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Editorial

Metabolism, cognition, and the brain throughout life

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In the last decade, there has been mounting interest in understanding how changes in metabolic function leads to increased disease risk, including diseases of the nervous system. Global dysfunction of metabolism leads to a disorder known as metabolic syndrome (MetS), which is a constellation of disorders, including obesity, hypertension, dyslipidemia, and impaired glucose tolerance, that underlie an increased risk for diabetes and cardiovascular disease by five-fold. Currently, 25% of all individuals worldwide have MetS (www.idf.org). Moreover, 400+ million people live with diabetes worldwide (http://professional.diabetes.org), and more than 2 in 3 adults from industrialized countries, including the USA, are considered overweight or obese (www.niddk.nih.gov). Compounding these alarming statistics, multiple studies report that patients with MetS, from young to old, are at increased risk of developing neurodevelopmental, neurodegenerative, and cognitive disorders. In some cases in youth, this is likely due to maternal metabolic conditions, which are associated with a broad spectrum of associated neurodevelopmental problems in offspring, including autism spectrum disorder (ASD) and neurodevelopmental delay. Several adult neurodegenerative disorders, such as Alzheimer's disease, similarly have an increased incidence in patients with the MetS or frank diabetes. Importantly, AD is the leading cause of dementia and currently affects over 50 million people worldwide, and this incidence is expected to reach over 100 million by 2030 (www.alz.co.uk). Patients with MetS have an increased AD risk, and alarmingly, patients with diabetes have a 50–75% increased risk of developing AD compared to age- and gender-matched controls. Despite these associations, however, the mechanisms connecting these conditions are unknown, although encouraging studies show that dietary modification, exercise, and sleep hygiene may all improve a wide spectrum of neurological disorders.

The goal of this special edition of *Neurobiology of Disease* is to better understand the connection between the individual and collective components of MetS and a wide array of neurological disorders that span the lifetime of individuals, from ASD and neurodevelopmental disorders in youth to chronic progressive neurodegenerative disorders in adults. These topics are covered in a collection of informative reviews coupled with primary research articles that can be divided into four main sections: 1) Neurodevelopmental implications of metabolism, 2) Effects of diabetes and obesity on cognition, 3) Lifestyle and metabolic interventions, and 4) Primary research articles. Together, these articles address aspects of the relationship between MetS and neurological disorders throughout life and offer a timely overview of the recent research advances, current clinical implications, and potential treatment strategies.

The issue begins with two reviews on neurodevelopmental implications of metabolism. In the first article, Drs. Jennifer Tuscher and Jeremy Day discuss the role of epigenetic modifications in the developing and adult brain, including the potential for these modifications to be transmitted across generations. They cover how epigenetic changes driven by exposures, experiences, stress, and diet can drive the metabolic phenotypes of individuals and their progeny, with particular attention to the implications epigenetic patterns have on metabolic health and on both normal functioning and disease states of the central nervous system. The following review article by Drs. Susanna Mierau and Ann Neumeyer focuses on links between metabolism and brain function in youth, with specific emphasis on the role metabolism plays in the pathogenesis and prognosis of ASD. Therapeutic considerations based on current knowledge are presented, including addressing nutritional needs along with dietary interventions and oral supplements. Together, these two articles highlight early advances that provide insights into the important consequences of metabolic disease in inheritance and youth.

Papers in the second section of this issue then focus on how diabetes and obesity impact central nervous system function and cognition. First, Drs. Eelco van Duinkerken and Christopher Ryan review the available clinical data from longitudinal studies that examined the differential impact of type 1 and type 2 diabetes on risk for cognitive complications. They explicitly discuss the implications of the increased risks for cognitive decline, and call for additional insights into the precise

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mechanisms that induce cognitive dysfunction, particularly for type 2 diabetes with its associated comorbidities. Among those concomitant factors is obesity, which is the topic of the second review in this section from Dr. Catrina Sims-Robinson and colleagues. In this review, the authors share data supporting a role for obesity in cognitive impairment and eloquently present an informative overview of how obesity-related metabolic effects on the gut, immune system, and insulin signaling culminate in endothelial dysfunction and blood brain barrier disruption. They further touch on how available therapeutic strategies for obesity impact cognitive function in obese individuals. Together, these articles provide an excellent foundation for the evidence and contributing mechanisms whereby the metabolic consequences of diabetes and obesity trigger increased risk of cognitive decline, and offer an exciting look forward to future advances and knowledge that will set the stage for the development of novel therapies.

The third section of the issue further expands on the potential efficacy of popular and emerging metabolic interventions on cognitive function. Dr. Anthony Hannan and colleagues begin by discussing the role of the gut-brain axis in health and neurodegeneration, as gut microbiota represent a dynamic system that can be influenced by exercise, diet, and stress-induced metabolic changes. As such, therapeutic approaches that target the gut microbiota represent appealing avenues to potentially circumvent central nervous system damage associated with metabolic conditions. Dr. Devin Wahl and colleagues then present an enlightening look at how aging and lifestyle can impact dementia risk. They specifically focus on interventions that improve metabolic health and demonstrate that diet, activity, and pharmacologic interventions that are proven to offer benefit against aging-related diseases may also be beneficial for long-term brain health. Together, these two reviews highlight the importance of maintaining metabolic health to support optimal neurologic functioning throughout life.

The final section of this issue includes three primary research articles that augment the knowledgebase on mechanisms and novel therapeutic approaches to mitigate cognitive decline associated with metabolic disease. First, Drs. Bhumsoo Kim, Sarah Elzinga, and colleagues examine how insulin resistance can impact the effectiveness of insulin and insulin-like growth factor I treatments currently being evaluated in clinical trials for Alzheimer's disease. Using *in vitro* and *in vivo* models, they uncover mechanisms underlying reduced effectiveness of these treatments in the context of insulin resistance, data which suggest that treatments that impact neurodegeneration may have diminished effectiveness for individuals with the MetS. Next, Dr. Michele Bastide and colleagues assess the impact a high fat diet can have on cognitive function in mid-life in mice. Through a thorough characterization of metabolic and cognitive phenotypes, they were able to show that visceral adiposity and cerebral blood flow may predict cognitive decline. Finally, Dr. Jennifer McGuire and colleagues examine how pioglitazone, a diabetes drug that modulates metabolic activity, affects cognitive function in rats with traumatic brain injury. Their findings suggest that therapies targeting brain metabolism may be beneficial for improving cognitive functioning in chronic traumatic brain injury.

Collectively, the articles in this issue provide an informative, detailed overview of the intricate relationships between metabolic health and brain function. From epigenetic inheritance across generations to neurodevelopmental delays in youth to conditions affecting adult brain health, metabolic changes and the components of the MetS play a relevant and intriguing role in the pathogenesis and prognosis of neurodegeneration and cognition. Moreover, therapeutic opportunities including lifestyle interventions offer considerable potential to circumvent neurologic complications associated with diabetes, obesity, stress, and other factors that alter metabolic health. While some of these concepts are only just emerging, the wealth of information acquired from recent and ongoing studies is encouraging. We believe this issue is enlightening and thought provoking, and we look forward to continuing to follow the advances made in understanding the connection between metabolism, cognition, and the brain throughout life.

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