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Opinion

Can brain neurons change identity? Lessons from obesity

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It has long been thought that the functional identity of mammalian brain neurons is programmed during development and remains stable throughout adult life; however, certain populations of neurons continue to express active regulators of neuronal identity into adulthood. Prolonged exposure to diet-induced metabolic stress induces features of neuronal identity modification in adult mice, and maladaptive changes in neuronal identity maintenance have been linked to cognitive impairment in humans suffering from neurodegenerative diseases often associated with obesity. Here we discuss how, by unraveling the neurological roots of obesity, we may solve the puzzle of whether mammalian brain neurons retain identity plasticity into adulthood, while advancing knowledge of the pathogenic mechanisms at the interface of metabolic and neurodegenerative disorders.

Highlights

Advances in single-cell transcriptomic tools are reshaping our understanding of how neuronal functional identity is regulated in the mammalian brain throughout the lifespan.

Mature selected brain neurons in the adult brain express functional identity gatekeepers and may be susceptible to losing or changing their post-embryonic identity.

In mouse models of adult-onset obesity, maladaptive shifts in cell identity regulation are observed in peripheral metabolic organs as well as in brain neurons involved in energy homeostasis.

Obesity is associated with neurodegenerative diseases characterized by impaired maintenance of neuronal identity, such as Alzheimer's disease.

Unraveling the neurological basis of obesity may shed light on forms of maladaptive neuronal plasticity at the interface of metabolic and neurodegenerative disorders.

The evolving concept of neuronal functional identity

For centuries, neurobiologists have sought to unravel the complexity of the brain by deconstructing this enigmatic organ into its functional components – neurons – and categorizing the different units based on their distinct identities. From a developmental biologist's viewpoint, a **cell's identity** (see Glossary) encompasses its current characteristics, its developmental lineage, and its future trajectory (e.g., the potential to adopt new phenotypes in response to stimuli, such as through processes of **dedifferentiation** or **transdifferentiation** [1]).

However, this definition does not fully capture how different neurons regulate specific brain circuits and orchestrate specific physiological or behavioral outcomes across the lifespan of an individual – what a neuroscientist might also call **neuronal functional identity**. Such a broader concept must take into account additional influencing factors such as neuronal morphology, electrophysiological properties, molecular signatures, and connectivity within existing neural networks [2], among others.

Neurons, like any other cell type, are programmed during development by differentiation genes that commit a progenitor to a defined neuronal type, with a specific set of molecular markers and functions. Such early life programming involves transcription factors that orchestrate cell-specific genes and functions, commonly known as **terminal selectors** [3,4]. Terminal selectors are continuously expressed from development to adulthood, but their expression levels are often downregulated in mature post-mitotic neurons [5–7], raising the question of whether additional mechanisms co-control the functional identity of adult neuronal cells compared with embryonic life.

Developmental maturation of mammalian neurons continues during critical post-embryonic periods, such as neonatal life, when neuronal projections and brain connectivity undergo plastic remodeling. However, it is widely accepted that in mammals, neuronal identities are stably maintained after embryonic development and throughout adulthood, as mature neurons are

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generally unable to dedifferentiate or lose the functional specificity acquired *in utero* [3]. In marine animals, cellular dedifferentiation and transdifferentiation are part of the organism's normal response to injury [8]. Thus, the lower differentiation plasticity of adult mammalian neurons may explain why neuronal regeneration after brain injury is negligible in higher species, including humans, compared with amphibians or invertebrates [9–11]. Post-embryonic stabilization of neuronal identity and differentiation state is critical for overall neuronal function, as dedifferentiation, for example, could render an adult neuron incapable of generating action potentials. Neurons are postmitotic and, therefore, unable to re-enter the cell cycle. Cell fate plasticity and proliferation are closely linked [12], further supporting the general view of stable neuronal identity.

However, this dominant model overlooks the possibility that dynamic changes in embryonically programmed neuronal functions may still occur in adult life, even independent of complete cell reprogramming or dedifferentiation mechanisms. For example, terminal selectors may remain active in specific neuronal cells throughout adult life, controlling neuronal identity through yet-to-be elucidated pathways. Accordingly, genetic deletion of the terminal selector co-factor lysine acetyltransferase type 3 (KAT3) in adult mouse forebrain excitatory neurons results in a rapid loss of neuronal molecular identity without triggering apparent changes in the cellular differentiation state [13]. Furthermore, recent advances in single-cell molecular transcriptomic tools reveal that mature cells in different tissues, including the brain, do not maintain a stable molecular profile. In fact, they often exhibit changes in genetic signatures of molecular identity that were dictated during development [14]. This challenges the definition of neuronal identity in the adult brain and the concept of **neuronal identity plasticity** itself, leading to conflicting interpretations across disciplines such as developmental biology, neuroscience, and physiology.

Many developmental biologists will still remain skeptical about the ability of mammalian neurons to change identity in adulthood, given the significant shifts in differentiation and maturation that such a process would require, and the limited evidence for complete reprogramming into alternative lineages after development. Nevertheless, the potential for alternative forms of cellular identity plasticity and partial reprogramming warrants further investigation. In this paper, we do not aim to establish a consensus on the still too broad concept of neuronal identity plasticity. Rather, we will examine whether the current evidence supports the notion that brain cells can lose or modify their developmentally programmed functions in response to obesogenic cues throughout adulthood.

The obese brain

Obesity has reached alarming levels worldwide, with nearly half of the global population being overweight or obese. Given the central role of the brain in integrating the body's energy needs with emotional responses to food, it is not surprising that this organ is at the core of the development and progression of obesity.

In the mid-20th century, brain lesion studies have revealed the role of several hypothalamic areas in the regulation of food intake and body weight [15]. Around the same time, it was proposed that an adipose-derived factor provided a relay signal of peripherally stored energy to these hypothalamic areas [16,17]. The subsequent identification of the weight-regulating hormone leptin [18] and its central actions [19,20] led to intensive research into the brain circuits that control feeding behavior and energy balance, which has now positioned obesity as a brain disease, also supported by genetic studies showing that obesity-related mutations occur predominantly in the central nervous system [21].

Over the years, research into the neurobiology of obesity has focused primarily on the melanocortin circuit and its two major components that regulate feeding behavior and energy

Glossary

Cell identity: refers to the unique set of characteristics that define a particular cell type, including its gene expression profile, morphology, function, and interactions with other cells. From a developmental perspective, it encompasses the past (lineage), present (current characteristic), and future trajectories (modification in response to stimuli) of a cell.
Cell identity maintenance: the mechanisms that preserve the specific characteristics and functional roles of a cell type over time. This involves the regulation of molecular and cellular pathways that reinforce a cell's identity and prevent it from reverting to a less specialized state. Identity maintenance is crucial for the proper cell functioning, ensuring that cells perform their designated roles consistently throughout their lifespan.
Dedifferentiation: the process by which a cell in terminally differentiated stage reverts to a less differentiated stage within its own lineage.
Epigenetic erosion: the gradual loss or modification of epigenetic marks – such as DNA methylation and histone modifications – that regulate gene expression without altering the underlying DNA sequence. This process can lead to destabilization of gene regulation and may contribute to several age-related diseases, including cancer and neurodegenerative disorders, and can result in disruption of cellular identity and function.
Neuronal functional identity: the specific characteristics and roles that distinguish one type of neuron from another within the nervous system in terms of their function, connectivity, and response to stimuli.
Neuronal identity plasticity: the ability of a neuron to change its functional identity in response to internal or external cues. It allows differentiated cells to change their characteristics, such as gene expression and functional roles, in ways that allow them to adapt to new conditions or demands. Identity plasticity is particularly relevant in contexts such as development, regeneration, and response to injury, where cells may need to adopt new functions to support tissue repair or adaptation. However, this concept is poorly understood and defined in the context of post-mitotic mature neurons in adult mammals.

balance: pro-opiomelanocortin (Pomc) and agouti-related protein (Agrp) neurons [22,23]. However, the melanocortin circuit is only one of several brain pathways affected in obesity, where multiple signs of dysfunction are observed, including inflammatory processes, altered mitochondrial dynamics, endoplasmic reticulum (ER) stress, impaired intracellular protein homeostasis (proteostasis), and disruption of receptor-mediated hormonal signaling pathways (for detailed reviews see [23,24]).

Our understanding of the neurological basis of obesity is rapidly evolving, but this endeavor presents unique challenges due to the extreme heterogeneity of the brain, with a multitude of different neuronal types that may differentially influence disease onset or progression. The recent advent of single cell or single nucleus mRNA sequencing (scRNAseq or snRNAseq) has been instrumental. By using these methods to profile obesity-related brain regions at the single-cell resolution in rodents [25–27] and higher species (e.g., macaques [28]), the field has begun to elucidate cell-specific molecular pathways that may explain neuronal dysfunction in response to metabolic stress.

The translation of these brain mapping efforts to humans is still in its infancy, but the achievement of single-cell molecular maps of the human hypothalamus [29] suggests a promising avenue. These advances offer insights into the neurobiological roots of metabolic diseases, but also raise new unresolved questions about brain plasticity: is neuronal heterogeneity – the result of diverse cells with different molecular and functional properties – a fixed trait, as the dogmatic model of fixed neuronal identity would imply? Or can it undergo plastic changes in response to obesogenic cues throughout the lifespan?

Peripheral identity (mis)maintenance in obesity

The nutrient excess and sedentary lifestyle characteristic of modern society, coupled with genetic and epigenetic predispositions, are the primary drivers of metabolic syndrome, in which excess fat mass triggers life-threatening conditions such as hypertension, dyslipidemia, and carbohydrate intolerance, increasing the risk of cardiovascular disease and type 2 diabetes mellitus (T2DM). Elevated blood glucose, increased free fatty acid levels, and inflammation in obesity initially cause the β-cells in the islets of Langerhans to mount a compensatory response to increase insulin secretion to meet the increased metabolic demand. However, in some individuals, this initial adaptive phase culminates in β-cell exhaustion and loss, a critical step in the progression to T2DM [30]. Traditionally, the loss of insulin-producing cells in late-stage T2DM was thought to be caused by β-cell apoptosis and other cell death mechanisms, but alternative pathways have been proposed whereby β-cells may respond to metabolic stress by dedifferentiation or transdifferentiation [31,32].

Lineage tracing is a technique in which reporter proteins are expressed in specific cell types to allow the fate of individual cells and their progeny to be tracked with minimal disruption to their physiological function. When exposed to β-cell stress conditions, lineage tracing mice with β-cell-specific deletion of the transcription factor FoxO, a terminal selector that also modulates insulin signaling in multiple tissues [33], exhibited impaired glucose homeostasis and reduced β-cell mass. However, mutant β-cells in this model were not lost by apoptosis, rather they dedifferentiated to return to a more progenitor-like state [33]. Subsequent studies have revealed that such dedifferentiated phenotype was a protective mechanism to support β-cell survival under conditions of stress, including diet-induced metabolic cues [30].

Once embryonic differentiation is complete, **cell identity maintenance** in the endocrine pancreas requires the activity of terminal selectors that are sensitive to metabolic insults [34].

Terminal selector: a type of transcription factor or epigenetic switch that plays a critical role in the final stages of cell differentiation during development. Specifically, it is a regulatory protein involved in determining the final identity and function of a cell, ensuring that it adopts its terminal, specialized state. Terminal selectors are continuously expressed throughout the life of a neuron to maintain its differentiated state.
Transdifferentiation: the process by which one type of cell can be transformed into another of a different lineage, with or without an undifferentiated intermediate.

Oxidative stress reduces the activity of β-cell-specific terminal selectors [35], whereas β-cell-specific genetic deletion of the identity gatekeeper Pax6 in adult mice results in lethal hyperglycemia, loss of β-cell function, and expansion of α-cells [36]. β-cell de- or transdifferentiation has mostly been studied in rodent models, but there is supporting evidence in humans [30,37–39]. For example, pancreatic islets from T2DM patients have been shown to contain insulin-producing β-cells that express multiple hormones in addition to their main identity-defining hormone, insulin [38]. However, unlike in mice, where genetic lineage tracing experiments can be performed, it is difficult to demonstrate in humans that polyhormonal cells can arise from transdifferentiation of monohormonal β-cells without lineage analysis.

Thus, peripheral metabolic organs may produce molecules that regulate their cell identity throughout life, making them susceptible to losing or changing their embryonic identity under metabolic stress. Evidence from a lineage tracing mouse model of mature adipocytes supports this model. Nutritional stress induces transcriptional and epigenomic events in adipocytes that are consistent with a cell identity switch [40]. Several genes defining mature adipocytes and their primary functions – lipogenesis, lipolysis, and insulin signaling – were downregulated after the onset of adult obesity, whereas genes associated with myofibroblast identity and function were upregulated, independent of changes in differentiation genes or a reversion to a preadipocyte-like state [40]. Therefore, changes in cell identity control in response to metabolic cues affect not only β-cells but also adipocytes, although the underlying mechanisms can involve dedifferentiation in the former and as yet undefined pathways in the latter. This supports the notion that changes in the differentiation state of a mature cell should not be the sole criterion for concluding whether a mature cell has lost or switched its identity in adulthood.

Among the possible upstream mediators influencing peripheral cell identity maintenance in obesity, inflammatory signals may play a central role. Proinflammatory cytokines, which are elevated during the disease, promote β-cell dedifferentiation in cultured human and mouse islets [41]. For example, TNFα induces a rapid genomic reprogramming in adipocytes, leading to the activation of inflammatory gene programs and repression of cell identity markers [42]. Obesity drives cell identity shifts in inflammatory cells that contribute to low-grade inflammation and disease comorbidities, such as in macrophages, where cell identity polarization (from anti-inflammatory to pro-inflammatory phenotypes) has been observed in a large number of studies [43]. Of note, obesity and T2DM may lead to an impairment of brown adipose tissue (BAT) activity via a loss of brown adipocyte identity, according to a recent study [44]. This is triggered by a subset of lipid-associated macrophages and their secretion of the proinflammatory cytokine transforming growth factor β1 (TGF-β1) [44], further highlighting a potential link between metabolic inflammation and altered cell fate regulation.

Metabolic inflammation is associated with mitochondrial dysfunction and ER stress [45], which may also contribute to the (mis)maintenance of cell identity. Chemically induced ER stress impairs β-cell identity, and when the stress is relieved, β-cells regain their mature identity, indicating plasticity [46]. By contrast, metabolic inflammation affects genes in adipocytes that are critical for controlling both mitochondrial function and cell differentiation programs [45], suggesting that mitochondrial dysfunction in obesity may be central in this context. In support of a potential role for mitochondria in mediating the maintenance of cell identity in the metabolic organ, mitochondrial adaptations to cold challenge contribute to the switch of mature adipocytes from the non-thermogenic white phenotype to the thermogenic beige counterpart [47].

Thus, while obesity and T2DM may influence peripheral cell identity through shared upstream pathways, distinct cellular phenotypes reflecting the loss or shift of specific functional identities

are evident in response to changes in metabolically sensitive pathways or dietary cues in adulthood (Table 1). This underscores the importance of recognizing that the mechanisms governing cell identity maintenance in the face of obesogenic cues in adulthood are likely nuanced and heterogeneous among various cell types.

Central identity (mis)maintenance in obesity

Metabolic syndrome often has multisystem effects with common pathological mechanisms in both peripheral organs and the central nervous system. For example, low-grade chronic inflammation, increased reactive oxygen species (ROS), impaired proteostasis, and ER stress are observed not only in peripheral organs in obesity, but also in the brain, particularly at the level of the melanocortin circuit [23,48,49]. Following this logic, it is tempting to speculate that mature brain neurons, similar to peripheral metabolic cells, may also undergo maladaptive cell identity control in obesity.

Hypothalamic neurons that express key terminal selectors and epigenetic coregulators of cell identity throughout adult life – such as T-box 3 (Tbx3) [50], Islet-1 [51], Bsx [52], and specific microRNAs [51] – exhibit significant molecular and functional heterogeneity, making them particularly attractive for investigating this hypothesis.

Among these neuronal clusters, *Pomc*-expressing neurons are ideal candidates to study because: (i) they maintain functional levels of the terminal selectors Tbx3 and Islet-1 throughout life [4,45]; (ii) they exhibit significant intrinsic molecular and functional heterogeneity [53–57]; and (iii) during development,*Tbx3/Pomc* coexpressing precursors silence their identity marker *Pomc* and generate distinct neuronal types involved in neuroendocrine and metabolic control, such as Agrp or kisspeptin (Kiss)-expressing neurons [58], as well as Pomc subtypes with varying levels of *Pomc* and unique combinations of transcription factors [59]. Given that significant cell-to-cell variability in hypothalamic *Pomc* expression persists into adulthood [53], certain subclusters within this population may retain a memory of their embryonic identity plasticity throughout life.

By combining genetic lineage tracing of Pomc neurons in adult mice with multimodal single cell profiling approaches, it has recently been observed that mature mouse Pomc neurons contain

Table 1. Effects of metabolic stressors and metabolically sensitive pathways on mechanisms of cell identity maintenance in mature peripheral organs

Tissues/ organs	Model	Mechanism proposed	Pathophysiological outcome	Refs
Pancreas (*in vivo*)	*FoxO* deletion (β-cells)	• β-cell dedifferentiation	• Impaired glucose homeostasis	[33]
Pancreas (*in vivo*)	*Pax6* deletion (β-cells)	• β-cells change from insulin-expressing to ghrelin-expressing; expansion of α-cells	• Lethal diabetes	[36]
β-cells (*in vitro*)	ER stress in β-cells	• Altered β-cell identity maintenance	• Impaired β-cell adaption to stress • Type 1 diabetes	[46]
White adipose tissue (*in vivo*)	Exposure to HFD in adult life	• Loss of functional identity (lipogenesis, lipolysis, insulin signaling) • Increased markers of myofibroblast identity	• Remodeling of cytoskeletal organization in adipocytes	[40]
BAT (*in vivo*)	Exposure to HFD in adult life	• Reduced BAT identity • TGF-β1 secretion from local macrophages • Aldh1a1 induction	• Transition into white adipose tissue-like phenotype	[44]
White adipose tissue (*in vivo*)	Cold sensing/ mitochondria proteolysis	• White-to-beige adipocyte identity switch	• Impaired cold-induced beiging of white adipocytes	[47]
Adipocyte macrophages (*in vivo*)	IL-10/TNFα axis	• Identity polarization from anti-inflammatory to proinflammatory phenotype	• Insulin resistance	[43]

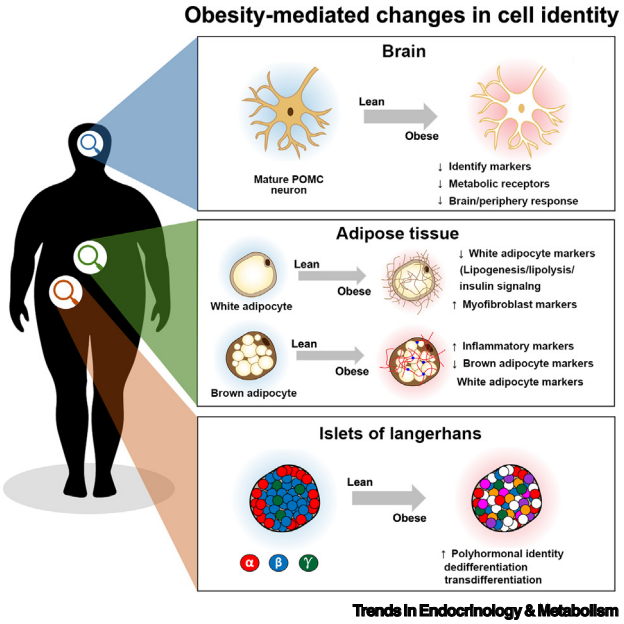

Figure 1. Side-by-side comparison of features of cell identity modification in obesity in the brain and peripheral organs. In response to obesogenic cues in adulthood, mature Pomc neurons may adopt an alternative conformation, marked by diminished expression of Pomc identity and function markers, reduced metabolic hormone receptors, and decreased sensitivity to the body's energy state. It remains unclear whether these changes signify a permanent loss of identity or partial reprogramming. Notably, similar features of identity loss have been observed in peripheral organs during obesity, suggesting potential upstream mechanisms linking the brain and periphery, though the downstream effects may differ between cell types.

neuronal subpopulations with atypical molecular and functional identity and negligible *Pomc* expression. These atypical cells have been termed 'Ghost' Pomc neurons because their *Pomc* mRNA and protein presence could not be detected using current neuroanatomical methods and promoter-based reporters, making them invisible in studies of Pomc neuron biology [25]. Importantly, Ghost neurons are recruited in a mouse model of adult-onset obesity, independent of neurogenesis or changes in neuronal turnover [25]. They also show diminished responsiveness to nutritional challenges (fasting-refeeding) and peripheral metabolic signals (leptin, insulin), as well as reduced expression of key receptors for metabolic hormones in the melanocortin circuit, including leptin, insulin, and the glucagon-like peptide 1 (GLP-1) receptor [25].

One interpretation of these findings is that subsets of Pomc neurons may undergo shifts in their functional identity, leading to changes in the expression of molecular machinery that enables responses to peripheral energy state signals following exposure to obesogenic stimuli in adulthood. This phenomenon may parallel the maladaptive cell identity dysfunction observed in peripheral organs in obesity (Figure 1). However, it remains to be determined whether such a neuronal phenotypic change represents a permanent loss of functional identity or a switch to alternative neuronal lineages. Furthermore, direct evidence that mature Pomc neurons switch to an atypical identity in obesity will require dynamic, in-depth analyses of cell fate trajectories over varying durations of exposure to obesogenic diets.

If confirmed, this model would imply that specialized neurons in the brain may undergo partial reprogramming of their molecular machinery to respond to peripheral metabolic signals in adulthood. This identity-switching mechanism could fine-tune whole-body energy requirements or regulate peripheral hormone production, which may be modulated in metabolic diseases.

Of note, the recruitment of Pomc neurons with atypical identities in obesity is not associated with classical markers of dedifferentiation [25] – and thus should not be considered a hallmark of identity change from the aforementioned developmental perspective. This is clearly an important

matter of definition and, regardless, our understanding of the molecular factors regulating adult neuronal differentiation state within the highly heterogeneous adult hypothalamic neuronal pool remains limited. Therefore, it is premature to dismiss the potential involvement of dedifferentiation or transdifferentiation mechanisms in the adult obese brain on the basis of current evidence. In addition, to fully interpret this putative evidence for neural identity plasticity, it is essential to recognize that, as seen in peripheral organs (Table 1 and Figure 1), alterations in cell-specific functional identities in obesity may be manifested by entirely different mechanisms in different neuronal populations within the same brain region or across different brain areas.

Following this logic, since hypothalamic neurons depend on non-neuronal cells (e.g., microglia, astrocytes, pericytes, and tanycytes, among others) to regulate circuit function and energy balance, and since these interactions are disrupted in obesity [49,60], it is plausible to speculate that hypothalamic non-neuronal cell types may also experience altered maintenance of cell identity in response to metabolic stress. Recent preclinical studies have highlighted the critical role of hypothalamic perineuronal nets (PNNs), a specific form of extracellular matrix, in glucose homeostasis in diabetic models [61] and in the regulation of hypothalamic sensing of metabolic hormones and energy balance in mice [62,63]. Brain PNNs orchestrate neuronal maturation during development and neuronal plasticity throughout adult life [64]. As hypothalamic PNNs are plastically modified by adult exposure to an obesogenic diet [62], investigating whether obesity-induced remodeling of PNNs influences, or is influenced by, mechanisms of neuronal identity maintenance is a compelling avenue for further research.

Linking obesity and neurodegeneration

Evidence linking obesity to cognitive dysfunction and structural brain changes has been accumulating [65]. Individuals with obesity face a 60–90% increased risk of developing dementia compared with lean subjects [66], with midlife obesity emerging as a prominent modifiable risk factor for Alzheimer's disease (AD) in the USA [67]. Obesity affects various cognitive domains, including executive function, attention, and working memory, corresponding to changes in the hippocampus and prefrontal regions [68]. In addition, metabolic diseases have been linked to other neurodegenerative diseases such as multiple sclerosis and Parkinson's disease [68]. Several structural alterations are observed in the brain of people suffering from obesity, including, enlarged ventricles, loss of white/gray matter, and demyelination [69,70].

Although the precise biological underpinnings of obesity-related neurodegeneration are not fully understood, multiple mechanisms have been proposed, including neuroinflammation, mitochondrial dysfunction, altered hormonal signaling, impaired blood–brain barrier permeability, and gut microbiota dysbiosis [68,71,72]. Given that many of these pathways can induce maladaptive changes in cell identity regulation, as discussed earlier, a plausible link could be made between impaired neuronal identity maintenance and neurodegeneration following metabolic stress, although this link remains speculative and awaits direct experimental confirmation.

Chronic neuroinflammation induced by exposure to hypercaloric diets may be central to linking altered cell identity maintenance with neurodegeneration. Diet-induced neuroinflammation in mice follows a biphasic mode within the hypothalamus, with acute inflammation resolving rapidly after a few weeks of high-fat feeding, only to reappear persistently after several months of diet-induced obesity [48], when signs of neurodegeneration and brain cell death occur [23,48,49].

Exposure to a high-fat diet (HFD) for 3/4 months in adult mice may cause apoptosis and neuronal loss of >40% of hypothalamic single-minded family basic helix-loop-helix transcription factor 1 (Sim1) neurons [73], which are essential for feeding and energy homeostasis. More prolonged

HFD exposure (6/8 months) may lead to a significant reduction of 25–50% of Pomc-expressing neurons in the hypothalamus, accompanied by signs of neuronal cellular stress [48]. However, not all studies agree with these findings, as the stereological assessment of different populations of hypothalamic neurons (including Pomc neurons) in mice exposed to up to 6 months of HFD showed no evidence of neuronal loss [74]. Several unresolved confounding variables could explain the inconsistency between studies, such as the type of diet used, the genetic background of the models used, and housing conditions. Among these factors, the duration of exposure to obesogenic cues is particularly important for translating the findings to human relevance.

Some people live with obesity for most of their lives (30 or more years), but the most commonly used chronic paradigm in mice to model the obese brain is exposure to obesogenic diets for 3–6 months, which does not reflect the human condition [75]. Therefore, it is crucial to demonstrate whether longer exposure to obesogenic diets in preclinical models (12 months or more) might reveal clearer and more consistent signs of neurodegeneration and cell death. Notably, the recruitment of Pomc neurons with atypical identity in mice exposed to an obesogenic diet for 6 months is not accompanied by signs of neuronal death [25]. This raises the possibility that maladaptive changes in neuronal identity maintenance may precede Pomc neurodegeneration in mice subjected to prolonged HFD feeding paradigms, possibly mirroring how loss of β-cell identity precedes and potentially triggers β-cell death.

In obesity, increased levels of circulating cytokines and peripheral immune cells, which are possible candidates for neuronal identity (dys)regulation, reach the hypothalamus to induce local inflammation, including the activation of tissue-resident microglial cells [49]. The local inflammatory response alters internal hypothalamic circuits and also hypothalamic outputs to other brain regions, contributing to functional alterations in the hippocampus, amygdala, and reward processing centers [76]. Given the association between obesity-induced neuroinflammation, cognitive impairment, and neurodegeneration, obesity may induce changes in neuronal identity maintenance in extra-hypothalamic areas that warrant further investigation.

In a severe form of early-onset AD, neuronal dedifferentiation is a defining mechanism [77]. Neurons derived from human iPSC (hiPSC) from affected patients repress their neuronal lineage gene programs and activate non-specific progenitor gene programs, accompanied by changes in chromatin accessibility and signs of neurodegeneration [77]. It remains to be seen whether this evidence reflects a true mechanism of dedifferentiation of a mature neuron into a stem cell-like phenotype, or a problem with the acquisition of neuronal identity and, therefore, a loss of identity. Nevertheless, a similar activation of dedifferentiation pathways and markers of neuronal fate loss have been observed in hiPSC-derived neurons from the more common sporadic form of AD [78], which exclusively affects elderly people, suggesting a link between altered neuronal identity maintenance and neurodegeneration associated with brain aging.

Accordingly, neural differentiation states a decrease in healthy aging adults compared with young controls, correlating with performance in several cognitive domains [79]. Such age-related phenomenon of neuronal identity loss may be mediated by **epigenetic erosion**, characterized by a weakening of a cell's epigenetic identity [80].

Notably, obesity and aging share a range of phenotypic features, including compromised genomic integrity, impaired mitochondrial function, accumulation of intracellular macromolecules, immune-metabolic dysfunction, and changes in adipose tissue composition [81]. Thus, these many similarities suggest an emerging model in which obesity may accelerate mechanisms of altered neuronal identity maintenance triggered by aging and/or AD in both hypothalamic and extra-hypothalamic areas.

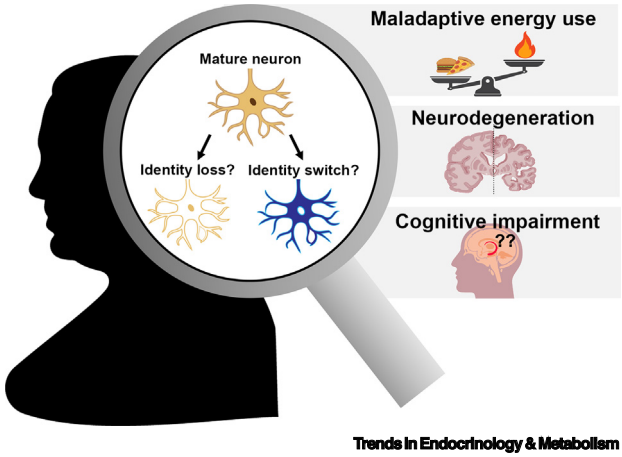

Figure 2. Putative integrative model linking neuronal identity (mis)maintenance and obesity. Based on our literature analysis, specific neuronal cells within previously identified neuronal populations may undergo maladaptive changes in their embryonically programmed identity in response to adult obesogenic cues, resulting in either loss of identity and/or novel neuronal conformations (partial reprogramming). Following prolonged exposure to metabolic stress, these mechanisms could become maladaptive, potentially leading to neurodegeneration and neuronal death. Thus, maladaptive mechanisms of altered cell identity maintenance may lie at the intersection of energy balance dysregulation and the increased risk of developing cognitive dysfunction and/or neurodegeneration in obesity.

Concluding remarks and future perspectives

The remarkable molecular diversity of brain neurons associated with the onset or progression of obesity, and the deregulation of their activity in the obese brain, may result from mechanisms of neuronal identity switching that occur throughout life. Through redundant pathogenic hubs between the brain and peripheral organs, long-term metabolic stress may affect the maintenance of neuronal identity within populations critical for energy balance and cognitive function, ultimately leading to maladaptive loss or alteration in functional identity, neurodegeneration, and cell death (Figure 2).

While this still hypothetical model may elucidate the link between the dysregulation of energy balance in obesity and cognitive decline in addition to neurodegeneration (Figure 2), several critical questions must be addressed to validate its relevance to metabolic physiology and brain disease (see Outstanding questions). Filling this knowledge gap may allow the discovery of cell identity switches that could be used to reprogram neuronal functions for long-term therapeutic benefit.

Ongoing efforts to refine the neurological basis of obesity at the single cell level may shed light on the long-standing question of whether brain neurons can change their identity after developmental maturation. However, solving this puzzle also requires reaching a consensus on what defines a neuron's identity – a crucial step in our understanding of neuronal plasticity and the development of brain diseases that afflict modern societies.

Outstanding questions

Can mature neurons change their identity throughout adult life without undergoing de- or transdifferentiation? If so, what mechanisms are involved, and what are the (patho)physiological consequences?

Does obesity alter the maintenance of neuronal identity in the adult brain? And is this a protective mechanism or a disease-promoting maladaptive event?

Are there common mechanisms linking peripheral and central cell identity dysregulation in obesity?

Can prolonged exposure to obesogenic diets induce aging-related epigenetic events of neuronal identity erosion? And does such loss of identity ultimately lead to cell death?

Can altered neuronal identity maintenance in obesity explain impaired cognitive performance and increased risk of AD?

Does remodeling of hypothalamic PNNs in mouse models of adult-onset obesity influence (or is it influenced by) changes in cell identity?

Does obesity affect mechanisms of cell identity maintenance in non-neuronal hypothalamic cells?

Obesity is increasing at an alarming rate in both sexes. Do changes in cell identity in obesity follow sex-specific mechanisms?

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Declaration of interests

No interests are declared.

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