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Insulin action on astrocytes: From energy homeostasis to behaviour

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Abstract

Astrocytes are specialised glial cells that integrate distinct inputs arising from neurones, other glial cells and the microcirculation to regulate diverse aspects of brain function. A growing body of emerging evidence supports that astrocytes, similar to neurones, also play active roles in the neuroendocrine control of metabolism by responding to afferent nutritional and hormonal cues and translating these metabolic cues into neuronal inputs. Specifically, insulin action in astrocytes has received special emphasis given its newly discovered regulatory role in brain glucose uptake, which until recently was assumed to be an insulin independent process. We now know that insulin signalling in astrocytes regulates metabolic processes and behavioural responses through coupling brain glucose uptake with nutrient availability to maintain energy balance and systemic glucose homeostasis. Moreover, genetic ablation of the insulin receptor in astrocytes is associated with anxiety- and depressive-like behaviours, confirming that these glial cells are involved in the regulation of cognition and mood via insulin action. Here, we provide a comprehensive review of the most relevant findings that have been made over the course of the last few years linking insulin signalling in astrocytes with the pathogenesis of brain metabolic and neurodegenerative diseases; a still unexplored field, but with a high translational potential for developing therapies.

KEYWORDS

astrocytes, central nervous system, cognition, food intake, glucose homeostasis, insulin

1 | INSULIN ACTION IN THE BRAIN

Subsequent to the discovery of insulin in 1921 by F. Banting and C. H. Best, the physiological actions of this hormone have been scrupulously investigated. The initial functional characterisation was focused on insulin action in peripheral tissues (eg, effects on glucose uptake, gluconeogenesis, glycogenolysis, lipolysis and growth promotion, amongst others). Yet, insulin receptors are also widely expressed in the mammalian brain,[1-7] where their crucial role in the regulation of glucose homeostasis, feeding behaviour, cognition and mood is now recognised.

Seminal studies previously reported the anorectic effect of insulin followed by a body weight loss[8] and its direct effect in the regulation of hypothalamic neuropeptides (ie, up-regulation of agouti-related peptide [AgRP] and neuropeptide Y [NPY] and down-regulation of pro-opiomelanocortin [POMC] and cocaine- and amphetamine-regulated trasnscript),[9-12] although it was not until the pioneering studies led by Brüning and collaborators with the

generation of brain specific insulin receptor (IR) knockout mouse models that insulin action in the central nervous system (CNS) began attracting more attention. These studies confirmed that the ablation of IR in the nestin-Cre mice (whole-brain specific IR knockout model) promotes the development of obesity as a result of increased food intake, which was accompanied by systemic insulin resistance and dyslipidaemia.[13] Specific ablation of the insulin receptor in both POMC and AgRP neurones revealed that signalling in these hypothalamic neuronal populations is not required for the regulation of food intake and body weight [14], whereas insulin signalling in NPY-expressing neurones exerts an active role on the regulation of feeding behaviour and energy balance.[15] Interestingly, insulin action alterations in neural circuits involved in metabolic control have been reported in both diabetic humans and CNS insulin-resistant experimental animal models, and these alterations have been shown to be a key mechanism in the development of obesity in both rodents and humans.[11,16-18]

The CNS is a complex collection of cells that work together to regulate all of the physiological and biochemical processes required for normal brain function including insulin signalling. Yet, most of these studies have been exclusively focused on exploring insulin action in neurones, ignoring the potential role of insulin in other types of cells in the brain such as astrocytes.[19,20] Astrocytes are a specialised type of glial cell and perform numerous vital functions such as the regulation of synaptic transmission [21,22], where their privileged location, at the interface between blood vessels and neurones, makes them essential cells for the supply of blood-derived metabolic cues into the parenchyma. Indeed, we now know that astrocytes are able to directly respond to insulin without neuronal intervention to translate metabolic cues into neuronal behavioural outputs including the regulation of feeding behaviour, cognition and mood.[23,24]

2 | INSULIN ACTION IN ASTROCYTES

Astrocytes are involved in neuronal proliferation, differentiation, migration, axon guidance, neuroprotection, synapse formation/elimination, plasticity and transmission during both brain development[25] and adulthood.[26-28] Astrocytes exert these multiple functions via their constant, dynamic and bidirectional interaction with neurones (and other cell types), acting as integral functional elements of a synapse, which was coined by Araque and collaborators as the 'tripartite synapse' in 1999.[29] This conceptual model describes how synapses between neurones (presynaptic and postsynaptic elements) can be influenced by the surrounding astrocytes, which are able to respond to neuronal activity by releasing signals for the regulation of synaptic transmission and plasticity (Box 1).[30] The recent advances regarding synapse interaction physiology have extended the understanding of synapse function, and we now know that, besides associated astrocytes, other cellular elements can also actively take part in synaptic assembly and function, such as perisynaptic microglia and oligodendrocyte processes, and the extracellular matrix present in the synaptic cleft and extra-synaptic area.[22,31,32] Nedergaard and Verkhratsky[33] developed this conceptual model in 2012, which entailed multiple-directional relationships between distinct and active cellular compounds to support the synapse and defined it as the 'synaptic cradle'.

BOX 1 Astrocytic control of synaptic function

Astrocytes are functionally integrated and interconnected elements of neural networks responsible for: shaping the structure of the networks (synaptic sculpting, water volume); regulating ionic homeostasis of the synaptic cleft (K^+ and H^+ buffering); controlling neurotransmitter dynamics (glutamate-glutamine cycle); preventing or allowing neurotransmitter (glutamate, GABA, adenosine and catecholamines) spillover via its uptake; maintaining redox homeostasis (in glutathione recycling); regulating cerebral blood flow by interacting with endothelial cells of microvessels and pericytes that form the blood-brain barrier; mounting the brain's first line of defence together with the meningeal lymphatic system and microglia; and ensuring proper neuronal connectivity, synaptic plasticity and synaptic transmission by providing neurones with energy substrates.[22,31,34-36] To exert these functions, astrocytes express a large number of receptors for neurotransmitters and other neuroactive substances (hormones, peptides, purines, cytokines) through which they respond by evoking their ionic excitability based on transient cytoplasmic changes in ions and other second messengers. Indeed, neurone-derived cues can activate G protein-coupled receptors in astrocytes, resulting in an elevation of intracellular Ca^{2+} concentrations, which translates into a fine-tuned and rapid astrocytic response which changes their functional and molecular phenotype for coupling local synaptic circuit demands.[35,37]

In addition to Ca^{2+}, astrocytes also exhibit transient changes in Na^+, Cl^-, K^+ and H^+ concentrations in response to certain physiological stimuli, which can trigger the release of neuroactive molecules also known as gliotransmitters (glutamate, ATP, GABA, L-serine) and ions [38] (Figure 1). Extensive reviews of the astrocytic control of synaptic function are provided elsewhere.[21,22,35]

2.1 | Insulin action in astrocytes: Energy balance regulation

Hyperinsulinaemia is a potent indicator of abundant energy availability, whereas insulin action within the brain has repeatedly been described to elicit anorexigenic effects. Until recently, the contributions of non-neuronal cell populations in mediating insulin's action on energy homeostasis remained elusive. Advances in neuroscience

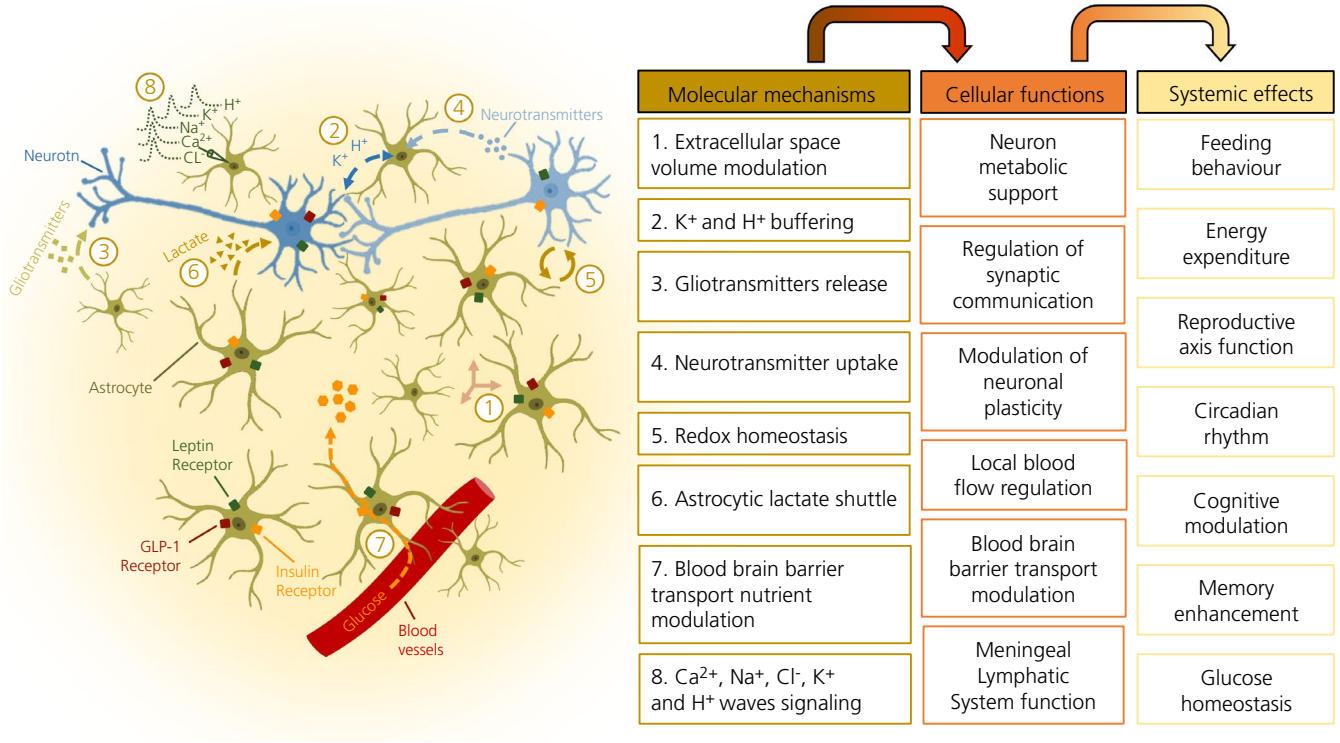

FIGURE 1 Common molecular mechanism of astrocytes associated with the cellular and systemic metabolic processes that they participate in. The astrocytic lactate shuttle, where glucose uptake is coupled with the release of lactate from astrocytes to be taken up by neurones, is an important mechanism of neuronal metabolic support. These glial cells regulate synaptic communication and homeostasis via neurotransmitter uptake from the synaptic space, K^+ and H^+ buffering, and redox balance maintenance, as well as the release of gliotransmitters. Importantly, astrocytes can communicate with the neighbouring astrocytes, but also with neurones through Ca^{2+}, Na^+, K^+, Cl^- and H^+ waves. The advantageous histological location of astrocytes in close contact with the brain blood vessels allows them to modulate the transport of nutrients into the brain. These mechanistic capabilities have set astrocytes as central players in the regulation of several metabolic functions not only with respect to glucose homeostasis, feeding behaviour, energy expenditure and circadian rhythms, but also as cognitive, memory and reproductive axis modulators. GLP-1, glucagon-like peptide-1

for targeting non-neuronal cells, and astrocytes in particular, have allowed us to understand their functional role in the regulation of energy balance [39-42] (Box 2). A series of elegant studies have shed new light on how astrocytes in particular are involved in the integration of information by the CNS regarding elevated serum insulin and/or glucose availability. Mice with postnatal ablation of the IR in astrocytes showed excessive re-feeding after an overnight fast and failed to appropriately curb the fasting-induced hyperphagia in response to glucose.[23,24] In addition, female mice lacking IR specifically in astrocytes exhibited a significantly reduced preference for sucrose.[24] Furthermore, it is intriguing to note that female mice devoid of astroglial IR exhibit a 90% increased latency to feed in a novelty-suppressed feeding test at the same time as presenting several additional anxiety-related behavioural traits.[24]

On the other hand, energy expenditure has recently been associated with astrocytic insulin signalling.[43] Mice with a constitutive ablation of IR in astrocytes exhibited decreased energy expenditure and reduced body temperature both with respect to ad libitum fed and upon fasting without any changes in total body weight. Such impairments in thermogenesis were linked to lower sympathetic innervation of brown adipose tissue, which exhibited morphological abnormalities such as increased lipid droplets.[43] Importantly, however, these changes that were observed upon congenital ablation of astrocytic IR were absent in a mouse model that allowed for postnatal IR ablation using tamoxifen-mediated induction,[24] thus raising the possibility that the astrocyte-specific loss of insulin signalling throughout development leads to permanent changes in the homeostatic neurocircuitry regulating body temperature.[43] Therefore, the effect of insulin signalling in astrocytes on metabolic function and thermogenesis could depend on the time of astroglial IR ablation. A marked sexual dimorphism was also exhibited, which will require further attention. Both female and male mice constitutively lacking IRs in astrocytes showed delayed puberty, hypothalamic-pituitary-gonadotropin axis dysfunction and reduced fertility.[44] This confirms that insulin action on astrocytes also has important developmental effects which impact adult reproductive function.

2.2 | Insulin action in astrocytes: Brain glucose homeostasis

The brain is a very energy-demanding organ. Despite making up only approximately 2% of the total body mass, it accounts for up to 25% of overall glucose utilisation. Importantly, glucose represents

BOX 2 Astrocytes as gatekeepers for energy homeostasis

Using designer receptor-exclusively activated by designed drugs (DREADDs) for the pharmacogenetic activation of Ca^{2+} in astrocytes of the mediobasal hypothalamus (mainly comprised of the arcuate [ARC] and the ventromedial nucleus of the hypothalamus), it was shown that astrocytes regulate appetite by reducing food intake, both in basal conditions and in response to ghrelin, and also potentiate the anorectic action of leptin,[39] which is independent of the emotional state of the animal. This study also demonstrated that astrocytes exert their inhibitory regulation of food intake by releasing adenosine to inactivate AgRP-expressing neurones via adenosine A1 receptors.[39] Intriguingly, an analogous study found that DREADD-mediated activation of astrocytes located exclusively in the ARC was associated with increased food intake as a result of induced sequential activation of AgRP neurones, whereas no direct anorectic effect was observed.[40] These reported discrepancies between studies could be explained by the fact that hypothalamic feeding circuits comprise intricate and diverse glia-neuronal interconnections in which activity is regulated by multiple peripheral factors with distinct stimulus-response specificity in the control of metabolism.[45] Thus, it is not surprising that minor variations in the experimental paradigm (such as time, animal's metabolic state and the environment [eg, stress, smells]), as well as millimetric anatomical alterations in viral vector delivery, changes in gene delivery efficiency and selective transduction targeting astrocytes could shift the affected neuronal networks and thus the resulting outcomes. This fact highlights the need to be cautious when designing experiments based on the manipulation of astrocytic activity in vivo, as well as the conclusions drawn from the results obtained. Other recent studies have also dissected how astrocytes communicate with melanocortin neurones via the release of gliotransmitters such as acyl-CoA-binding protein-derived (ACBP-derived) endozepines to control food intake and energy balance.[41]

Aside from the hypothalamic-centred studies, astrocytes located on the nucleus of the solitary tract (NTS), within the brainstem dorsal vagal complex (DVC), have also been recently reported to play a key role in regulating food intake. Indeed, chemogenetic activation of DVC astrocytes reduced dark-phase feeding behaviour and also decreased refeeding after an overnight fast.[42] Interestingly, mitochondrial fission in DVC astrocytes was reported as one of the mechanisms mediating high fat diet (HFD)-dependent insulin resistance, hyperphagia, weight gain and fat deposition.[46] In addition, studies carried out on rats have highlighted that that DVC astrocytes partly mediate the anorectic effects of leptin and pharmacological glucagon-like peptide-1 receptor ligands.[47,48] Overall, these findings suggest that NTS astrocytes are involved in the integration of peripheral satiety signals to control feeding behaviour.

by and large the obligatory energy substrate for the brain, where it is primarily funnelled into oxidative metabolism.[49] Despite these substantial energetic needs, the brain possesses rather limited reserves and thus critically relies on a constant and uninterrupted supply of glucose from the circulation. Therefore, brain glucose uptake has historically been considered to underlie powerful autoregulatory mechanisms, being largely independent of peripheral fluctuation in energy availability (ie, during states of fasting, exercise or after a meal). A major mechanism by which the body regulates glucose excursions in response to a carbohydrate-containing meal is the secretion of insulin from pancreatic ß-cells, which consequently acts on peripheral tissues expressing IR such as the liver, adipose tissue and skeletal muscle where insulin action balances the production of endogenous, as well as the disposal of exogenous glucose. However, as mentioned above, IR is also abundantly expressed within the brain, and we are still far from completely understanding how insulin exerts its glucoregulatory actions.

Given the essentiality of a constant metabolic milieu in the brain, cerebral glucose utilisation has generally been assumed to be regulated independent of insulin. Interestingly, in healthy non-diabetic human subjects, it has been demonstrated that brain glucose uptake correlates positively with basal insulin secretion rate and total insulin output as assessed by fluorodeoxyglucose-positron emission tomography scans in conjunction with hyperinsulinaemic-euglycaemic clamps. Intriguingly, this correlation was absent in type 2 diabetes (T2D) patients, suggesting an uncoupling of central and peripheral glucoregulatory elements in pathological states of insulin resistance.[50] The implications of functional insulin signalling in the brain for overall metabolic health were recently highlighted in a functional magnetic resonance imaging (MRI) study in which high brain insulin sensitivity was linked to successful weight loss during lifestyle interventions.[17] Thus, marked postprandial spikes of insulin could still be conceived to result in functional changes at the brain-body interface, where astrocytes take centre stage.

Being situated directly between neurones and the vasculature, astrocytes are perfectly positioned to be pertinent for the integration and conveyance of insulin signalling within the brain. Indeed, ablation of IR from astrocytes throughout the entire CNS significantly hampered glucose transport into the brain, which was accompanied by a blunted pattern of neural activity in several glucose-sensitive nuclei of the hypothalamus.[23] Notably, our own work in mice has demonstrated that the ablation of astroglial IR results in comparable metabolic phenotypes regardless if targeting glial fibrillary acidic

protein (GFAP)$^+$ or glutamate aspartate transporter (GLAST)$^+$ astrocytic subtypes. Both astrocyte specific IR mouse models failed to suppress food intake in response to elevated glucose availability, became glucose intolerant and were unable to control glycaemia upon an i.p. glucose challenge [23,24] (Figure 2). Additionally, the lack of astrocytic IR led to a profound reprogramming of astroglial energy production and metabolism. Consistent with reduced glucose transport into the brain, both in vivo and in vitro experiments confirmed that the lack of IR in astrocytes significantly decreased the expression of glucose transporter 1 (GLUT-1),[23,51] one of the major glucose transporters in astrocytes that intriguingly exhibits partial sensitivity to insulin.[52] As a consequence, the lack of IR in primary astrocytes led to a marked reduction in overall astrocytic glucose uptake and a lower glycolytic rate, as well as decreased efflux of L-lactate,[23] the putatively preferred energy substrate of neurones in vivo.[53] Conversely, and likely to sustain intracellular energy, astrocytes lacking IR exhibited a compensatory increase in fatty acid metabolism as indicated by the up-regulation of carnitine palmitoyl transferase 1c (CPT1c), the rate-limiting enzyme in fatty acid ß-oxidation.[23] Consistently, IR-deficient astrocytes presented the characteristic increase in oxygen consumption upon shifting towards fatty acid catabolism, which was normalised upon pharmacological inhibition of CPT1c using etomoxir.[53] Of note, some studies have shown that the ablation of IR in astrocytes induces a compensatory up-regulation of insulin-like growth factor 1 receptor (IGF1-R). Despite being assumed to mimic many signalling and gene expression profiles of IR as a result of its high grade of homology, so far, in vitro studies indicate that the ablation of IGF1 signalling in astrocytes promotes glucose uptake via the translocation of GLUT-1 to the plasma membrane, as opposed to the effects observed in IR-deficient astrocytes.[51] Thus, further studies will need to be performed to untangle the distinct contribution of each receptor in astrocyte-mediated insulin action.

2.2.1 | Glucose sensing in hypothalamic astrocytes

Astrocytes located within the hypothalamus are clearly associated with glucose sensing mainly via regulating GLUT-1 expression. A study with streptozocin (STZ)-induced diabetic rats showed that overexpression of GLUT-1 in the hypothalamus was able to restore plasma glucose levels.[54] On the other hand, although mice with a genetic absence of endogenous GLUT-2 expression had a normal glucose-regulated insulin secretion, their glucagon secretion was altered in response to glycaemia perturbations. Interestingly, the GLUT-2 re-expression by transgenesis in (GFAP)$^+$ astrocytes of these mice restored glucagon secretion.[55] Such regulatory roles of astrocytes also require that astrocytes be interconnected through connexin-mediated gap junction channels to regulate activity-dependent trafficking of glucose from blood vessels to neurones imbedded into these astrocytic networks. Indeed, genetic ablation of astrocytic connexin 43 in the ARC diminishes the release of insulin from the pancreas in response to central glucose up-regulation.[56]

Besides these alterations in astroglial bioenergetics, the loss of IR further severely impacted astroglial morphology in the hypothalamus where it caused significant anatomical rearrangements of select glia-neuronal networks. For example, IR signalling in hypothalamic astrocytes proved necessary to functionally remodel the melanocortin neurocircuit of the hypothalamus, a major pathway for regulating

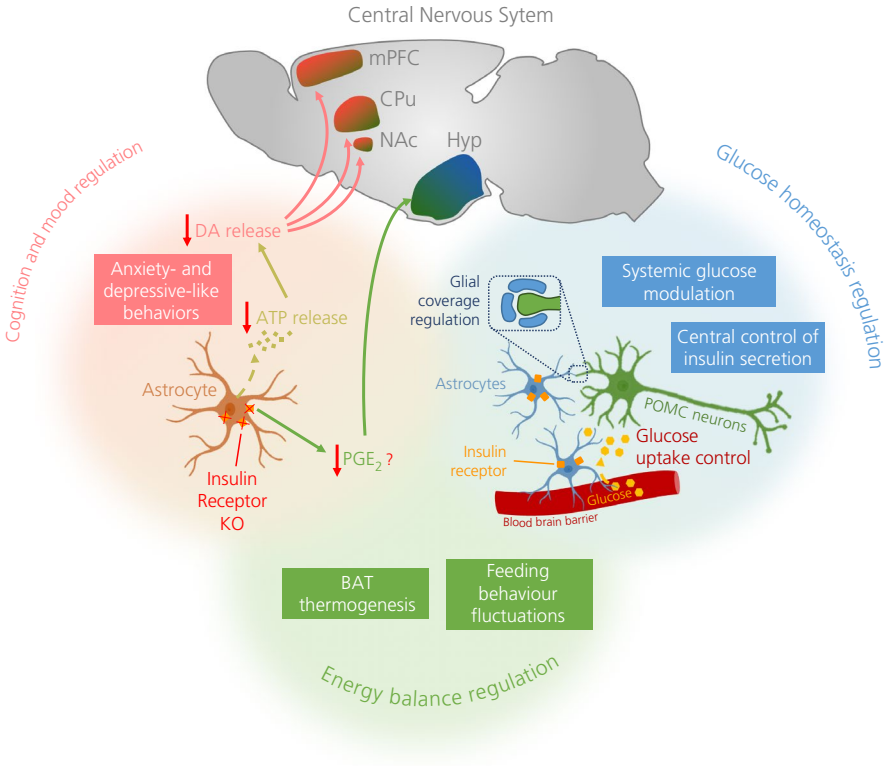

FIGURE 2 Insulin signalling in astrocytes modulates glucose homeostasis, energy balance, and cognition. Hypothalamic insulin receptors in astrocytes are required for the glucose transport into the central nervous system. This effect, together with the modulation of the glial coverage, is used by insulin to control glucose-induced activation of hypothalamic pro-opiomelanocortin (POMC) neurones and regulate feeding behaviour. Ablation of insulin receptor in astrocytes exhorts cognition and mood alterations. The lack of insulin signalling in astrocytes impairs their ATP release, resulting in a decrease in dopamine release within brain areas associated with cognition. BAT, brown adipose tissue; CPu, caudate putamen; DA, dopamine; Hyp, hypothalamus; KO, knockout; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; PGE_2, prostaglandin E_2

homeostatic processes. Intriguingly, the lack of IR signalling in astrocytes resulted in the abnormal ensheathment of POMC-expressing neurones in the hypothalamus and thus ultimately altered melanocortin synaptology.[23] This, in turn, rendered an otherwise glucose-sensitive subpopulation of POMC neurones unresponsive to hyperglycaemia. In a more recent study, the concept of astrocytes tuning to a melanocortinergic tone in response to glucose availability was examined. Nuzzaci et al[57] provided evidence suggesting that the retraction of glial processes is paramount for postprandial synaptic plasticity of POMC neurones, a dynamic process dependent on hyperglycaemia. In conjunction, these findings further add to the rapidly growing body of literature suggesting that astroglia-neuronal networks in the brain operate in close and reciprocal cooperation with the pancreatic islet in order to maintain whole-body glucose homeostasis.[58]

2.2.2 | Glucose sensing in NTS astrocytes

Besides the hypothalamus, the hindbrain harbours several areas that are of paramount importance for the astrocyte-mediated detection of fluctuations in glucose levels. Interestingly, almost half of all astrocytes within the NTS are sensitive to decreased glucose availability and respond to low glucose with increases in intracellular Ca^{2+}[59,60] by a mechanism proposed to be GLUT-2-dependent.[61] Nevertheless, it remains to be determined whether it is an insulin-dependent mechanism and what functional consequences are attributed to the regulation of neuronal glucose availability as observed in other studies mainly focused on the hypothalamus.[23] Especially in light of the fact that astrocytes constitute a highly diverse class of cells with inter- and intra-regional heterogeneity, a more detailed interrogation of astrocytic subtypes with specialised roles in brain insulin signalling and glucose homeostasis is clearly required, as well as the investigation of whether such functional distinction is defined by their anatomical distribution in the brain, local environment and/or neuronal circuit function in which they are embedded.

2.3 | Insulin action in astrocytes: Cognition and mood regulation

Besides metabolic homeostasis, insulin action in astrocytes also plays a role in the regulation of cognition and mood. Beyond that, impairment in learning and memory was previously documented as being a complication of diabetes.[62-65] Studies in T2D patients have shown reduced brain functional connectivity compared to control subjects, which was associated with insulin resistance in specific brain regions and cognitive impairment.[66,67] Likewise, a defect in insulin action in the brain was also linked with cognitive decline observed in Alzheimer's disease (AD) and several studies have proposed that impaired central insulin signalling is an important factor for the development of this malady.[68-71] Specifically, hippocampal insulin resistance has been proposed as the important area associated with cognitive impairment in T2D and AD.[72]

When it comes to insulin and mood, a substantial set of evidence supports an important role for the pancreatic hormone. Starting with the clinical evidence, both type 1 diabetes (T1D) and T2D patients have historically shown higher frequencies of depression and anxiety, together with the age-related cognitive decline and dementia.[73-76] As mentioned above, the basis of all these associations point to deficient insulin signalling in the brain. For example, functional MRI studies have shown an altered blood-oxygen level (a surrogate for neuronal function) in different brain areas both activated and deactivated in the case of T1D patients.[77]

Intranasal studies have been a helpful tool for discriminating the central effects of insulin from the peripheral changes. Studies conducted in humans suggest that insulin, administered intranasally, can improve memory and mood in healthy men and women.[78,79] Moreover, intranasal insulin administered to individuals with AD improved memory and preserved general cognition and functional abilities.[80] However, caution should be taken regarding the potential use of intranasal insulin as a treatment because more recent studies could not observe cognitive or functional benefits regarding intranasal insulin treatment of patients with mild cognitive impairment and AD dementia.[81]

Animal models were also conclusive in dissecting the insulin-cognition-mood link. Studies in rodents have shown that spatial learning was impaired in severely hyperglycaemic STZ-treated rats,[82] whereas central insulin infusion was able to prevent the learning deficit present in the same diabetic animal model.[83] In line with this, central administration of insulin in non-diabetic rats was associated with an enhancement in memory, indicating that these effects of insulin are present in a physiological context.[84] The whole brain IR knockout mice develop signs of depression-like behaviour, although it appears that both traits appear in a sex (females)- and age (17 months old)-dependent manner.[85] Indeed, previous reports in the same animal model had not seen differences between the wild-type and the knockout mice regarding spatial learning and memory, both short- and long-term, although, in this case, animals were slightly younger males.[86] A more recent report showed that insulin signalling in the hippocampus and amygdala also regulates behaviour in mice. Following a virogenetic approach, IR and IGF1-R were deleted in either the hippocampus or the amygdala, and both models developed an anxiety-like behaviour measured through different tests (ie, open field, marble marble-burying task and light/dark box test).[87] Interestingly, hippocampal-double knockout mice showed spatial memory deficit as a result of the exploration time expended in novel object recognition test being independent of familiarity of where the object was placed, along with significantly slower learning. When the same tests were applied to the amygdala double-knockout animals, novel object recognition was worse compared to wild-types, yet they correctly remembered the location of the object. In the Stone T-maze test, amygdala-specific double knockout mice showed normal learning and only a slightly impaired ability to

remember the maze, suggesting that IR and IGF1R signalling in the central amygdala mediates both recognition memory and spatial memory.[87]

Mechanistically, most of these insulin effects on cognition and mood previously described in this section were attributed to its action on neurones.[14,15,85,88] However, the growing knowledge about insulin action on astrocytes has also resulted in new studies showing that these glial cells mediate the insulin-dependent behaviour. Cai et al[24] were the first to show that mice constitutively lacking IR in astrocytes exhibit anxiety- and depressive-like behaviours. Interestingly, these behavioural abnormalities were more predominant in females than in males, consistent with previous findings concerning anxiety and depression murine models.[89] Mechanistically, the loss of insulin signalling in astrocytes appears to impair the ability of these glial cells to release ATP, resulting in a strong decrease in dopamine release within the nucleus accumbens, dorsal caudate putamen and medial prefrontal cortex and, accordingly, affecting the connectivity of neuronal circuits involved in cognition and mood [24] (Figure 2). It is worth mentioning that the described impact of insulin on astrocytes regarding mood could influence feeding behaviour via its effects on motivation and reward. Thus, the role of astrocytes in controlling energy homeostasis via insulin action could result from a multifactorial origin (ie, action in neuronal circuits involved in satiety, palatability, food addiction, liking, wanting and/or motivation). To test the contribution of each circuit, further studies should be designed and performed focusing on targeting distinct neural-circuit-specialised astrocytes rather than using whole-brain astrocyte IR knockout models. Lastly, and as previously introduced, the functional role of insulin action in astrocytes in the regulation of behaviour also translates to patho-physiological conditions. Thus, some evidence points toward an existing link between some neurodegenerative diseases and insulin action in astrocytes. In this sense, transcriptomic analyses of isolated astrocytes by laser capture microdissection from postmortem cortex of AD-type pathology patients showed an association between alterations in intracellular insulin targets (eg, phosphoinositide 3-kinase [PI3K]/Akt and mitogen-activated protein kinase) and the severity of the symptoms observed in the pathology.[90] Likewise, other studies have described a mislocation of IR substrate 1 in astrocytes in association with tau-pathology in AD using human post-mortem AD brains and immunohistochemistry.[91] Additionally, STZ treatment induced an IR dysfunction in astrocyte cultures and showed an induction in amyloidogenesis promotion, neuroinflammation and apoptosis, whereas insulin treatment attenuated these effects.[92] Other hypotheses describe that astrocytes protect neurones from the toxicity and deposition of amyloid beta peptide oligomers by the release of insulin and IGF1.[93] Interestingly, AβPP/PS1 mice, an experimental genetic murine model for AD pathology, showed chronically elevated hippocampal extracellular glutamate (a sign of excitotoxicity proposed as a mechanism underlying the neurodegeneration associated with AD), astrogliosis, and impaired insulin sensitivity independent of diet, and these effects were exacerbated by exposure to a HFD.[94] Parkinson's disease (PD) is another neurodegenerative disease that has been linked with brain insulin action defects, although little is known about the role of astrocytes in that pathological nexus. In vitro studies in astrocytes treated with 1-methyl-4-phenyl pyridinium (MPP+), a mitochondrial complex I inhibitor used as an experimental model for the study of PD pathology, have shown that insulin treatment prevents MPP+-induced toxicity through activation of downstream targets of insulin (eg, PI3K, p-glycogen synthase kinase-3β), autophagy, integrins and syndecans signalling pathways.[95] Despite increasing evidence proposing a strong association between insulin signalling in astrocytes and the pathophysiological mechanisms associated with the development and progression of AD and other neurodegenerative diseases, many questions still remain to be answered.

3 | INSULIN ACTION IN OTHER GLIAL CELLS

The growing interest with respect to exploring the role of insulin action in non-neuronal cells has not been restricted to astrocytes; emerging insights have highlighted the active role of insulin in other types of glial cells, such as microglia, tanycytes and oligodendrocytes.

3.1 | Microglia

Microglia are known as the brain immune cells, and have several physiological functions such as phagocytosis of cellular debris, modulation of synapses, and the secretion of several signalling molecules and cytokines. Similar to astrocytes, microglia also express both insulin and IGF1 receptors.[96] When in vitro studies were conducted in the microglial cell line BV2, it was found that insulin decreased the production of nitrous oxide (NO), reactive oxygen species and tumor necrosis factor α, and induced NO synthase expression, as well as amplified phagocytic activity when the cells were exposed to a pro-inflammatory stimulus.[97] However, as opposed to in vitro findings, in vivo functional studies with microglia have shown that insulin induces the activation of PI3K and Akt, downstream insulin receptor signals, as well as the up-regulation of interleukin-8, a pro-inflammatory cytokine, in a dose-dependent manner.[98] Moreover, central insulin treatment triggered microglia activation in the hippocampus, an effect that was reduced by age, being absent in 22-month-old rats.[98] These data show that inflammatory status regulation of glial cells by insulin may be a complex phenomenon with different effects depending on insulin levels and age.[96,98]

3.2 | Oligodendrocytes

Oligodendrocytes are the glial cells that form the myelin sheaths around neuronal axons in the CNS. Insulin at high concentrations has been shown to up-regulate the number of oligodendrocytes in rat brain cell cultures and thus exerts a proliferative stimulating effect.[99-101] Such an effect was associated with an increase in the

myelin content in culture, which was independent of a direct increase in oligodendrocyte-derived myelin.[102]

3.3 | Tanycytes

Tanycytes are specialised ependymal cells that play an additional, critical role in the regulation of the neuroendocrine control of metabolism. Located padding the third ventricle, near the dorsomedial hypothalamus and the median eminence (ME), these glial cells extend their lengthy processes toward the brain parenchyma and physically engage with fenestrated vessels within the ME, a circumventricular organ with an incomplete blood-brain barrier. Their privileged location along the third ventricle gives them a singular role in sensing both cerebral spinal fluid-derived and peripheral signals and conveying them to hypothalamic neurones. Regarding insulin's direct action on tanycytes, evidence is currently rather sparse. Nevertheless, Guillebaud et al[103] have reported an interesting finding in which insulin enhances tanycytic endozepine expression and release. Contextually, these endozepines were proposed as paracrine factors with a positive effect on diet induced obesity.

4 | CONCLUDING REMARKS

Over recent decades, increasing evidence supports a more comprehensive view between neurones and associated glia, moving away from the neurocentric view, for understanding insulin action in the brain. Specifically, the discovery that insulin regulates brain glucose metabolism via astrocytes has provided a switch in the paradigm of glucose entry into the brain, which, until recently, was assumed to be an insulin-independent process. This significant finding opens up new avenues in the development of a new generation of antidiabetic drugs based on non-neuronal insulin-dependent strategies. Likewise, and considering the neuroprotective role of insulin signalling, substantial efforts have been made in the last years in search of brain-specific insulin sensitiser therapies not only for use in the management of diabetes mellitus, but also as a treatment for brain diseases such as obesity, vascular dementia, and cognitive and memory decline related diseases. However, whether there is possibly a direct link between astrocytic insulin signalling and glucose transporter defects in the pathogenesis of these diseases, and whether the defective insulin-like peptide signalling in astrocytes is the foregoing mechanism to altered brain glucose metabolism, still remains to be determined.

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AUTHOR CONTRIBUTIONS

Ismael González-García: Writing – original draft; Writing – review & editing. **Tim Gruber:** Writing – original draft; Writing-review & editing. **Cristina García-Cáceres:** Supervision; Writing – original draft; Writing – review & editing.

DATA AVAILABILITY

Data sharing is not applicable to this article because no new data were created or analysed in this study.

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