Metabolic diseases and the brain: Obesity, type 2 diabetes and neurofibrosis

openaccessgovernment.org/article/metabolic-diseases-and-the-brain-obesity-type-2-diabetes-and-neurofibrosis/194321

Emily Warrender June 19, 2025

Garron Dodd, Head of the Metabolic Neuroscience Laboratory at The University of Melbourne, Australia and Founder, Chief Scientific Officer of Gallant Bio, investigates the brain 'goo' behind obesity and type-2 diabetes – and how we can treat it

Metabolic diseases, including obesity and type 2 diabetes, represent some of the most pressing global health challenges today. Over 1.9 billion adults worldwide are considered overweight, with more than 650 million categorised as obese. Additionally, type 2 diabetes impacts more than 537 million people globally – a number expected to increase to 643 million by 2030 and 783 million by 2045, as reported by the International Diabetes Federation(1).

These conditions are not only chronic and progressive, but they are also major contributors to cardiovascular disease, stroke, nearly all cancers, and neurodegenerative disorders(2). In fact, obesity alone is estimated to account for 4 million deaths annually(3), making it one of the leading global causes of preventable mortality. Beyond the devastating health toll, the global economic burden of diabetes alone is estimated to exceed USD $1.3 trillion per year(4).

For decades, obesity and type 2 diabetes were framed primarily as lifestyle diseases – a failure of individual willpower in the face of unhealthy choices. But this narrative has shifted dramatically. Over the past 10 to 20 years, a growing body of research has revealed complex pathophysiological mechanisms underpinning these conditions(5). Many of these mechanisms are rooted not in the muscles or fat, but in the brain(6).

Emerging neuroscience research has highlighted how the brain plays a central role in regulating appetite, energy expenditure, and glucose homeostasis(7). Dysregulation in specific brain circuits, particularly in the hypothalamus, leads to hormonal resistance, altered energy balance, and impaired metabolic function(7). Obesity and type 2 diabetes are not simply lifestyle problems – they are brain-driven disorders demanding medical solutions.

As researchers, we now understand that treating obesity and type 2 diabetes requires a paradigm shift. It is no longer enough to tell people to "eat less and move more." Instead, we must tackle the underlying biological drivers, including the brain-based changes perpetuating disease.

Our latest research, published in Nature[8], contributes to this evolving understanding by identifying a novel brain-based mechanism – neurofibrosis – that contributes to insulin resistance and metabolic dysfunction[8].

The brain's role in metabolism

Our research reveals a previously unknown mechanism driving obesity and type 2 diabetes: a thick, glue-like accumulation of extracellular matrix (ECM) around hunger-regulating neurons in the brain. We have termed this condition neurofibrosis because neurons become encapsulated in a fibrotic, sticky mesh, much like scar tissue.

The hypothalamus, specifically the arcuate nucleus (ARC), regulates metabolism by sensing insulin, a hormone that controls blood sugar and hunger[6]. When insulin binds to receptors on ARC neurons, it triggers a cascade of metabolic signals that regulate appetite, fat storage, and energy expenditure. However, in obesity and type 2 diabetes, neurofibrosis develops around these neurons, preventing insulin from the bloodstream from entering the brain and interacting with its receptors, resulting in insulin resistance within the brain[8].

The discovery of neurofibrosis

In our study, we used well-established pre-clinical models to investigate how obesity and type 2 diabetes influence brain function. Mice fed a high-fat, high-sugar "fast food" diet for just four weeks showed significant ECM accumulation around key appetite-regulating neurons in the hypothalamus. Normally, this matrix helps support cell structure and communication, but in obesity, it becomes excessively dense and adhesive, forming a glue-like barrier that blocks insulin receptor access[8].

Reversing neurofibrosis to restore metabolic function

Previously, ECM thickening was considered irreversible, as seen in liver and adipose tissue fibrosis[9]. However, for the first time, we showed that neurofibrosis in the brain can be reversed. Using novel neurofibrosis inhibitors that either degrade ECM or prevent its synthesis, we restored insulin sensitivity in the hypothalamus. Treated mice reduced their appetite and lost significant body weight, despite remaining on the high-fat, high-sugar diet[8].

In addition to decreased food intake, treated mice demonstrated a significant increase in energy expenditure, indicating enhanced adaptive thermogenesis. These effects suggest that neurofibrosis-targeting therapies may complement or even surpass the benefits of current GLP-1R agonists, such as semaglutide and tirzepatide[10].

A shift in perspective: Beyond neurons

Historically, research has focused on neurons themselves, but our findings emphasise the importance of the extracellular environment that surrounds them. The ECM – comprised of proteins and glycosaminoglycans – not only supports neural structure but also

regulates receptor accessibility and signal transduction[11].

Obese mice showed a significant decrease in the ECM-degrading enzyme matrix metalloproteinase-9 (MMP-9) and a corresponding increase in tissue inhibitors of metalloproteinases (TIMPs), tipping the balance toward ECM accumulation[8]. By restoring this enzymatic balance, we prevented further neurofibrosis and restored hypothalamic insulin sensitivity.

The role of inflammation in neurofibrosis

One of the key drivers of ECM remodelling appears to be neuroinflammation. Obesity is associated with elevated levels of pro-inflammatory cytokines such as TNF-α and IL-6, particularly in the hypothalamus[12, 13]. In our study, these cytokines were elevated in the hypothalamus of obese mice, which we found accelerated the development of neurofibrosis[8].

Suppression of inflammation reversed ECM accumulation, restored insulin sensitivity, and improved energy balance, supporting the conclusion that inflammation-induced ECM remodelling is a key driver of metabolic dysfunction[12, 13].

From mice to humans: Implications for treatment

Although our experiments were conducted in mice, neurons within the human arcuate nucleus (ARC) are also enmeshed in extracellular matrix (ECM) structures[14]. Recent single-cell transcriptomic analyses of the human hypothalamus reveal that it possesses the full molecular machinery required to generate neurofibrosis. This strongly suggests that neurofibrosis may be a conserved pathological feature, pointing to shared disease mechanisms between humans and animal models.

Non-invasive delivery of neurofibrosis inhibitors – particularly via the intranasal route – was effective in mice, suggesting that similar approaches may be viable in humans. However, visualising the ECM in the living human brain remains a technical challenge, as the hypothalamus is deep-seated and poorly accessible with current imaging methods[15].

The future of brain-based metabolic therapies

Our findings align with a broader shift in the field toward recognising the brain's pivotal role in metabolic disease. While drugs like Ozempic and Mounjaro act directly on brain receptors, they do not address the physical barriers like ECM that impair hormone signalling. By targeting neurofibrosis, we offer a fundamentally different approach – one that aims to restore, rather than bypass, native metabolic pathways[8].

Ongoing studies will explore the link between ECM pathology and other disorders, including Alzheimer's disease and depression, where brain ECM accumulation has also been observed[16]. This may open up new avenues for cross-cutting neurological-metabolic therapeutics.

Metabolic diseases affect over half the world's population and their global impact is accelerating. Our identification of neurofibrosis as a reversible driver of obesity and diabetes, along with the development of targeted ECM inhibitors, represents a significant breakthrough.

By focusing not just on neurons, but the structural brain environment that shapes their function, we may be able to restore insulin sensitivity and metabolic health. With continued research and translational development, we aim to bring these therapies to clinical trials within the next three to five years.

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