoids, the end-effectors of the hypothalamic–pituitary–adrenal (HPA) axis. Both the HPA axis and glucocorticoid hormones are pivotal in the adaptive response to various internal or external stressors (3,7). Overactivation of the HPA axis is known to result in insulin resistance, predisposition to diabetes, obesity, atherosclerosis, and hypertension. This system also exerts a strong effect on the hippocampus, causing changes in its major functions, such as cognition, memory, behavior, and mood (7).

Bipolar disorder (BD) is a chronic, disabling brain disease that follows a relapsing and remitting course (8-10). The terms "kindling" and "episode sensitization" are used to model cycle acceleration and illness progression occurring in the longitudinal course of mood disorders (11). According to this model, the first few mood episodes are mostly triggered by various life events. After multiple recurrences, episodes may appear spontaneously as well. The concept is supported by longitudinal studies where the number of prior episodes was shown to be a strong predictor of the recurring episodes in both unipolar and BD (12), and psychosocial stressors were less likely to be involved in the precipitation of the recurrences after the first few episodes (13,14).

In line with this model, there is evidence that acute mood episodes are associated with significant alterations related to neurochemical components (i.e. catecholamines), neurotrophins, oxidative stress, and inflammation, and that this so called "systemic toxicity", which involves systems that play a key role in allostasis such as the HPA axis, becomes more evident

at later stages of illness (15). Evolving systemic toxicity leads to a system less resilient to stressors and perhaps to accelerated cycling, medical comorbidities, cognitive impairment, and difficulties in treatment response.

For several years, brain derived neurotrophic factor (BDNF) has been one of the most studied neurotrophins in BD (16). Recent studies reported decreased BDNF and increased glia-derived neurotrophic factor (GDNF) levels in both mania and depression (17), increased GDNF/BDNF ratio in mania (18), and increased GDNF levels during manic switch due to ECT (19) confirming the role of the disrupted supportive cellular network in BD. Altered antioxidant enzymes, lipid peroxidation and nitric oxide levels (20-22), as well as increased DNA damage (23-27) in BD and a probable coactivation of oxidative damage and repair mechanisms have been reported, particularly in a depressive state of BD (28). Also various inflammatory markers such as TNF-α, interleukin (IL) 1β, IL-6, IL-10, IL-18, IL-4, interferon-γ, monocyte chemotactic protein-1, fibroblast growth factor β, vascular endothelial growth factor, and hs-CRP were reported to be activated in both manic and depressive states of BD (29,30). HPA axis dysfunction, as determined by enhanced cortisol response to the dex/CRH test, was shown in both remitted and non-remitted patients (31).

The interplay between the abovementioned mediators is hypothesized to be nonlinear, meaning that any alteration in each of these domains may induce further changes in others (15). For example, microglial activation caused by neuro-inflammation results in a cascade of increased oxidative stress, pathologic synaptic pruning, and disturbed neuroplasticity. Occurrence of these events in major brain areas where mood and cognition are regulated results in both core clinical symptoms of mood disorders as well as cognitive dysfunction, which is a part of active episodes and known to be sustained even in euthymia. In addition, immune dysregulation also leads to activation of the HPA axis, which results in hypercortisolemia and metabolic dysfunction. This in return induces further neuronal dysfunction (32). These multisystem alterations defined as "systemic toxicity" take place in systems that are involved in allostasis (33).

Accumulation of such toxicity becomes more evident at later stages of illness (33-38), causing less efficient cellular resilience mechanisms that may be leading to a pathological reorganization between different brain areas (39). This rewiring of the brain within the context of clinical and cognitive deterioration is called "neuroprogression". Neuroprogression is suggested to be associated with the impaired resilience to stress in patients with BD (39). In sum, it has been proposed that mood episodes generate an extra load on the allostasis that is responsible for the illness progression (15).

Structural alterations and volumetric changes in BD in brain areas that are involved in emotion regulation and executive functions and response inhibition have been repeatedly reported (40-43). There is evidence for time-related gray matter volume increases in bipolar patients that vary by age (44). However, whether these changes result directly from toxic effects of the illness or if they are related to medication use or comorbid conditions has not been fully uncovered.

Despite persisting uncertainties about the origin of structural brain changes, progressive dysfunction is a commonly seen and well established feature of BD. Neurocognitive impairment that is evident across all states of BD (mania, depression and euthymia), subservient to a disturbance in functionality, is another core feature of BD (45). The degree of impairment in working memory in euthymic bipolar patients was shown to be positively correlated with post-dexamethasone cortisol levels, suggesting a role of abnormally functioning glucocorticoid receptors (46). Persistence of cognitive decline during euthymia and its being related to the abnormally functioning HPA axis is consistent with the concept of allostatic load: the continuing stress, through its interaction with the HPA axis, gives way to new mood episodes, each of which in turn causes further disturbance in the system.

Patients with BD are predisposed to increased rates of metabolic syndrome (47) and suffer from frequently occurring general medical conditions such as cardiovascular diseases, various cancers, obesity, and

diabetes, all of which individually lead to increased morbidity and mortality during the course of the illness (48-68). Major markers of allostatic load, such as oxidative stress and increased cortisol, are known to be related to increased risk for cardiovascular diseases, through involvement in mechanisms of atherosclerosis. It has been shown that the atherosclerosis process is associated with an inflammatory response, and both phenomena together could contribute to cognitive decline (69). On the other hand, increased rates of obesity, metabolic syndrome, and diabetes independently show a deteriorating effect on the course of BD. Therefore, it has been hypothesized that the cumulative effect of increased oxidative stress in mood episodes and increased allostatic load may partially explain the increased morbidity in BD (2). Cognitive deficits related to obesity and neuropsychiatric diseases in general (70), and BD in particular (71,72), have been reviewed as expression of abnormalities in brain structure and function. In a recent study, BMI was found to be negatively correlated with attention and psychomotor processing speed. In addition, overweight and obese patients with BD scored significantly lower on the Verbal Fluency Test in comparison to normal weight patients (73). In another recent study that included patients with BD and patients with schizophrenia, obesity and worse overall cognitive performance as well as poorer performance on processing speed, reasoning/problem-solving, and sustained attention were found to be associated in BD. A similar association was not found in patients with schizophrenia. Obesity did not correlate with symptom severity in either mental illness (74).

In conclusion, accumulated data support the concept that bipolar disorder is a condition that involves various systems from micro to macro level. The non-linear interaction between systems that are involved in allostasis may help to elucidate the pathophysiology of bipolar disorder, where genetic vulnerability interacting with environmental challenges triggers the illness, which in turn increases the load on allostasis and therefore leads to illness progression in emotional, cognitive and behavioral domains as well as to detrimental metabolic and systemic conditions, causing increased morbidity and mortality in patients. In this review, the treatment effect within the context of allostasis or allostatic role has not been discussed. Scarcity of data on prospectively-designed studies exploring the change in allostatic load in bipolar disorder was evident. There seems to be a need for prospectively-designed studies measuring various allostasis-related parameters with the inclusion of at risk population and/or drug naive first/multiple episode patients before and after treatment to explore the illness toxicity and progression as well as the effect of treatment on the pathogenesis of bipolar disorder. The approach is crucial in order to provide the clinician tools for early detection of illness in genetically vulnerable individuals as well as to researchers for developing new treatment options.

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