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Translational validity of rodent diet-induced obesity models for cognitive impairment in human metabolic disease

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Abstract: Type 2 diabetes and obesity, often modelled in rodents through high-fat diet interventions, are associated with altered brain energy metabolism and cognitive impairments. However, discrepancies between rodent high-fat diet models and human metabolic diseases challenge the translation of findings. This review provides a view on clinical and preclinical studies examining the effects of high-fat diet-induced metabolic dysfunction on brain function, focusing on the limitations of current rodent models, including diet composition, duration, and control diets. It is discussed how these factors influence brain metabolism and cognition, and highlight the need for standardized, longitudinal, and sex-inclusive studies. The present analysis underscores that while studies using high-fat diet-fed rodents provide valuable mechanistic insights, their metabolic profiles do not fully replicate human obesity and type 2 diabetes. These findings emphasize the importance of refining experimental models to better understand diet-induced brain dysfunction and to develop effective interventions.

Key words: Type 2 Diabetes, Insulin Resistance, Brain Metabolism, High-Fat Diet, Cognitive Impairment.

INTRODUCTION

In 2024, 588.7 million adults aged 30-79 were living with diabetes world-wide, and a 45% increase is predicted for 2050 (International Diabetes Federation 2025). Type 2 diabetes (T2D), a condition characterized by insulin resistance and progressive insulin deficiency, accounts for the vast majority (>90%) of diabetes cases and is largely preventable through lifestyle interventions and potentially reversible with adequate disease management at early stages (GBD 2021 Diabetes Collaborators 2023).

Sedentary lifestyles and excessive intake of calories drive the development of obesity and metabolic syndrome or prediabetes, which have been associated with all-cause dementia, vascular dementia, Alzheimer's disease and Parkinson's disease in a variety of epidemiological studies (e.g., Gudala et al. 2013, Schlesinger et al. 2022, Aune et al. 2023). Furthermore, obesity comorbidities such as hypertension, cardiovascular disease, metabolic syndrome, and insulin resistance or T2D, have all been proposed to contribute to cognitive decline (Livingston et al. 2020, Schlesinger et al. 2022). A recent study in middle-aged to older adults found that unhealthy diets and abdominal fat have are associated with poorer brain connectivity and worse cognitive performance in older age, suggesting that dietary and lifestyle intervention in adulthood is beneficial for brain and cognitive health (Jensen et al. 2025). In young men and women, higher consumption of foods rich in fat or sugar over a year (traced through questionnaires) was

also found to associate with spatial memory in a virtual reality task (Tran et al. 2025). There is thus no doubt today that metabolic imbalances resulting from obesogenic dietary patterns have a negative impact on cognition in either young or aged individuals.

Abbreviations: HFD, high-fat diet; HFHSD, high-fat and high-sucrose diet; T2D, type 2 diabetes.

Brain energy metabolism at the crossroads of T2D and cognitive impairment

Brain metabolism is exquisitely compartmentalized between neurons and glial cells, with astrocytic metabolism being particularly critical for fuelling the functioning of neurons as well as their connectivity within cerebral networks (Sonnay et al. 2017). Cerebral energetics relies on continuous supply of glucose, which supply is tightly regulated to match the needs of neuronal activity (for extensive review of brain glucose metabolism compartmentalization and regulations, see Dienel, 2019). Therefore, disturbances of metabolism underly virtually any pathological state, including diseases that impact brain function (Duarte et al. 2013, Błaszczyk 2020). A link between diabetes and cognitive impairment is well established (see Duarte 2015 and references therein), and it is even suggested that gestational diabetes impacts the brain of the offspring (Sousa et al. 2018). T2D is acknowledged to involve a certain degree of mitochondrial dysregulation in both neurons and glial cells and, therefore, it causes important brain energy metabolism alterations (Duarte 2015, Sickmann & Waagepetersen 2015), which constitute a mechanism by which insulin resistance impacts fuelling of synaptic activity and plasticity, contributing to brain dysfunction and memory impairments (for review, see Duarte 2023). In fact, impairments on brain insulin signalling in T2D result in important metabolic derangements at level of mitochondria (e.g., Lanzillotta et al. 2024) and upstream metabolism of glucose and glycogen (Sickmann et al. 2010, 2012, Soares et al. 2019, Girault et al. 2019). Noteworthy, insulin resistance (important component of T2D) is also a proposed mechanism of brain dysfunction in neurodegenerative disorders, namely Alzheimer's disease (Lanzillotta et al. 2025).

Systemic metabolic challenges affect the central nervous system. That includes hypercaloric feeding, or the exposure to diets rich in saturated fat leading to obesity, a feature used to experimentally model T2D. The impact of T2D on brain function and metabolism through the lens of diet-induced obesity models has been reviewed elsewhere (Kanoski & Davidson 2011, Garcia-Serrano & Duarte 2020). These previous review articles summarized findings from various rodent studies that demonstrate how diets rich in fat and sugar lead to cognitive impairments, particularly in hippocampal-dependent memory tasks, and highlight the peculiar role of altered glucose metabolism and mitochondrial dysfunction in these neurobiological processes. Since astrocytes are important modulators of neuronal function, especially through supporting excitatory glutamatergic neurotransmission (Sonnay et al. 2017), it should not be surprizing that their dysfunction in T2D impacts learning and memory (Garcia-Serrano & Duarte 2020). Indeed, T2D is characterized by simultaneous neuronal dysfunction and astrogliosis (e.g., Duarte et al. 2012, 2019, Calvo-Ochoa et al. 2014) and gliotic astrocytes upon insulin resistance conditions do not seem to adequately support neuronal function and rather contribute to the above-mentioned impairments in synaptic activity, glutamate neurotransmission and memory, despite an exacerbated oxidative metabolism that may produce an excess of ATP (Girault

et al. 2019). Furthermore, in the context of obesity, saturated fatty acids such as palmitate are thought to be important in eliciting a neuroinflammatory profile that contributes to astrogliosis and neuronal dysfunction (Melo et al. 2020).

The present article does not aim to detail our current understanding of how obesity and T2D impact the interconnected brain insulin signalling, regulation of energy metabolism, and brain dysfunction and cognitive impairment. That interconnected triangle has been extensively covered elsewhere (Duarte 2023). Instead, this review aims to address the limitations in translating research findings on mechanisms of memory dysfunction from rodent models of obesity and T2D elicited by excessive caloric intake from saturated fat, the so-called high-fat diets (HFDs), into cognitive derangements in individuals suffering of metabolic disease. Given the susceptibility of cerebral energetics to nutrition and systemic metabolic imbalances, it is critical to be aware of the handicaps of HFD feeding in rodents.

Obesity and HFD interventions in clinical settings

In contrast to epidemiology studies, not many obesogenic intervention studies have investigated the impact on cognitive performance. Indeed, although various studies show that short-term overeating can induce insulin resistance and systemic metabolism alterations in lean humans (e.g., Danielsson et al. 2009), dietary interventions in humans that can be related to HFD-induced memory impairment in rodents are rather scarce. Nevertheless, the available studies contribute to pinpointing direct effects of overfeeding on cognition. Compared with a standard diet, young, healthy men consuming a high-fat, low-carbohydrate diet for 5 days showed impairments in attention, cognitive speed, and mood (Holloway et al. 2011). A randomized, controlled study with normal-weight participants exposed to a high-fat/high-sugar snack or a low-fat/low-sugar snack for 8 weeks in addition to their regular diet found that high-fat/high-sugar intervention decreased the preference for low-fat food while increasing brain response to food and associative learning independent of food cues or reward (Edwin Thanarajah et al. 2023). Interestingly, the authors reported that such effects were not related to changes in body weight and systemic metabolism outcomes, suggesting direct effects of the high-fat and high-sugar on the brain. Another recent randomized, controlled study in young healthy individuals showed alterations of brain insulin action as detected with functional magnetic resonance imaging after short-term overeating calorie-rich snacks relative to a regular diet; alterations included the hippocampus, which is an area involved in spatial memory performance (Kullmann et al. 2025). Together, these studies are supportive of a role of brain insulin resistance in mediating negative effects of short-term hypercaloric intake on cognitive capacities.

HFD feeding in rodents is an invaluable research tool

Diet-induced obesity in rodent models offers a powerful research tool for studying the consequences of obesity and diabetes on brain function, including the deficits in learning, memory, and neural plasticity (Spencer et al. 2017, Lizarbe et al. 2019, Melo et al. 2020, González et al. 2023). Unlike monogenic obesity models (see Robinson et al. 2000), diet-induced obesity replicates the slow development of human metabolic disease through exposure to high-fat or cafeteria-style diets, providing translational relevance and allowing to investigate the early mechanisms that involve fat exposure without

chronic obesity. Indeed, short-term HFD feeding of only a few days has provided evidence that inflammatory signals, exacerbated microglia reactivity, and increased blood-brain-barrier permeability are key mediators of early signs of memory impairment and impaired synaptic plasticity (e.g., Spencer et al. 2017, de Paula et al. 2021). Notably, mechanisms of blood-brain barrier integrity and neurovascular coupling under metabolic stress can only be addressed in the entire organism, and important findings have been obtained from diet-induced obesity rodents (recently reviewed by Feng et al. 2024).

Importantly, experiments employing such short-term HFD exposure have found distinct neuroinflammatory responses in young and aged rats, highlighting an age-associated interaction with exposure to saturated fat (González et al. 2023). A particularly insightful study with HFD-fed mice demonstrated that episodic and associative memory can decline within just one day, yet rapidly recover upon diet reversal (McLean et al. 2018). This underscores the dynamic interplay between diet, integration of neuronal circuits, and cognition, pinpointing critical windows for intervention. While providing striking evidence that fat feeding elicits rapid-onset cognitive effects even preceding peripheral important metabolic derangements (Butler et al. 2025), HFD and cafeteria diet studies in rodents provides a means of studying obesity progression and the impact on the brain that is associated with the instalment of metabolic syndrome factors such as hyperglycaemia, hyperinsulinaemia, dyslipidaemia, and systemic inflammation (Lewis et al. 2019, Garcia-Serrano et al. 2022).

These findings showcase strengths of diet-induced obesity models. They reproduce a gradual progression from diet to metabolic syndrome and brain dysfunction, allowing the study of early mechanisms underlying brain dysfunction during fat exposure, progression across the development of metabolic syndrome, and eventual reversibility or response to preventive measures and treatments. Thus, there is an important aspect of temporal resolution that allows research on both rapid and chronic cognitive changes, namely from acute neuroinflammation to long-term synaptic protein modulation (Spencer et al. 2017, McLean et al. 2018, de Paula et al. 2021, González et al. 2023). Secondly, rodents can be tested in standard learning and memory tasks such as the Barnes maze, Morris water maze, novel object recognition or operant conditioning to provide robust behavioural data. In addition, these tasks can be combined with or followed by neuroimaging or electrophysiology measurements to link behaviour with changes in brain metabolism and neuronal activity. Therefore, studies in rodents exposed to saturated fat provide a unique opportunity for linking cognition and behaviour to molecular events that can be further dissected in studies in vitro (e.g., Melo et al. 2020, Vilela et al. 2025). Finally, such models allow to dissect cellular and molecular mechanisms involved in intervention testing of diet reversibility studies, anti-inflammatory treatment, nutritional interventions and others (Melo et al. 2020, Garcia Serrano et al. 2022, 2023, 2024, de Paiva et al. 2023, Vanherle et al. 2025).

An enormous value of modelling obesity with a diet intervention is that it can be easily applied on top of other disease models, namely models used to study neurodegenerative diseases. While this approach adds experimental complexity, it is of proven usefulness to study comorbidities observed in human obesity and diabetes. For instance, feeding fat and/or sugar-rich diets to various models used in Alzheimer's disease research has supported the notion that metabolic derangements contribute to accelerate and exacerbate the deposition of amyloid-β, neurodegeneration, neuroinflammation and

memory performance impairments (reviewed by Valentin-Escalera et al. 2024). HFD feeding in toxin models of Parkinson's disease have also provided evidence for exacerbation of cerebral alterations by fat-induced metabolic stress, namely dopaminergic degeneration, vascular alterations, and neuroinflammation (Busquet et al. 2012, Elabi et al. 2021, Singh et al. 2025). However, the most interesting results come from models of comorbid diabetes and Parkinson's disease that combine HFD and α-synuclein overexpression: not only HFD exposure worsens the parkinsonian phenotype and accelerates its progression (Rotermund et al. 2014), α-synuclein overexpression is also implicated in worsening metabolic performance in obesity (Biju et al. 2025).

HFD-fed rodents are far from replicating human metabolic disease

Obesity and diabetes induced experimentally in rodents by exposure to fat-rich diets constitute extremely valuable models for studying disease mechanisms in a longitudinal manner, and also provide a means of addressing HFD withdrawal, since the diabetic phenotype and various endpoints of brain dysfunction can be reversible, at least for exposures up to 4-6 months (Soares et al. 2018, Garcia-Serrano et al. 2022). Attention should be drawn to the fact that after HFD exposure for longer periods such as a year, insulin resistance cannot be completely normalized when animals are transferred to a low-fat diet (e.g., Karampatsi et al. 2021). On the other hand, many studies have conveniently used HFD exposures of very short duration such as a couple of months (Garcia-Serrano et al. 2024, Skoug et al. 2024) or even as short as a few days (de Paula et al. 2021, 2024). While this approach might be useful for studying early aspects of a metabolic challenge, it is far from being comparable to human metabolic diseases that develop over years or decades.

Not only do rodents and humans differ significantly in metabolism, brain structure, and lifespan, rodent models are often exposed to extreme diets such as 60% fat from lard (e.g., Soares et al. 2018, Lizarbe et al. 2019), which may not accurately reflect typical human dietary patterns (Bortolin et al. 2018, Lang et al. 2019). In terms of impacting the brain, feeding mice with diets containing 10% (considered control diet), 45% and 60% of lard-based fat revealed different neurochemical alterations at fat contents of 45% and 60% despite similar degrees of memory impairment, when compared to the ingredient-matched control diet of 10% fat (Lizarbe et al. 2019).

Many studies induce obesity/diabetes employing HFD and using the grain-based standard chow available at the respective animal housing facility as control diet (e.g., Evans et al. 2024, Dreux et al. 2025). In such experimental settings, there are marked differences in macro- and micronutrient composition (including vitamins and minerals), and further potential composition changes across chow batches (Pellizzon & Ricci 2018, Warden & Fisler 2008). For studies of brain energy metabolism, the use of standardized, ingredient-matched control diets has been preferred so that any differences in the content of vitamins and minerals that impact brain function are negligible (Lizarbe et al. 2019, Garcia-Serrano et al. 2022, de Paula et al. 2024). This is particularly important when studying additional food supplements (Garcia-Serrano et al. 2023, 2024) or pharmacological treatments (Vanherle et al. 2025) in conjunction with the HFD. Nevertheless, with either employing an ingredient-matched control diet or a regular chow diet, these HFDs delivered continuously for weeks or months are far from mimicking human dietary patterns.

To address the discrepancy between HFD feeding in rodents and diet-associated development of human obesity, the so-called cafeteria diets have been introduced. In this experimental setting, mice are fed ad libitum with a variety of highly palatable, high-salt, high-fat and low-fiber, energy dense foods in addition to their normal chow (e.g., Higa et al. 2014, Lang et al. 2019). Both cafeteria diets and HFD lead to comparable weight gain, glucose intolerance and insulin resistance, but differ in the development of comorbidities (Bortolin et al. 2018, Lang et al. 2019). Although a cafeteria diet is an interesting approach to represent the food sources available in Western societies and could be considered a more robust way of inducing a metabolic syndrome model, there are drawbacks of its employment in the study of brain metabolism. The most important limitation is surely that cafeteria diets are of difficult, if not impossible, standardization across labs due to the different availability in local supermarkets (Lalanza & Snoeren 2021), hindering data comparison and reproducibility across research institutions. Next, the nutritional differences between cafeteria diets and the respective chow might be substantial, imposing the need of characterization within each study. In general, the cafeteria diet has lower content of protein, fiber, minerals and vitamins. Another important aspect of this cafeteria diet intervention is the inclusion of salt-rich food components (Lalanza & Snoeren 2021). High-salt consumption per se could be a driver of cardiovascular and cerebrovascular impairment, as well as brain metabolism alterations (Meissner et al. 2022, Duarte et al. 2025). These aspects of the cafeteria diet versus chow, mainly deficiency in protein, vitamins and minerals, and high-salt content, might mask effects of obesity/diabetes on the brain. However, they can be viewed as part of establishing a model of unhealthy eating habits and contribute to inducing additional co-morbidities in the rodent model that are present in human obesity and diabetes.

Conclusion and questions for future research

There is no doubt that diet-induced obesity in rodent models provides a unique opportunity for mechanistic investigation of how metabolic stress, obesity, and diabetes impact the brain. However, despite the efforts in understanding the distinct metabolic features and comorbidities developed in rodents under different HFDs and cafeteria diets, the varied impact on learning and memory remains understudied. Further work is warranted to establish how distinct metabolic profiles arising from various diet-induced T2D models affect brain function and cognition (Figure 1). Comprehensive studies employing a range of HFDs, ingredient-matched controls, cafeteria-style diets, and standard chow diet are necessary to elucidate these effects. Importantly, in contrast to age effects (Karampatsi et al. 2021, Evans et al. 2024), both male and female rodents should be included to address the often-overlooked influence of sex on metabolic and cognitive outcomes in HFD-induced obesity (de Paula et al. 2024, Evans et al. 2024, Dreux et al. 2025; for discussion see Sadie-Van Gijsen & Kotzé-Hörstmann 2023). Longitudinal assessments are essential to capture the progression and temporal dynamics of diet-induced cognitive changes (e.g., Soares et al. 2018, Garcia-Serrano et al. 2022). Additionally, environmental factors such as housing conditions, cage space, number of mice per cage, environmental complexity (such as enrichment with nesting materials, hiding places and climbing structures; Cait et al. 2024) are known to significantly impact behavior, learning, and memory (Nithianantharajah & Hannan 2006), and must be considered for better understand susceptibility to obesity/T2D-associated

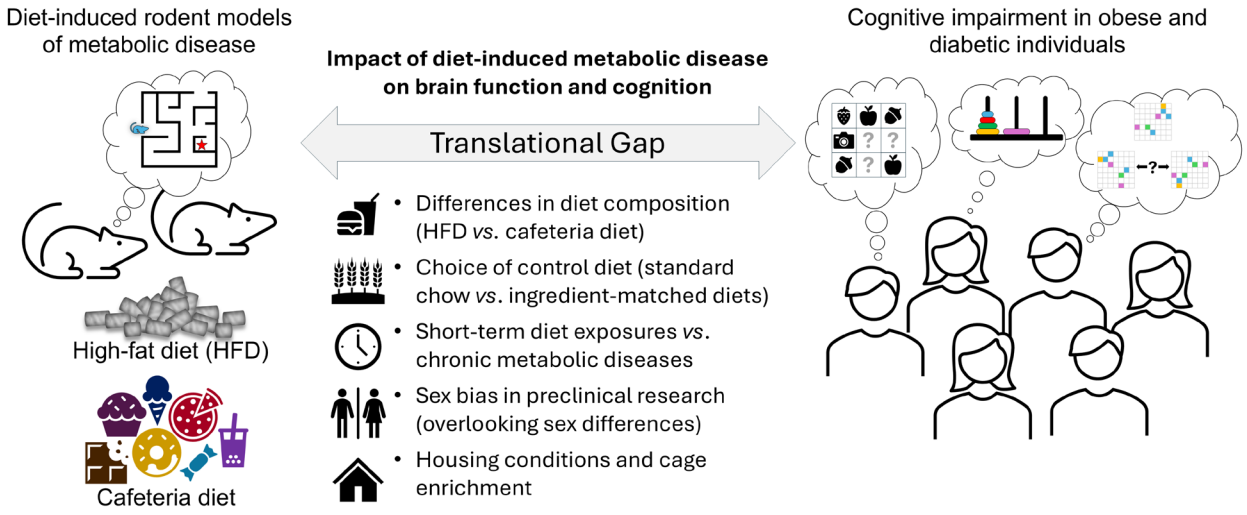

Figure 1. Major points that must be addressed in diet-induced obesity/diabetes studies for bridging the translational gaps and improving our understanding of mechanisms by which metabolic disease impacts cognitive processes.

cognitive impairment. Finally, the relationship between gut microbiota composition and brain metabolism in the context of diet-induced diabetes warrants further exploration, as it may provide key insights into the mechanisms linking peripheral metabolic disturbances with central nervous system dysfunction (Cryan et al. 2019, Kim 2024).

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