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GUEST EDITORIAL

Insulin resistance—a missing link no more

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Fifteen years ago, one of us proposed the hypothesis that insulin resistance (IR) is a missing link between mood disorders and dementia.[1,2] See Figure 1. Recently, the field has exploded with the data supporting all components of the model, especially the connection between depressive disorders and IR.[3,4] Increasing number of studies also confirm a role of depressive disorders in accelerating onset of dementia.[5–7] IR is a modifiable metabolic proinflammatory state underlying type 2 diabetes mellitus (T2DM), cardiovascular disease, vascular dementia and Alzheimer's disease. Today both, mass media and specialty literature are replete with information on the topic and 'stress' is often cited as the cause. Yet, while 'stress' is invoked, the profound epigenetic effects of stressful and other daily experiences and the resulting health-related behaviors resulting from them need to be more clearly recognized and defined.

Now with the growing crisis of IR and T2DM throughout the world, it is important to understand that the mechanisms for development of IR involve experiences over the life course, including pre-conception epigenetic factors, influences during gestation, early life adversity and the effects of poverty and the effects of modern lifestyle, with a central role of the brain as a target and mediator of these effects.[8–13] This means that there are many points during the life course where one can intervene and change trajectory toward a better outcome. This has advantages but can also lead to premature expectations, as will be elaborated.

STRESS AND ALLOSTATIC LOAD AND OVERLOAD

'Stress' is a known precursor of depressive disorders and one of us has pioneered the neurobiology of the stress response and its role both in successful adaptation and in pathophysiology and psychopathology.[11,13,14] We define 'stress' here as 'allostatic load and overload' involving the cumulative wear-and-tear on the body and brain from adverse experiences over the life course in the social and physical environment along with resulting health-damaging behaviors.[12,14] This definition steers away from the ambiguity of the word 'stress' and focuses on the biphasic protective and damaging effects of the biological mediators of allostasis, the active process that leads to adaptation. Together, an individual's daily experiences and health-damaging or health-promoting behaviors result in different degrees of dysregulation of the mediators of the neuroendocrine, autonomic, immune and metabolic systems that normally help the body adapt to a changing environment but can also cause a cumulative load of pathophysiology.

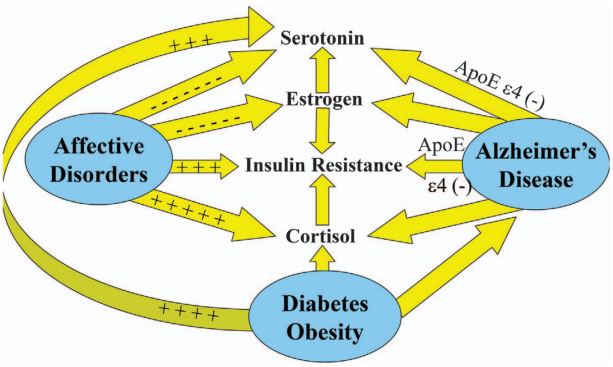

Figure 1. Initial schematic view of IR and some hypothesized mediators that are involved which originated from finding a high prevalence of depression in patients with the primary IR disorder PCOS and recognition that the same brain regions affected are involved in cognitive deciine and dementia. IR, insulin resistance; PCOS, polycystic ovary syndrome.

Insulin resistance, an example of the consequences of allostatic overload, is intrinsically connected to oxidative stress and inflammation,[15] which result from dysregulation of mechanisms and mediators that, as stated, normally help the body and brain adapt. A recent study identified biomarkers related to inflammation, glucose and lipids as key players in allostatic overload.[16] And multiple factors contribute to this dysregulation and later risk for IR, including epigenetic modifications of germ cell DNA pre-conception[9] and physiological imbalances during gestation,[17] along with later health-damaging behaviors involving diet, smoking, alcohol and lack of adequate physical activity. These are all important contributors to allostatic overload that can lead to T2DM. Moreover, often overlooked as sources of allostatic overload are circadian disruption and inadequate sleep that also contribute to the development of insulin and leptin resistance and its consequences.[18,19] In addition, sleep disordered breathing is a contributor to metabolic syndrome and visceral obesity, all of which are proinflammatory conditions.[15]

CENTRAL ROLE OF THE BRAIN

The adult, as well as developing, brain has the capacity for structural plasticity involving growth and shrinkage of dendrites, turnover of a subset of synapses with experience and during the circadian cycle, and neurogenesis in the dentate gyrus of the hippocampal formation.[11,20,21] See Figure 2. Mediators of this plasticity include glucocorticoids, excitatory amino acids, growth factors such as brain derived neurotrophic factor, circulating hormones such as insulin, insulin-like growth factor-1, leptin and ghrelin.[11,22]

Moreover, as shown by gene expression changes,[23] the brain, master controller of perceiving and responding to experiences that we often call 'stressors', is continually changing and one cannot 'roll back the clock'. 'Reversal' *per se* is not possible; rather, resilience and re-directing trajectories across the life course to reduce allostatic overload is the goal by opening 'windows of plasticity'.[10,24]

The allostasis/allostatic load model implies that the same mediators that promote adaptation, such as glucocorticoids and excitatory amino acids in the brain, can also contribute to damage. This is described as an inverted-U-shaped dose–response curve, in which acutely activated physiological levels of mediators enhance synaptic functions and memory whereas more intense acute activation has the opposite effect. See Figure 3. Chronic activation by repeated stressors or circadian disruption produces adaptive plasticity, with resilience, in the healthy brain. Loss of resilience, by definition, is found in anxiety and depressive disorders where IR has a role and contributes to cognitive impairment (Figure 4). With persistence of this condition, involving excessive activation of excitatory amino acids, potentiated by glucocorticoids, irreversible damage occurs; this is postulated to be a key step in the

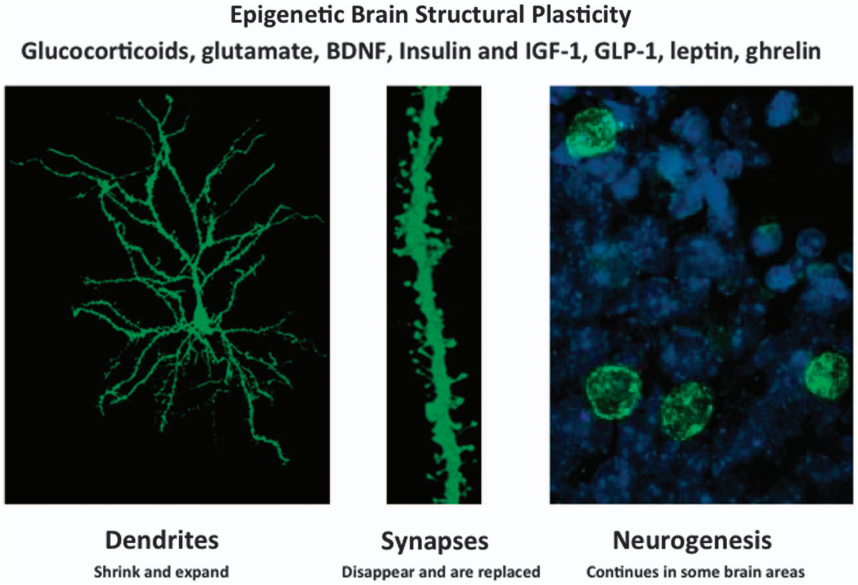

Figure 2. The adult as well as developing brain shows structural plasticity that involves remodeling of dendrites, turnover of a subset of synapses and neurogenesis in the dentate gyrus region of the hippocampal formation. BDNF, brain derived neurotrophic factor; GLP-1, glucagon-like peptide; IGF-1, insulin-like growth factor-1.

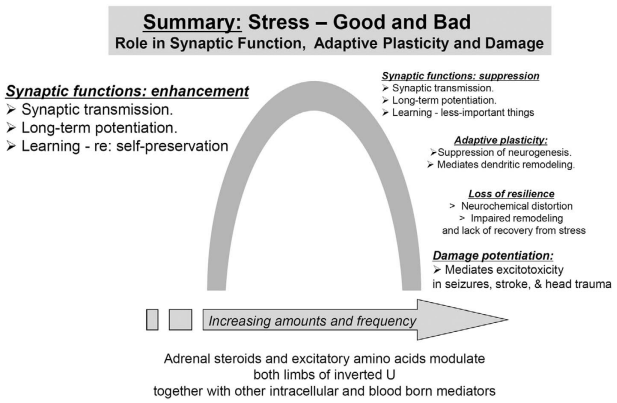

Figure 3. The biphasic actions of mediators of allostasis to promote adaptation and also damage is described in an inverted-U-shaped dose–response curve, in which acutely activated physiological levels of mediators enhance synaptic functions and memory, whereas more intense acute activation has the opposite effect. Chronic activation by repeated stressors or circadian disruption produces adaptive plasticity, with resilience, in the healthy brain. Loss of resilience is found in anxiety and depressive disorders where IR has a role and contributes to cognitive impairment. With damage, involving excessive activation of excitatory amino acids, potentiated by glucocorticoids, irreversible damage occurs; this is postulated to be a key step in the irreversible activation of the cascade leading to Alzheimer's disease involving inactivation of the adaptive insulin receptor mechanism.[5] In contrast, normal brain aging involves potentially reversible loss of resilience, which, for example, can be overcome by regular physical activity.[25] IR, insulin resistance.

irreversible activation of the cascade leading to Alzheimer's disease involving inactivation of the adaptive insulin receptor mechanism.[5] In contrast, normal brain aging involves potentially reversible loss of resilience, which, for example, can be counteracted by regular physical activity.[25]

Putting this into perspective, the neural circuits in a healthy brain are remodeled by experiences to enable behavioral responses that are appropriate to what the individual is experiencing, for example, being more vigilant and anxious in an potentially dangerous environment.[13] The healthy brain is resilient and neural circuitry adapts to a new situation along with underlying changes in gene expression.[23] The unhealthy brain is not so plastic and the brain in someone suffering from IR is less able to adapt and likely to 'get stuck' and need external intervention involving pharmacological agents or behavior (for example, exercise).[25] Ultimately, detecting early changes in biomarkers of IR, oxidative stress and dyslipidemia as part of allostatic overload[16] will allow rapid evaluation of pre-symptomatic treatments in in proof-of-concept primary prevention interventions.

Because of the multi-systems actions of the mediators of allostasis (adaptation) and allostatic overload (pathophysiology), there is multi-morbidity of disorders of brain and body (for example, IR with depression, cognitive impairment, cardiovascular disease and later dementia) and a long-term impact of early life events, involving adverse childhood experiences and poverty, on this multi-morbidity, within 'sensitive periods' that do not, however, preclude promoting positive trajectories later on via the continuing capacity for plasticity.[10,26]

INSULIN RESISTANCE IN THE BRAIN AND APPROACHES TO TREATMENT

The brain is, indeed, a major target of IR and one of us was the first to demonstrate structural and functional deficits in hippocampal integrity in relation to insulin resistance among persons at genetic risk for Alzheimer's disease. Our cumulative findings to date suggest that in middle-aged adults, IR is associated with disrupted memory and executive function, and corresponding metabolic decline in the medial prefrontal cortex, reductions in hippocampal volumes, and aberrant intrinsic connectivity between the hippocampus and medial prefrontal cortex.[27–29] These findings are supported by recent work in animal models, in which antisense inactivation of the insulin receptor in hippocampus leads to cognitive impairment without systemic consequences,[30] whereas antisense inactivation of the hypothalamic insulin receptor creates systemic insulin resistance and dyslipidemia and also insulin resistance in the hippocampus along with depressive-like behavior and cognitive impairment.[31] Remarkably, these changes are reversed by dietary restriction[32,33] indicating that the brain can be resilient.

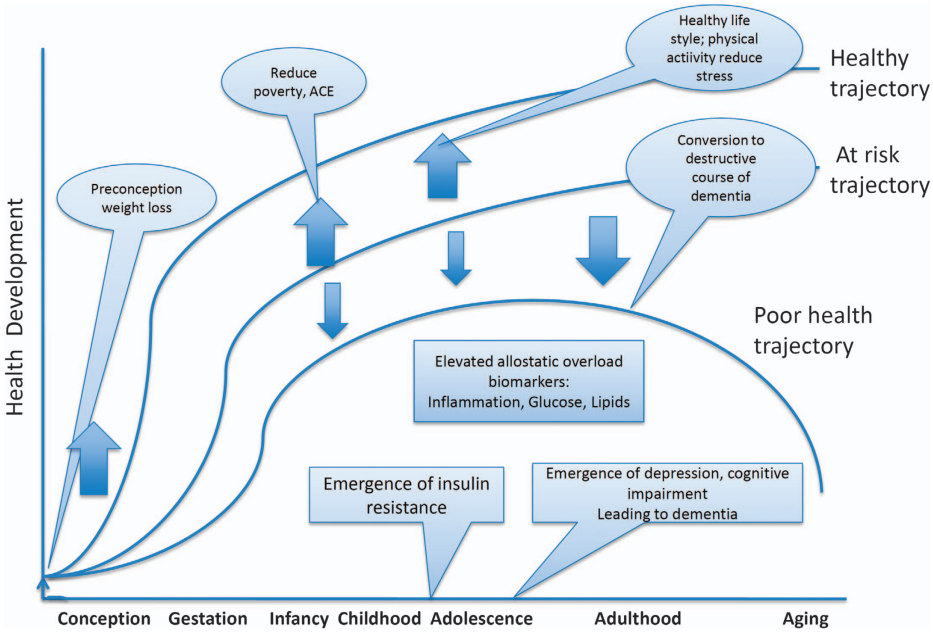

Figure 4. Timeline of health development for allostatic overload, particularly pertaining to insulin resistance and inflammation, summarizing life trajectory during which interventions for weight loss pre-conception and during gestation, as well as reduction of the effects of poverty and adverse experiences, and improved health-promoting behaviors can all contribute to reductions of the overload and prevent the irreversible conversion to this condition to dementia.

Yet, there is at some point, a 'switch' that triggers irreversible changes that lead toward amyloid beta (Abeta) toxicity and dementia.[5] These authors point out that synaptic NMDA receptor activation normally has an antioxidant role by suppressing FOXO1 transcription factor in hippocampus, but abnormal and excessive NMDA activation in the insulin resistant state appears to enable FOXO1 translocation to the cell nucleus leading to the generation of reactive oxygen species and possibly also activation of stress kinases, which further impairs insulin signaling. Moreover, Abeta production is accelerated and Abeta oligomers enter into a vicious cycle leading to further damage.[5] Mitochondrial function declines under these conditions contributes to the positive feedback cycle of toxicity.[34]

Yet, on a positive note, glucagon-like peptide (GLP-1) has insulinotrophic actions and promotes weight loss and has been shown to exert neuroprotective and anti-apoptotic effects, to reduce Abeta plaque accumulation, modulate long-term potentiation and synaptic plasticity and promote differentiation of neuronal progenitor cells.[35,36] Behaviorally, in animal models, treatment with GLP-1 receptor agonists improve learning and memory, as well as reduce depressive-like behaviors.[36] Another potential intervention with a natural molecule, based on animal models, is acetyl-L-carnitine (LAC) which has not only rapid anti-depresssant-like effects but also has metabolic functions that rapidly reverses hyperinsulinemia and hyperglycemia in the Flinders Sensitive Line, rat which is deficient in LAC.[37,38] In addition to defined molecules, the gut microbiome is recognized as a potential target of probiotic therapy for diabetes that alters the qualitative content of commensal bacteria and corrects dysbiosis and, as a result, also treats the imbalance of parasympathetic vs sympathetic activity that contributes to chronic inflammation and T2DM.[39]

INTERVENTIONS MUST TAKE ADVANTAGE OF THE WHOLE LIFE COURSE

Walter Cannon introduced the concept of the 'wisdom of the body' and now we can add 'and the brain', referring to the efficient neural as well as systemic activation and turning off of allostasis to maintain homeostasis. Turning on a robust response to a challenge and turning it off when not needed is the key to successful allostasis and minimizes allostatic load/overload.[14] Yet modern lifestyle works against successful allostasis via circadian disruption and poor health behaviors, among other influences. For the 'wisdom of the body and brain' to operate, more integrative interventions are needed that open 'windows of plasticity' and allow the brain and body to change itself in a healthier direction. Pharmacological agents may be useful as facilitators but will not work alone!

Within this framework, the underreported, and therefore, lesser known fact, is that depressive disorders and diabetes are treatable, but not curable diseases, whereas the course of dementia can be mitigated at best. The growth of IR is in direct association with the overall worsening of rates of obesity and increasingly poor diet and exercise habits in the US[40] that are occurring independently of genetic risk.[41] In particular, chronic diseases now begin in childhood and even before as a result of prenatal and in utero influences[9,17] as well as the result of poverty and abuse and neglect.[42–44] Thus, interventions must take advantage of the fact that insulin resistance is a malleable pathophysiological condition with multiple peripheral and central targets for intervention before the 'switch' occurs into irreversible excitatory/inflammatory toxicity. In particular, prenatal weight loss by both parents will begin to slow the transgenerational transmission of propensity for IR[9,17] and efforts to reduce adverse early life events, improve nutrition and mitigate poverty will also help.

Interventions that build self-efficacy in general and in managing insulin resistance, in particular, such as healthy diet, regular sleep and regular physical activity, promote better continuing health and will also lead to decreased incidence of major chronic illnesses associated with it.[45] Yet, our recent results showing executive function deficits in relation to worsening IR assessed by direct measures of insulin action in adults younger than age 45 support early detrimental effects of IR on prefrontal cortical brain function involving decision making and self-regulation that can further weaken an individual's ability to improve their health.[46] Indeed, changing lifestyle requires motivation and having a

meaning and purpose in life,[47] which itself can have a beneficial effects on markers of allostatic overload.[48,49] Moreover, given the need to develop interventions at many levels to redirect biology before the irreversible aspects of dementia take hold, the other, more sobering, message is that, because there are many points during the life course where one can change trajectory, we must not expect immediate miracles, at least as far as the T2DM epidemic. This is because of the transgenerational epigenetic aspects that are likely to last for generations, just as the build-up of this epidemic has been gradual since WWII. Yet, as we have noted, there are many opportunities, from pre-conception, during gestation, infancy and childhood onwards to prevent the irreversible aspects of dementia along with improving 'healthspan'.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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