Insights from animal models on insulin signalling disturbances and related diseases in neurological and mental conditions

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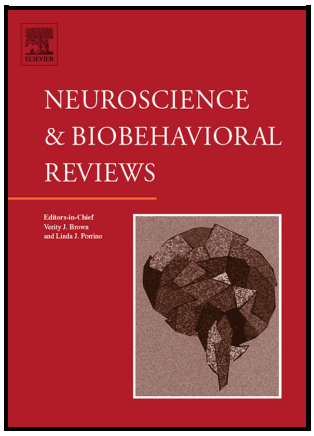

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TITLE PAGE

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Abstract:
There has been a growing awareness of the need for scientific research to focus on somatic and mental comorbidities in recent years due to the emerging evidence showing their substantial overlap at numerous levels. In this special issue, initiated by members of the EU-funded PRIME consortium ("Prevention and Remediation of Insulin Multimorbidity in Europe; www.prime-study.eu), the focus is on the comorbidities of metabolic disturbances, especially related to insulin signalling dysregulation and mental and neurological disorders. Thus, while obesity, type 2 diabetes, and metabolic syndrome are commonly known to be insulin-related disorders, the last decades have shown that neurodegenerative disorders, such as Alzheimer's disease, as well as neurodevelopment disorders, such as obsessive-compulsive disorder (OCD), autism spectrum disorders (ASDs) and attention deficit / hyperactivity disorder (ADHD) also fall into this category. The special issue draws together a series of basic and clinical review articles that describe the current knowledge and future perspectives regarding insulin comorbidities across a multidisciplinary group of experts

Keywords: insulin, diabetes, Alzheimer's disease, cognition, animal models

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There has been a growing awareness of the need for scientific research to focus on somatic and mental comorbidities in recent years due to the emerging evidence showing their substantial overlap at numerous levels. In this special issue, initiated by members of the EU-funded PRIME consortium ("Prevention and Remediation of Insulin Multimorbidity in Europe; www.prime-study.eu), the focus is on the comorbidities of metabolic disturbances, especially related to insulin signalling dysregulation and mental and neurological disorders. Thus, while obesity, type 2 diabetes, and metabolic syndrome are commonly known to be insulin-related disorders, the last decades have shown that neurodegenerative disorders, such as Alzheimer's disease, as well as neurodevelopmental disorders, such as obsessive-compulsive disorder (OCD), autism spectrum disorders (ASDs) and attention deficit/hyperactivity disorder (ADHD) also fall into this category. The special issue draws together a series of basic and clinical review articles that describe the current knowledge and future perspectives regarding insulin comorbidities across a multidisciplinary group of experts. This commentary provides a primer regarding the collated articles that focus predominantly on preclinical findings and synthesises their major messages, which can be viewed in greater depth in the articles themselves.

A variety of different rodent models have been developed in order to mimic insulin-related disorders, including inbreeding and genetic approaches and pharmacological (environmental) manipulations at different developmental timepoints. In their systematic review, Ottomana et al., (Ottomana et al., 2023) draw together the available preclinical studies in rats and mice that investigate the association between hyperglycemia and impairments in attention, spatial- and working- memory. While the majority of the studies were performed in male rodents, a theme that recurs in the article, the evidence from genetic and pharmacological approaches to cause hyperglycemia supports the idea that disrupted insulin signalling is associated with cognitive impairments.

Cognitive inflexibility, the inability to alter responses to changing environmental challenges or rules, is another major domain that is affected by neurodevelopmental disorders. The review by Sullivan et al., (Sullivan et al., 2023) assesses the key brain circuits that are involved in governing this behaviour, as well as how insulin-related disorders impinge on these circuits and ultimately cognitive flexibility. Here, the authors describe the major brain regions, such as the orbitofrontal cortex, cingulate cortex, amygdala and nucleus accumbens, that play a

role in behavioural flexibility via a variety of neurotransmitters such as GABA, glutamate and dopamine, and the changes through which type 2 diabetes (and other metabolic diseases) impact their structure, morphology and functional connectivity taking both preclinical and clinical findings into consideration. Interestingly, they also propose evidence showing that type 2 diabetes medications, such as metformin, may be beneficial in central disorders of cognitive inflexibility and thus have potential to be repurposed.

While briefly described in the aforementioned article, the central focus of the article by Gruber et al., (Gruber et al., 2023) is the impact that insulin-related disorders have on the brain dopamine system and reward processing. The review first describes the findings of insulin receptors throughout the brain reward system (i.e. nucleus accumbens, ventral tegmental area, substantia nigra) and the complex mechanisms via which they can affect dopamine signalling in these regions. Unsurprisingly, metabolic disorders have a substantial impact on the role that insulin signalling within the reward circuit plays, predominantly due to insulin resistance. To conclude, the authors collate findings showing the impact this has on anhedonia and other depressive symptomology in rodents and highlight the clinical evidence supporting the link between insulin-signalling and depression. Finally, they conclude by suggesting that drugs used for the treatment of somatic insulin-related disorders could be effective in a subset of patients with mood disorders.

Using animal models, it is also possible to address the question of the comorbidity in reverse. This is the focus of Alves and colleagues (Alves et al., 2023) who summarise the literature showing how insulin signalling is effected in Alzheimer's disease rodent models. The premise of the review is based around ideas that Alzheimer's disease could be viewed as a third type of diabetes and that insulinopathies provide an overarching link bringing together various Alzheimer's disease hypotheses. Across multiple different animal models, including transgenic and sporadic models, the authors provide compelling evidence of a bidirectional link between Alzheimer's disease and changes in peripheral (and central) insulin signalling; not only at old age, but from a rather young onset. Based on the available data, the authors postulate that this link may be mediated via the PI3K-Akt-GSK3 pathway, and thus targeting this pathway could represent a tractable target for future studies. Intriguingly, in another article in the

special issue, similar pathways are postulated to be altered in human iPSC neuronal models that assess insulin-like growth factor 1 signalling in neurodevelopmental and neuropsychiatric disorders. These studies support bidirectional involvement of the insulin signalling pathways with those of the RAS/ERK and PI3K/mTOR pathways; again supporting their role in potential therapeutic strategies (Réthelyi et al., 2023).

The final review assessing preclinical (and clinical) literature assessing the comorbidity between insulin-signalling and neurodevelopmental disorders focusses on the impact that early-life stress plays in this. It is well-established that early-life stress is a significant risk factor for the development of numerous disorders later in life, and these include both somatic and psychiatric diseases. Here, Alberry and Silveira elegantly describe how early-life stress causes substantial disruptions of insulin signalling, in a variety of brain regions, including many of those mentioned above (e.g. prefronal cortex, hippocampus, nucleus accumbens), as well as other structural and functional changes (Alberry and Silveira, 2023). These changes are then placed into the context of how early-life stress, and its impact on central insulin signalling, are associated with the increased risk of somatic and psychiatric disorders.

Taken together, these articles provide a comprehensive and multidisciplinary guide demonstrating the current landscape of our understanding of how insulin-related signalling disorders not only include the well-descripted somatic disorders (e.g. type 2 diabetes) but also associated psychiatric and neurodegenerative disorders. While the overall evidence is compelling, the articles also show the sex-bias in the current studies with a lack of female studies to support those findings from male rodents. Moreover, the narrative shows that there are potential risks of biases in some of the studies, based on incomplete reporting of how changes in insulin signalling are monitored across studies and the need for more studies which include additional behavioural (cognitive) tests in their batteries. Thus, further studies, especially those including male and female rodents are required to further assess the role of insulin signalling in somatic, central and comorbid disorders are warranted in order to find potential novel therapeutic approaches and strategies for the treatment of these debilitating disorders.

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