Does obesity and diabetes mellitus metastasize to the brain? “Metaboptosis” and implications for drug discovery and development

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The overarching aim of this commentary is to press the point that alterations in bioenergetics are hypothesized to play a critical role in the pathophysiology of many brain-based disorders (e.g., major depressive disorder, bipolar disorder). As a derivative of this hypothesis, it is further conjectured that agents capable of targeting bioenergetic effector systems may be potentially therapeutic.

Existing pharmacological treatments for mood, psychotic, as well as cognitive disorders in psychiatry, are insufficient from the point of view of achieving robust symptomatic control, functional improvement, reliable quality of life enhancement, and other patient-reported outcomes (PROs). Moreover, no FDA-approved agent for the foregoing disorders has demonstrated disease modification capability, the holy grail of treatment.

The cul de sac we find ourselves in with respect to psychiatric drug discovery and development, and the absence of a direct line of sight, is largely due to insufficient disease model characterization. Consequently, recapitulating disease models for mental disorders has been elusive and a priority research vista. Notwithstanding, the availability of exciting new technological approaches (e.g. inducible pluripotent stem cell research), computational statistical approaches, as well as surreal insights in neuroscience are providing the reasons to believe that future drugs in psychiatry will be not only based on disease models but possibly also modifying disease processes.

Molecular, cellular, pharmacologic, animal, human, and clinical data provide convergent evidence indicating that alterations in bioenergetics are critical pathoetiologic processes within abnormal central nervous system (CNS) circuit and network function. For example, it is amply documented that sub-chronic and chronic alterations in central/peripheral glucose-insulin homeostasis, sirtuin, and incretin function are associated with maladaptive changes in neuronal and glial cellular architecture, morphology, number, density, and function.

It is further observed that chronic alterations in each of the foregoing effectors result in apoptosis and epigenetic aging in animal models. Accelerated apoptosis is also reported in mood, psychotic, and cognitive disorders, and may in some cases be a consequence of central bioenergetic abnormalities. Herein, we propose the moniker “Metaboptosis” to refer to the premature cellular aging and death as a consequence of alterations in intra- and extracellular processes relevant to metabolic effector systems (glucose-insulin homeostasis).

We also introduce the notion of obesity and type 2 diabetes mellitus (TDM2) “metastasizing” to the CNS, to both explore a unique brain-body heuristic, and more specifically, to underscore the deleterious effects that “metabolic obesity” and/or TDM2 exert on the human CNS. Results from both population and clinical studies in both general and mixed clinical populations indicate that metabolic obesity and TDM2 are modifiable brain hazards, as evidenced by an increased incidence of domain-based psychopathology (e.g., cognitive impairment), as well as syndromal DSM-5-defined psychopathologies (e.g., mood disorders) in affected persons.

During the past decade, compelling proof-of-concept data has emerged, indicating that pharmacological treatments that target aberrant intracellular and/or
extracellular metabolic processes exert salutary effects on neuronal cellular and sub-cellular function (e.g., mitochondria).\textsuperscript{13} The foregoing observations are replicated in animal studies with accumulating evidence indicating that appropriate “target engagement” with metabolic-based treatments exert beneficial effects, and possibly disease modifying effects, across multiple domains of psychopathology (general cognitive function).

For example, intranasal insulin, incretins (e.g., liraglutide), thiazolidinediones, caloric restriction mimetics (e.g., metformin, resveratrol), as well as SGLT-2 inhibitors, have all exhibited beneficial effects in animal models of depression, reward (e.g., motivation), and general cognitive dysfunction.\textsuperscript{14,15} It is intriguing that select agents (e.g., SGLT-2 inhibitors) have demonstrated anti-apoptotic effects in neuronal cell lines. Several of the foregoing agents have empirical evidence indicating beneficial effects in healthy control and psychiatric populations (without comorbid TDM2).\textsuperscript{16} For example, it has emerged that intranasal insulin improves measures of executive function in adults with bipolar disorder, as well as measures of memory in persons with ApoE4-mild cognitive impairment (MCI).\textsuperscript{17–19} Moreover, liraglutide demonstrates beneficial effects across several measures of cognitive function (e.g., executive function) in individuals with mood disorders, independent of its known effect on weight, and coincident with changes in CNS biomarkers of neuronal health.\textsuperscript{20,21}

Drug discovery and development in psychiatry has stalled during the last 10 years, resulting in the retreat of significant research and development investment. Truly exciting developments have occurred with respect to developing glutamatergic treatments for treatment-resistant syndromes (e.g., intravenous ketamine), with the hope that related agents would be capable of providing rapid onset, robust treatment efficacy with an improved safety profile (e.g., rapastinel).\textsuperscript{22} Notwithstanding, the need exists for scalable and novel treatments for brain-based disorders that engage metabolic systems may not only be symptom suppressing but disease modifying for mood, psychotic, and cognitive disorders.

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