EXPERT REVIEWS

Insulin dysfunction and allostatic load in bipolar disorder

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Bipolar disorder (BD) is associated with substantial morbidity, as well as premature mortality. Available evidence indicates that 'stress-sensitive' chronic medical disorders, such as cardiovascular disease, obesity and Type 2 diabetes mellitus, are critical mediators and/or moderators of BD. Changes in physiologic systems implicated in allostasis have been proposed to impact brain structures and neurocognition, as well as medical comorbidity in this population. For example, abnormalities in insulin physiology, for example, insulin resistance, hyperinsulinemia and central insulinopenia, are implicated as effectors of allostatic load in BD. Insulin's critical role in CNS physiological (e.g., neurotrophism and synaptic plasticity) and pathophysiological (e.g., neurocognitive deficits, pro-apoptosis and amyloid deposition) processes is amply documented. This article introduces the concept that insulin is a mediator of allostatic load in the BD and possibly a therapeutic target.

KEYWORDS: allostatic load • bipolar disorder • cognition • cytokines • early life stress • general medical comorbidities • HPA • insulin • neuroplasticity • oxidative stress

Bipolar disorder (BD) is an episodic, often chronic, mood disorder with an estimated lifetime prevalence of approximately 2–4% [1]. Individuals with BD have high rates of disability, and the illness has been consistently associated with increased morbidity and premature mortality [2]. An important determinant of the morbidity and psychosocial impact of BD is the cognitive impairment observed in a large proportion of BD patients. During the past decade, neurocognitive deficits in BD have been documented across disparate patient populations, affecting all domains of neurocognitive function, including, but not limited to, verbal memory, executive function and emotional processing. It is also reported that patients with a more severe illness – as indicated by greater lifetime duration of illness, higher frequency of episodes, psychotic symptoms, chronic symptoms and more hospitalizations – may have more pronounced neurocognitive deficits [3,4].

Mortality studies indicate that chronic stress-sensitive medical conditions, such as cardiovascular disease, obesity and Type 2 diabetes mellitus, are the most important specific causes of mortality amongst individuals with BD [5–7]. The excess mortality in BD populations due to these illnesses relates to a clustering of traditional (e.g.,

the metabolic syndrome), as well as emerging (e.g., inflammation) risk factors. The metabolic syndrome is a multidimensional risk factor for cardiovascular disease and Type 2 diabetes mellitus, and is related to mortality in the general population. A confluence of reports from more than a dozen countries indicates that BD is differentially associated with the metabolic syndrome [8,9]. Taken together, it is estimated that approximately 25–60% of individuals with BD meet the International Diabetes Federation (IDF) or Adult Treatment Panel (ATP-III) criteria for the metabolic syndrome [10].

Components of the metabolic syndrome have also been reported to be over-represented in BD populations. For example, an increased prevalence of overweight, obesity and abdominal obesity (i.e., ~20–35%) in individuals with BD, relative to the general population, has been reported [11]. Fagiolini and collaborators reported an obesity prevalence of 32% in subjects with BD, compared to 19.8% in the general population [12]. Several other studies have replicated these findings, reporting prevalences of between 20 and 35% [13,14]. Moreover, individuals with BD are also differentially affected by hyperglycemia, insulin resistance and Type 2 diabetes mellitus [6]. Although psychopharmacological

agents contribute to the metabolic risk, the relationship between BD and abnormal glucose insulin homeostasis cannot be entirely explained by iatrogenic factors [15].

Metabolic abnormalities (i.e., obesity, Type 2 diabetes mellitus and the metabolic syndrome) in bipolar populations are also associated with more severe illness presentations, a greater number of lifetime depressive and manic episodes, more hospitalizations, suicidality and a lower probability of recovery, and with an unfavorable course and poor response to lithium [16–20]. Observations of a bidirectional relationship between the metabolic syndrome and depressive symptomatology have also been documented in epidemiological surveys [21].

The explanation for these findings is not simple, but they are probably connected to neuroendocrine alterations via hypothalamic–pituitary–adrenal (HPA) axis activation, hyperglycemia and consequently hyperinsulinemia. In keeping with this view, this article introduces the model of allostasis and allostatic load (AL) as a conceptual framework for integrating the diverse abnormalities and 'end-organ damage' observed in BD.

Allostasis is the term used to refer to adapting processes used to maintain the stability of an organism (its homeostasis) through active processes that, when active, imply a 'price to be paid' by the organism. When allostatic response is excessive or inefficient, the organism develops an AL. If these adaptive mechanisms are repeatedly activated, the organism starts functioning in an allostatic state. It is then presumed that an 'AL state' (overload) would have a great cost to the organism [22].

Insulin is a pleiotropic peptide best known for its role in peripheral glucose homeostasis. In addition, insulin is also implicated in CNS physiology (e.g., neuronal survival and synaptic plasticity) and pathophysiology (e.g., premature apoptosis and amyloid deposition). Notwithstanding insulin's role in brain structure and function, it has received less attention in models of AL in BD and other mental disorders. Herein, we review the literature pertinent to insulin putative action in the CNS, as well as its role in AL and, consequently, in the pathophysiology of BD. In addition, the potential impact of childhood trauma in AL and in insulin metabolism will be reviewed.

Insulin & the brain

Since its first clinical application in 1922, insulin has been established as the primary hormonal regulator of systemic glucose concentration. Insulin acts both to suppress hepatic glucose output and to stimulate glucose uptake in muscle and adipose tissue [23]. Insulin resistance is a metabolic abnormality, wherein there is a reduced sensitivity to physiological levels of insulin, resulting in a compensatory heightened insulinemia [24]. The brain has generally been considered to be an insulin-insensitive organ, largely based on the fact that whole-brain glucose uptake and metabolism measurements have consistently shown minimal effect of insulin on total cerebral glucose metabolism, as measured by PET studies of the cerebral cortex [25,26]. Recent studies have refined the understanding of the action of insulin in the brain [27] based on the demonstrated transport of insulin to the CNS across the BBB by a saturable receptor-mediated process [27]. Insulin receptors, located in astrocytes and neuronal synapses, are highly concentrated in the olfactory bulb, cerebral cortex, hippocampus, hypothalamus, amygdala and septum [28]. In addition, insulin has been associated with the regulation of neuroplasticity in critical regions of the CNS, especially in the hippocampus [29,30], with the administration of insulin enhancing performance on hippocampal-dependent memory tasks. The passive-avoidance memory task and spatial memory training has been reported to alter hippocampal expression of insulin receptors [30–32].

In keeping with this possibility, recent clinical observations in Alzheimer's disease (AD) patients suggest that glucose and insulin may enhance performance on hippocampal-mediated tasks [33,34]. Moreover, insulin can modulate tau phosphorylation *in vitro* [35], a critical step to the production of neurofibrillary tangles. Moreover, insulin and IGF-1 induce tau dephosphorylation and increased microtubule binding of tau, through inhibition of glycogen synthase kinase 3 (GSK-3) [35].

Other interesting insights regarding glucose and insulin functioning disturbances in the CNS may be offered by the relatively well-documented brain changes and cognitive impairment associated with diabetes mellitus. Streptozotocin (STZ) diabetic rats, an experimental model of Type 1 diabetes, rapidly exhibit dendritic remodeling in the CA3 region of the hippocampus [36], with redistribution of synaptic proteins that may affect neurotransmission and plasticity [37]. In humans, Type 2 diabetes mellitus, in addition to its recognized associated complications, is also linked to cognitive dysfunction [38,39], with recent or declarative memory being the domain most frequently affected [40,41]. Memory impairments are associated with a hippocampal volume reduction in late middle-aged and elderly patients with Type 2 diabetes mellitus [41,42], and also in white matter abnormalities, especially located in frontal and temporal regions, when studied through the diffusion tensor imaging (DTI) method [43]. Type 2 diabetes mellitus has also been associated with AD in several epidemiological studies [44,45].

Chronic peripheral hyperinsulinemia is associated with relative decreases in insulin concentrations in the CNS as a result of the compensatory downregulation of the saturable insulin receptor-mediated process in the BBB. When the peripheral levels of insulin are consistently abnormaly high, there is a decrease in CSF insulin concentration [46], therefore medical disorders characterized by altered insulin sensitivity and/or chronic hyperinsulinemia, such as diabetes, are in fact brain insulinopenic states [47]. The moniker Type 3 diabetes mellitus has been proposed to describe the combination of both relative insulin decreases in the CNS, as well as insulin resistance, which possibly leads to AD neuropathology [48]. As AD and mood disorders have some neurobiological similarities, it is possible that these mechanisms are shared between them. For example, the presence of a lifetime history of major depressive disorder may be an important factor in the progression of AD, with major depressive disorder prior the onset of AD being associated with a larger number of neuritic plaques and neurofibrillary tangles in the hippocampus of patients with AD [49].

In the CNS, insulin is implicated in synaptic plasticity, cell resilience and apoptosis. Intracellular scaffolding proteins and signaling pathways mediating these processes are targeted by insulin. For example, insulin binds to specific receptors (IRS-1 and IRS-2) [50], and activates two distinct signaling pathways identified as the PI3K–PKB/Akt pathway and the classical MAPK pathway (**Figure 1**) [51]. These two pathways have distinct effects, with the first being associated with neuronal survival and the second with cell death. PI3K can be activated by multiple ligands, including NGF, BDNF, GDNF, IGF-1, NMDA and insulin [52,53]. Activation of PI3K results in the generation of the phosphoinositide phosphates PIP2 and PIP3 [54], whcih trigger downstream activation of serine/threonine kinases, including 30-phosphoinositide-dependent kinase-1 (PDK-1) and PKB/Akt [54,55]. Evidence suggests that PKB/Akt is of major importance in mediating neuronal survival, since expression and activation of PKB/Akt protects against apoptosis, hypoxic stress and nitric oxide toxicity [52,56]. Once activated, PKB/Akt protects cells against apoptotic stimuli by inactivating proteins belonging to the apoptotic machinery, such as the Bad and caspase 9, GSK-3 and transcription factors, including those of the FoxO family, CREB and IkB kinase (IKK), a regulator of NF-kB [51]. All of the aforementioned PKB/Akt targets probably function in a harmonized manner to mediate cell survival [54,57].

ERK1/2 forms a parallel branch and is implicated in the reduction of synaptic plasticity and cell death. The activation of ERK1/2 activates transcription factors, including Elk-1 and c-Myc. ERK1/2 activity is counterbalanced by specific ERK1/2 phosphatases, which can be induced by several stimulants, such as glucocorticoids, nitric oxide and insulin itself [58].

Regulation of signaling pathway of insulin is largely unclear, but it can be hypothesized that in the presence of other antiapoptotic factors, such as neurotrophins, the PI3K will have the predominant effect. Neuronal loss and apoptosis following extended periods of insulinopenia may have additive or synergistic effects when combined with the other neurotoxic stimuli [59]. Hyperglycemia may also induce oxidative stress, and this mechanism is well demonstrated in diabetes mellitus [60]. In addition, the production of advanced glycation end products (AGEs), a frequent feature of sustained hyperglycemic states, could be another important pathway of interplay between oxidative stress and diabetes. AGEs are formed by a sequence of events during which reducing sugars can react with the amino groups of proteins to produce crosslinked complexes and unstable
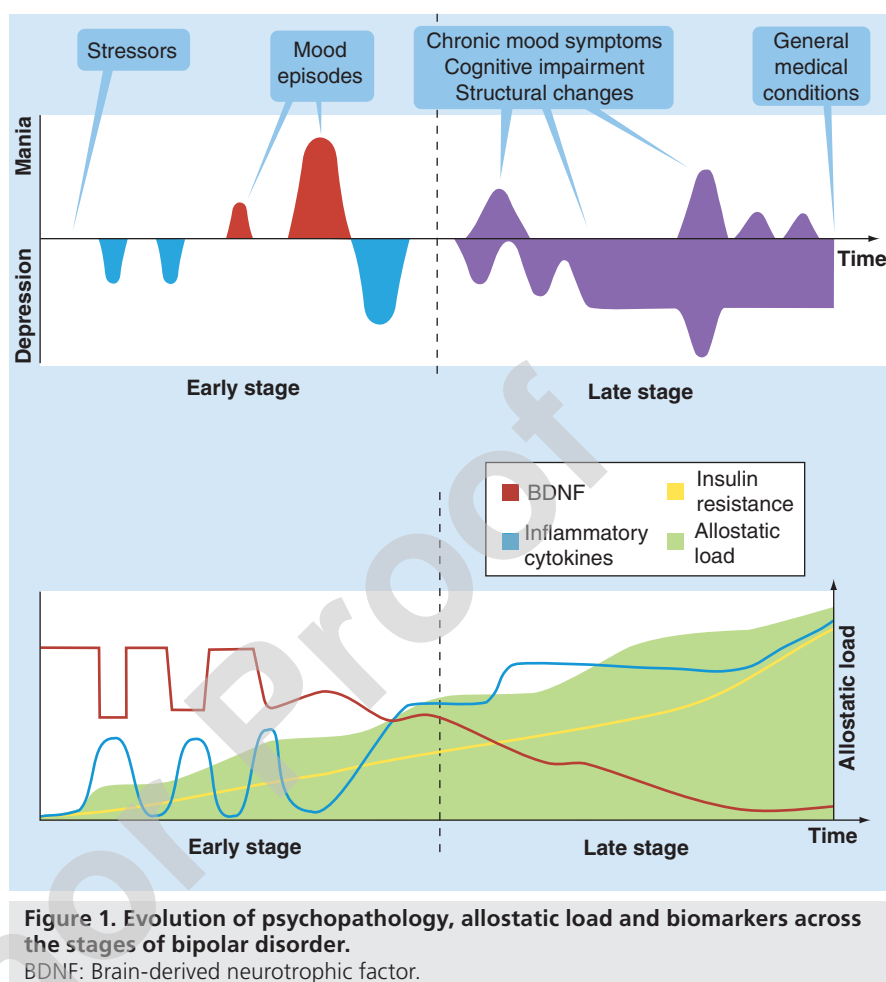

Figure 1. Evolution of psychopathology, allostatic load and biomarkers across the stages of bipolar disorder.
BDNF: Brain-derived neurotrophic factor.

compounds [61]. AGEs have a wide range of chemical, cellular and tissue actions, including endothelial damage [62]. AGEs bind to several ligands, but the most relevant is the receptor for AGEs (RAGE), and this link activates a signaling pathway that induces transcription of inflammatory genes, including cytokines [63]. In addition to inflammatory functions, the binding of AGE to RAGE serves as an adhesion receptor in the endothelium, facilitating macro- and micro-vascular damage [62]. AGEs have been consistently implicated in the pathophysiology of AD, and the measurement of AGEs in serum or cerebrospinal fluid has been proposed as a potential biomarker for its early detection [61]. Therefore, insulin and glucose metabolism seem to play an important role in maintaining the stability of CNS through active processes (allostasis).

Allostasis & AL in BD

The objective of allostasis would be to adapt to environmental demand. AL occurs when chronic adaptation goes awry [64,65]. Although adaptive mechanisms of allostasis can be protective for the individual, when continually activated there is a forced resetting of such parameters. Maintenance of stability through change requires energy and may be associated with unwanted collateral damage. It is the 'wear and tear' of the body and brain resulting from chronic overactivity or inactivity of physiological

systems that are involved in the adaptation to environmental challenges [66]. The final stage of AL progression is allostatic overload, a state in which allostatic mechanisms, instead of protecting, lead the individual to physiological deregulation predisposing to disease [65,67]. Excessive AL is associated with several pathological conditions, most notably seen during the processes of aging and acute and chronic stress. Recently, BD was described as a disease associated with excessive and longstanding effects of AL and allostatic overload [68].

The effects of AL in BD are cumulative and can be viewed in several adaptive systems of the body, such as the cardiovascular, endocrine and immunological systems [69]. As these systems are in interplay with each other, alterations in one system will affect others, initiating a cascade of events, with resultant deleterious consequences to the organism. Recently, several mediators involved in the regulation of important biological systems were described as having a significant role in AL processes [67], including stress hormones, epinephrine, norepinephrine and cortisol, which can, instead of protecting, start to damage the brain and body [70]. Disturbances in the HPA axis have been hypothesized to occupy a central position in AL models. The cumulative effects of corticosteroids may lead to hippocampal damage, neuroendocrine abnormalities, cognitive impairment and also to insulin resistance and immune dysregulation [68,71–74]. BD has been associated with hyperactivity of the HPA axis and with a dysfunctional response to stress. Both factors have been implicated in increases of vulnerability to mood episodes [75–79].

Another possible mediator of allostasis is the immune system. Inflammatory cytokines, such as IL-6 and TNF-α, may reduce the efficiency of allostatic mechanisms, acting synergistically in several cellular activities, including the action of enzymes, receptors, ion channels and transcription factors [80,81]. Because of that, cytokines may have pronounced effects on apoptosis control, cellular integrity and function (**Figure 2**) [82,83]. Increased plasma IL-6 is an independent risk factor for many diseases associated with aging, including Type 2 diabetes mellitus, atherosclerosis, hypertension, coronary artery disease, stroke and the progression from mild cognitive impairment to AD [84–86]. As expected, disturbances in both pro- and anti-inflammatory cytokines (e.g. IL-6, IL-4, IL-2, IL-10 and TNF-α) have been associated with BD [87,88].

Another important effector of AL is oxidative and nitrosative stress [89]. An increased production of oxidants leads to lipid peroxidation, with changes in cell function, such as altered neurotransmitter release and increased membrane permeability. Under physiological conditions, mitochondria are the major sources of reactive oxygen species (ROS), which are quenched by the antioxidant defense system. However, in situations where there is an imbalance between pro-oxidant/antioxidant states, oxidative damage may occur. The CNS is highly vulnerable to peroxidative damage, and has a relatively low endogenous antioxidant capacity [90,91]. Excessive formation of ROS may damage mitochondria, and in turn, mitochondrial dysfunction can further increase the production of ROS [92]. Reactive nitrogen species are derived from nitric oxide and facilitated by the activation of nitric oxide synthase 2 (NOS2). NOS2 is expressed on the surface of macrophages and is activated by the proinflammatory cytokine system, notably INF-γ and TNF-α [93]. Oxidative damage has been well documented during acute episodes and, to a lesser extent, during the euthymic phases in BD [94–96].

A hierarchical model of biomarkers of AL has been proposed wherein, cortisol and markers of sympathetic nervous system functioning, epinephrine and norepinephrine, are conceived as the 'primary mediators' in the cascade of events that ultimately affects 'secondary' outcomes, such as increased insulin resistance, abdominal obesity and cholesterol levels, ending in the 'tertiary' outcomes of increased inflammation and cardiovascular outcomes [80]. These markers can easily be measured and combined in an index producing a quantification of AL. Patients with higher AL were found to have increased risk for incident cardiovascular disease, physical and cognitive decline, and all-cause mortality in cross-sectional and longitudinal studies [97–99].

Maybe the most interesting aspect of AL in BD is the influence of environmental stressors in the neurobiological cascade associated with progression of the disorder. It is well defined that life events, particularly those that occur early in life, could drastically impact the course of BD [100], probably due to HPA axis reprogramming [100].
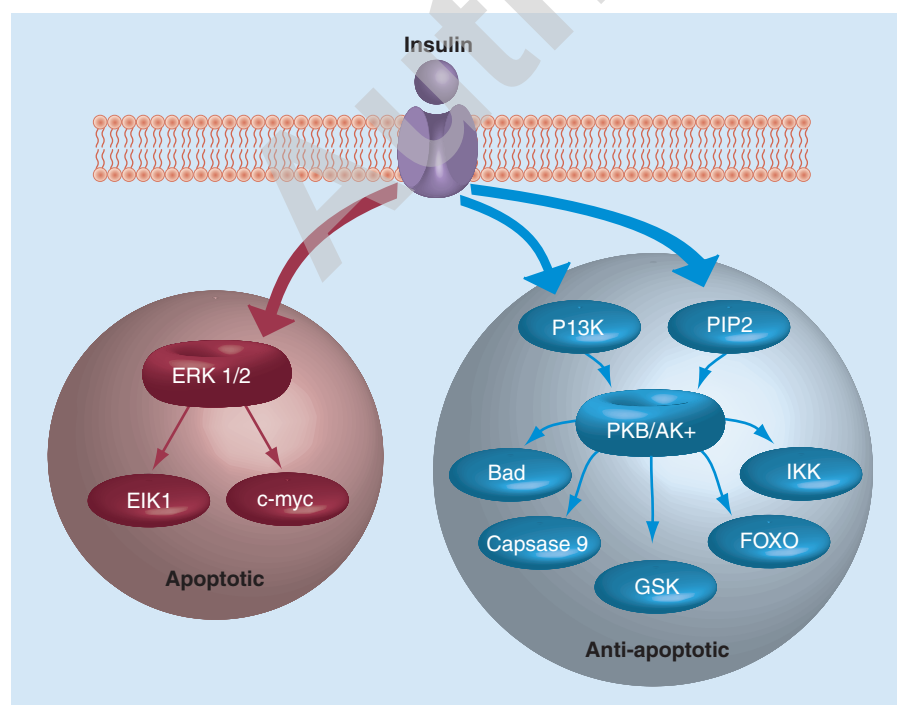

Figure 2. Apoptotic and antiapoptotic pathways of insulin signaling in neurons.

Early life stress, metabolic abnormalities & AL in BD

Different genetic, epigenetic and early life experiences are factors that interact, determining the capacity of the organism to cope with stress [101]. Childhood adverse experiences, such as abuse and neglect, might be a determinant for reprogramming set points in multiple regulatory parameters of AL. Several data from animal and human studies demonstrate the relationship between childhood stress and persistent behavioral alterations, modulation of neuroendocrine and immunological systems, and permanent changes in neuroanatomical architecture [102]. In animal experiments, neonatal maternal separation produces a set of abnormalities with biological markers very similar to AL mediators [103]. In humans, there is a replicated body of evidence reporting on the relationship between early trauma and adult development of chronic medical disorders, such as diabetes and metabolic-related disorders [104–106]. In a prospective longitudinal study involving 9310 subjects, it was found that the risk of obesity increased by 20–50% in people with history of early life stress (ELS), such as abuse and neglect. The strongest association with adiposity was found with participants reporting childhood physical abuse, and this tended to be associated with higher glycosylated hemoglobin levels [107].

Childhood trauma has been suggested to mediate vulnerability to affective disorders [108], although the exact mechanism of this association is not completely understood. Childhood abuse and neglect have been reported to be very common amongst individuals with BD [109]. For example, Leverich et al. reported on the association between a history of physical or sexual abuse as a child or an adolescent, and the course of illness variables, comorbidity and prior suicide attempts in a large clinical sample of individuals (n = 631) with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-defined bipolar I/II disorder [109]. A total of 49% (n = 185) of female patients and 36% (n = 99) of male patients reported being abused in childhood or adolescence. There were no significant gender differences in the incidence of physical abuse, but there were significantly more females reporting a history of sexual abuse. Both physical and sexual abuse were highly associated with an increased incidence of suicide attempts; the physically abused group reported increased suicidal ideation when manic, and the sexually abused group reported greater suicidal ideation when depressed [110]. In keeping with the view that distal trauma, such as childhood adversity, has persistent effects on brain development, several studies have documented an association between childhood maltreatment and long-term structural and functional brain alterations [111–113], involving dysfunctions in the prefrontal cortex (PFC), amygdala and hippocampus [114]. These changes have been taking place in the pathophysiology of BD and have been consistently related with its severity [115].

Early activation of the HPA and its consequences may function as an allostatic correlate even before the clinical onset of BD. People who were abused and neglected in childhood will presumably have an early beginning in the activation of allostatic mechanisms. If a mood disorder supervenes, they will be less resilient to allostatic insults. Since ELS and HPA activations are related to BD, and also to metabolic abnormalities, it is possible that both of these clinical entities share some pathophysiological mechanisms, including changes in insulin metabolism. Although the possible impact of ELS in the deprivation of insulin neurotrophic effects is still speculative, it potentially offers a promising avenue of investigation.

Expert commentary

A synthetic view of the literature would indicate that genetic and environmental factors in BD may act simultaneously to produce HPA activation, hyperglycemia and consequently hyperinsulinemia. These changes are associated with a low activity of brain insulin, which has neurotrophic properties, leading to deleterious effects in the integrity of some cerebral areas, especially the hippocampus, a mechanism possibly implicated in cognitive impairments. Sustained activation of stress response mechanisms in an individual with BD results in the lowering of peripheral BDNF and increases in inflammatory cytokines and oxidative mediators (Figure 3). Most of these contemporaneous abnormalities may occur as part of an allostatic effort to adapt and adequately respond to environmental demands.

As a cumulative phenomenon, AL will develop over the life course, with individuals accumulating it at different rates [97]. It may be possible that the beginning of abnormalities in substances involved in AL occurs even before the first mood episode, in latent or prodromal stages of the disorder. If future studies show this, allostatic mediators could be a useful tool to develop interventions with the objective to prevent or minimize AL, even in initials stages of BD. Genetic and ELA experiences will probably modulate the evolution of BD across progressively more severe stages. Interestingly, some recent studies have emphasized the role of socioeconomic status on diverse mediators of AL [116]. Socioeconomic status exerts effects in brain development beginning in early life and progressing across the life course. It impacts peripheral biology through cortico–limbic pathways, including known interconnections between the PFC, hippocampus and amygdala, and more downstream regulation of the HPA axis and sympathetic nervous system, orchestrated in large part through the hypothalamus and adrenal gland [97]. A growing body of evidence documents socioeconomical gradients for nearly all of the biological risk parameters for mood disorders, immune disorders and metabolic disorders, including unfavorable metabolic profiles (blood pressure, cholesterol levels, C-reactive protein and glycosylated hemoglobin) [97].

The opportunity afforded by the model of AL, taking into consideration all effectors, including the stress response axis and insulin, is an opportunity to refine and provide for a comprehensive and coherent disease model in BD. Such modeling will enable researchers to better understand the pathophysiological correlates of the exophenotype of BD and its comorbidities, as well as provide a nexus for genuinely novel disease modifying therapies (Table 1). Hitherto, until now, no available treatment to BD has been developed based on a disease model. All of the available medications were discovered by serendipity. The promise for successful innovation will be fulfilled when the pathophysiological model has been refined.
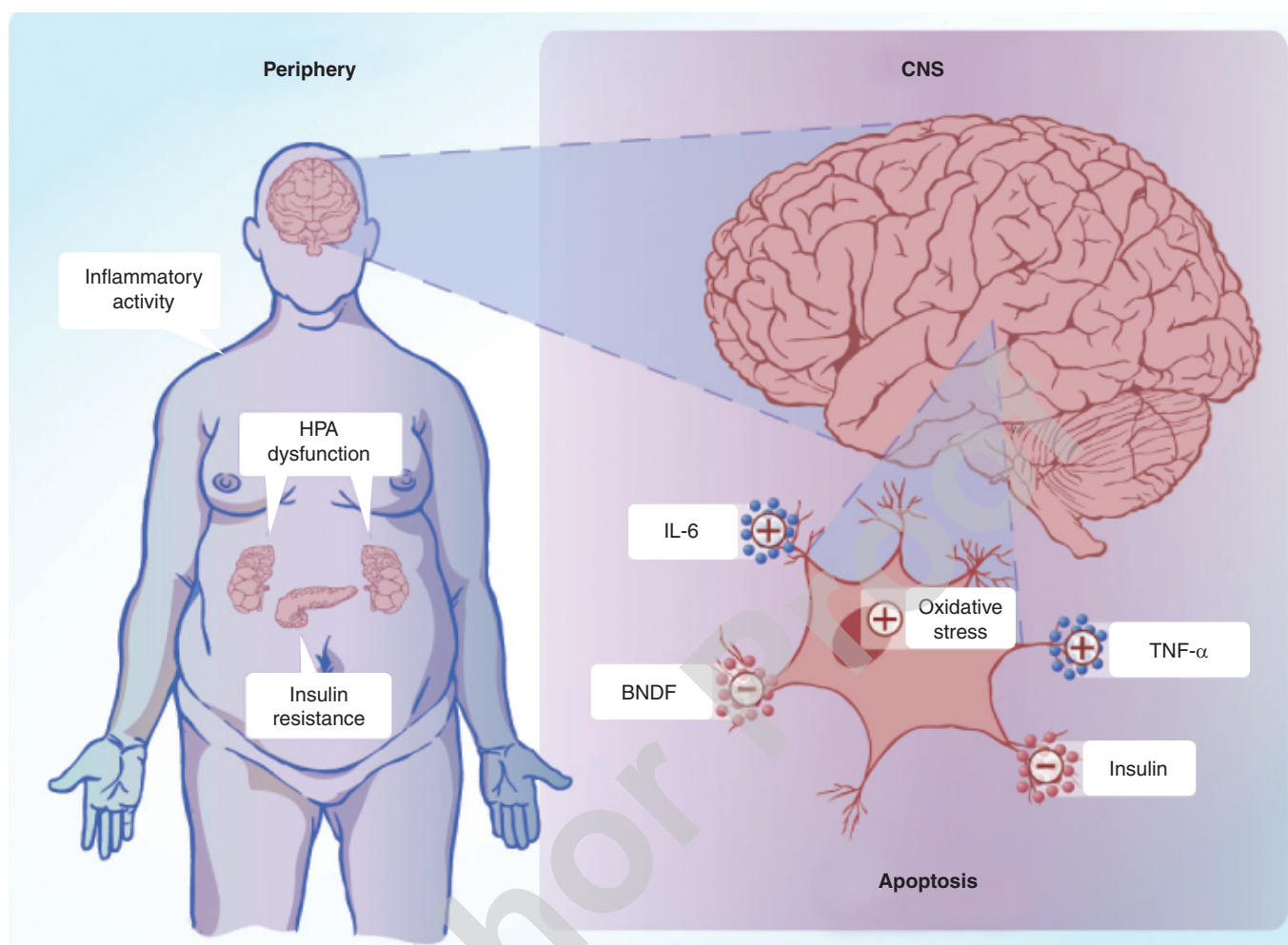
Figure 3. Central impact of peripheral insulin resistance and inflammation.

Five-year view

Taking into account the data about AL and the role of insulin in AL, some questions naturally emerge, including: 'Can we reverse or ameliorate AL in BD?' and 'How could we use de knowledge about insulin to develop beneficial interventions in BD?' The AL model in psychiatric disorders, and particularly in BD, has been progressively receiving empirical support in its ability to predict unfavorable outcomes [67]. The implications of these findings is a necessary change in the focus of treatment, incorporating the control and reversal of systemic abnormalities and the prevention of the evolution of the disorder to more severe stages, in addition to symptomatic control. There are several therapeutic possibilities, most of them without sufficient empirical evidence, but they indicate a new avenue of investigation.

One of the most important and understudied interventions may be physical activity [117]. It is well established that a sedentary lifestyle is a major risk factor for many diseases, including obesity, diabetes, cardiovascular disease, depression and dementia. Recent studies have shown that moderate physical activity can be beneficial for the brain, cardiovascular and metabolic systems [116,118,119]. Exercise has been shown to increase neurotrophin expression in the cortex and hippocampal regions of the brain [119].

Short-term aerobic fitness has been demonstrated to significantly increase hippocampal volume in individuals with schizophrenia and the increase in hippocampal volume was correlated with the *N*-acetylaspartate-to-creatine ratio, as well as test scores in short-term memory [120]. The salutary effects of exercise in the AL mediators provide the basis for hypothesizing that exercise could reverse some of the deleterious effects of AL in BD.

Moreover, data regarding glucose intolerance and insulin provides the basis for hypothesizing that control of this key mediator of AL can potentially offer the possibility to prevent the progression of the disorder, intervening positively in the course of BD. Delaying and even preventing neuropathological changes associated with excessive apoptosis has a crucial role in the management of people with BD. One possibility for manipulation of the neuroprotective effect of insulin is the administration of intranasal insulin – a pathway for a rapid penetration through the BBB without the risk of hypoglycemia associated with peripheral administration. Intranasal insulin administration has demonstrated action in memory improvement in healthy volunteers [121], as well as people with AD [122–124].

Another possible strategy is the use of novel insulin modulating interventions, such as the incretin hormone glucagon-like peptide-1 (GLP-1), as a new treatment for AD [125]. GLP-1 is

Table 1. Allostatic load biomarkers demonstrated to be abnormal in bipolar disorder.

Mediator	Function	Findings in bipolar disorder	Ref.
Neuroendocrine	Cortisol	Increased in mania and depression	[78]
	DHEA	Increased cortisol:DHEA ratio	[131]
Immune	TNF-α	Progressively increased with time and severity of BD	[132]
	IL-1	Increased transcription of IL-1 in a post-mortem study	[133]
	IL-6	Increased during manic and depressive episodes	[88,134]
	CRP	Increased in manic episodes	[135]
	Fibrinogen	Elevated in mania and depression	[136]
Metabolic	Triglycerides	Increased serum triglycerides in BD	[137,138]
	Glycosylated hemoglobin	Increased glycosylated hemoglobin in BD patients, increased use of atypical antipsychotics	[139]
	Insulin	Hyperinsulinemia in BD and increased of insulin resistance	[140]
	Homocysteine	High homocysteine levels in BD, which are correlated with cognitive impairment	[141]
	Cholesterol fractions	Lower HDL in BD	[137,138]
Cardiovascular	Systolic blood pressure	Increased in BD people	[142]
	Diastolic blood pressure	Increased in people with BD	[142]
	BMI	Higher frequency of obesity	[138]

BD: Bipolar disorder; CRP: C-reactive protein; DHEA: dehydroepiandrosterone; HDL: High density lipoprotein.

an hormone that regulates postprandial glucose levels through glucose-dependent insulin secretion. Currently, the GLP-1 receptor agonists exendin-4 and liraglutide are approved for the treatment of Type 2 diabetes [126], and others are in late-stage clinical trials. Interestingly, GLP-1 also plays an important role in the brain, its receptors are expressed in neurons and it acts as a neurotransmitter and neurotrophic factor [125,126], reducing apoptosis in hippocampal neurons and improving spatial and associative learning [127].

Thiazolidinediones (TZDs) are other potentially useful drugs. They are pleiotropic molecules that possess insulin-sensitizing properties and several TZDs are commercially available for the treatment of Type 2 diabetes mellitus. In addition to their well-established insulin-sensitizing properties, these agents also possess antioxidant, as well as anti-inflammatory properties. In animal models, this group of medications had been shown to have properties that enhance cognitive functions, as well as reduce the production of AGEs, oxidative products and inflammatory cytokines, such as IL-1 and TNF-α [128]. As a possible proof of concept, TZD therapy has been reported to enhance cognitive function in patients with AD [129] and depressive symptoms in unipolar and bipolar depression [130].

Conclusion

Notwithstanding intensified efforts to uncover the pathophysiology and causative factors of BD and its associated morbidity, most of these aspects remain largely unknown. Because of that, this article should be considered to be a theoretical development of a new hypothesis regarding the pathophysiology of BD, which needs to be tested and confirmed in further studies. However, accumulating evidence indicates that BD shares pathophysiological mediators (and moderators) with several 'stress-sensitive' non-communicable chronic medical disorders. Allostasis and AL provide a valuable heuristic explaining the differential association of select medical disorders, as well as neurobiological abnormalities

associated with BD. In this article, we explored how obesity, insulin resistance and brain insulinopenic states can provide a potential mechanism that integrates the diverse manifestations of increased AL in BD. We propose that in order to successfully address the negative impact of BD on the brain and in the periphery, treatment should go beyond keeping patients in euthymia and must include the search for better metabolic profiles, weight reduction and particularly effective stress management. Psychoeducation, neurocognitive remediation and lifestyle-related interventions may help to reduce AL and its impact on the course of the illness and the general health of patients with BD. The combination of these techniques with specific pharmacotherapy, including those that may work through the insulin pathway, may be the future avenue for improved functional outcome of bipolar illness.

Key issues

- Mortality studies indicate that chronic stress-sensitive medical conditions, such as cardiovascular disease, obesity and Type 2 diabetes mellitus, are the most important specific causes of mortality amongst individuals with bipolar disorder (BD).
- In the CNS, insulin is implicated in synaptic plasticity, cell resilience and apoptosis.
- Glucose and insulin functioning disturbances in the CNS are associated with brain changes, and cognitive impairments are associated with diabetes mellitus.
- Disturbances in the hypothalamic–pituitary–adrenal (HPA) axis have been hypothesized to occupy a central position in the allostatic load (AL) model of BD.
- The cumulative effects of corticosteroids may lead to hippocampal damage, neuroendocrine abnormalities, cognitive impairment and also to insulin resistance and immune dysregulation.
- A hierarchical model of biomarkers of AL has been proposed wherein, cortisol and markers of sympathetic nervous system functioning, epinephrine and norepinephrine are conceived as the 'primary mediators' in the cascade of events that ultimately affects the 'secondary' outcomes, such as increased insulin resistance, abdominal obesity and cholesterol levels, ending in the 'tertiary' outcomes of increased inflammation and cardiovascular outcomes.
- Environmental stressors, particularly those that occurr early in life, play an important role in the AL model of BD due to the early activation of HPA and they are with the associated adult development of chronic medical disorders, such as diabetes and metabolic-related disorders, as well as being an important risk factor to BD.
- BD may act simultaneously to produce HPA activation, hyperglycemia and consequently hyperinsulinemia. These changes are associated with low activity of brain insulin, which has neurotrophic properties, leading to deleterious effects in the integrity of some cerebral areas, especially the hippocampus, a mechanism possibly implicated in cognitive impairments. Sustained activation of stress response mechanisms in an individual with BD results in the lowering of peripheral BDNF and increases in inflammatory cytokines and oxidative mediators.
- Data regarding glucose intolerance and insulin provides the basis for hypothesizing that control of this key mediator of AL can potentially offer a possibility to prevent the progression of the disorder, intervening positively in the course of BD.

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