Themed Issue: GLP1 receptor ligands (BJP 75th Anniversary)

THEMED ISSUE REVIEW

The role of glia in the physiology and pharmacology of glucagon-like peptide-1: implications for obesity, diabetes, neurodegeneration and glaucoma

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The medical applications of glucagon-like peptide-1 receptor (GLP-1R) agonists is evergrowing in scope, highlighting the urgent need for a comprehensive understanding of the mechanisms through which GLP-1R activation impacts physiology and behaviour. A new area of research aims to elucidate the role GLP-1R signalling in glia, which play a role in regulating energy balance, glycemic control, neuroinflammation and oxidative stress. Once controversial, existing evidence now suggests that subsets of glia (e.g. microglia, tanycytes and astrocytes) and infiltrating macrophages express GLP-1Rs. In this review, we discuss the implications of these findings, with particular focus on the effectiveness of both clinically available and novel GLP-1R agonists for treating metabolic and neurodegenerative diseases, enhancing cognition and combating substance abuse.

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1 | INTRODUCTION

Glia denotes several groups of nonneuronal cell types (e.g. astrocytes, microglia, tanycytes and oligodendrocytes) traditionally understudied in the many disciplines of neuroscience, including in the context of energy balance and glycaemic control. With respect to glucagon-like peptide-1 (GLP-1) physiology, an up-to-date PubMed search using keywords 'GLP-1 and glia' returned fewer than 100 papers, a tiny portion of the 17,000+ publications containing the keyword 'GLP-1'. Recently, however, interests in understanding the role glia plays in the physiology and pharmacology of GLP-1 have intensified. Accumulating evidence overwhelmingly support the assertion that glia are cellular substrates modulated by GLP-1 signalling, whether through direct ligand action and/or through indirect recruitment. GLP-1 receptor (GLP-1R) agonists have been shown to exert antiapoptotic and neuroprotective effects (Li et al., 2009; McClean et al., 2011; Perry et al., 2002; Sterling et al., 2020b), while reducing β-amyloid plaque accumulation (Li et al., 2009; McClean et al., 2011; Perry et al., 2003), enhancing neuronal progenitor cell differentiation (Hamilton et al., 2011; McClean et al., 2011) and modulating LTP and synaptic plasticity (Kobayashi et al., 2013; McClean et al., 2010) through glia-mediated mechanisms. Fittingly, GLP-1R agonists are presently being investigated as a means to improve cognitive function, reduce depressive behaviours and, as a potential treatment for alcohol and drug abuse (Erreger et al., 2012; Graham et al., 2013; Hayes

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Abbreviations: AP, area postrema; BBB, blood–brain barrier; DMV, dorsal motor nucleus of the vagus; EAAT1, aka GLAST and SLC1A3, excitatory amino acid transporter; EAAT2, aka GLT-1 and SLC1A2, excitatory amino acid transporter 2; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; IOP, intraocular pressure; NTS, nucleus tractus solitarius.

et al., 2014; Hsu et al., 2015; Isacson et al., 2011; Shirazi, Dickson, & Skibicka, 2013; Skibicka, 2013; Sorensen et al., 2015; Wang et al., 2010). This brief review highlights recent evidence exploring the neuroprotective potential of GLP-1R agonists in neuroinflammation and neurologic disorders, and the contribution of GLP-1R signalling in astrocytes as a putative means to regulate ingestive behaviour and body weight. Where relevant, discussions involve exploring the role glia plays in mediating the physiological effects of central GLP-1 signalling, the limitations of existing studies and the ongoing challenges facing the GLP-1 field in the effort to understand GLP-1–glia interactions.

2 | ROLE OF GLIA IN CNS TRAFFICKING GLP-1R LIGANDS

Astrocytes occupy a strategic position between the capillary endothelial cells and neurons to help form the blood–brain barrier (BBB). Astrocytes that contribute perivascular endfeet to the BBB have a unique role in ionic, amino acid, neurotransmitter, neuropeptide and water homeostasis in the brain. This subset of astrocytes are ideally positioned to detect circulating neuroendocrine signals, pharmacological ligands and modulate the processing of neural circuitries relevant to energy balance (Hermann & Rogers, 2009; J. G. Kim et al., 2014; McDougal, Hermann, & Rogers, 2013; McDougal, Viard, et al., 2013). Another intriguing but understudied glial population relevant to CNS ligand trafficking are tanycytes. Tanycytes are specialized, polarized ependymocytes that line the floor of the third ventricle in the median eminence and the subpostrema subnuclei that connects the area postrema (AP) to the nucleus tractus solitarius (NTS) in the caudal brainstem (Guillebaud et al., 2017; Langlet et al., 2013; Liberini et al., 2020; Prevot et al., 2013). These unique cells allow for trafficking of circulating signals relevant to food intake and energy balance control to adjacent neurons in the basal hypothalamic arcuate nucleus and the AP/NTS, respectively.

A subset of astrocytes and tanycytes both express the GLP-1R and the GLP-1R is internalized along with its ligand following binding (Gabery et al., 2020; Reiner et al., 2016; Secher et al., 2014), suggesting that glial cells facilitate the trafficking of GLP-1 ligands across the BBB (Gabery et al., 2020). Multiple studies from both pharma and academia have begun to map the neuroanatomical distribution of GLP-1R agonists in rodent models (Fortin et al., 2020; Gabery et al., 2020; Hernandez et al., 2018; Reiner et al., 2016; Secher et al., 2014). Such studies clearly demonstrate GLP-1R agonist accumulation in circumventricular nuclei of the AP and median eminence, as well as in adjacent nuclei of the basal hypothalamus and NTS. To a lesser degree, GLP-1R agonists were also present but more sparsely in distributed in nuclei throughout the brain, depending in part on what GLP-1R ligand is being analysed (Gabery et al., 2020; Secher et al., 2014). Because many existing GLP-1R agonists have prolonged half-lives, often of the order of days, what is understudied is whether ligand distribution changes following acute versus chronic weekly treatment. What is also unknown is whether glia-facilitated penetration of GLP-1 ligands into the CNS is altered by chronic GLP-1R agonist treatment, changes in metabolic and neurodegenerative disease states or with aging in general.

3 | CONTRIBUTION OF GLIA IN MEDIATING THE EFFECT OF GLP-1 ON ENERGY BALANCE

Acknowledging that a subset of glia, including a heterogeneous group of astrocytes, express GLP-1Rs and/or are responsive to GLP-1 pharmacology (C. H. Lee et al., 2018; Gong et al., 2014; Reiner et al., 2016; Sterling et al., 2020b; Yun et al., 2018), along with the idea that glia may facilitate the transport of GLP-1R ligands into specific nuclei of the CNS, necessitates a discussion of the role of glia in controlling energy balance. Although multiple studies have shown that intraparenchymal delivery of GLP-1R agonists to distributed CNS nuclei suppresses food intake and body weight, modulates reward, and/or produces behavioural measures of malaise (Kanoski et al., 2016), the contribution of glia in mediating GLP-1R agonist's action has not been investigated in the majority of these nuclei.

Astrocytes are critical for the modulation of L-glutamic acid in the extracellular space via two subtypes of astrocytic L-glutamic acid transporters, **excitatory amino acid transporter 2 (EAAT2 aka GLT-1 and SLC1A2)** and **excitatory amino acid transporter 1 (EAAT1 aka GLAST and SLC1A3)** (Danbolt, 2001; Perego et al., 2000). The idea that GLP-1R ligands may act directly on astrocytes in nuclei that receive glutamatergic inputs relevant to food intake and body weight regulation is supported by circumstantial evidence. The NTS of the dorsal vagal complex (DVC; composed of the NTS, AP and dorsal motor nucleus of the vagus [DMV]) is the first central nucleus to receive and process within-meal information, vagally mediated glutamatergic signals arising from the gastrointestinal (GI) tract (Grill & Hayes, 2009; Moran, 2006). The DVC expresses the GLP-1R (Hayes, 2012; Hayes, De Jonghe, & Kanoski, 2010; Merchenthaler et al., 1999; Reiner et al., 2016) and also acts as a critical sensor for circulating endocrine factors and nutrients (Blouet & Schwartz, 2012; Filippi et al., 2012; Hayes, Skibicka, et al., 2010; Huo et al., 2007; Marty et al., 2005; R. C. Ritter et al., 1981; S. Ritter et al., 2006). Not only are axons of GLP-1 producing preproglucagon (PPG) neurons in close apposition with NTS astrocytes, approximately one third of NTS astrocytes respond to GLP-1R agonists by intracellular calcium signalling (Reiner et al., 2016). In addition, pharmacological blockade of NTS astrocytes has been shown to attenuate the intake and body weight-suppressive effects of GLP-1R agonists (Reiner et al., 2016). It is important to point out that these data do not suggest that astrocytes are the cellular population required for all of the metabolic effects of GLP-1 signalling but rather are likely to be one of many cellular substrates by which GLP-1 and GLP-1R ligands control food intake and body weight. Indeed, even within the NTS, recent reports have clearly indicated that glutamatergic (Adams et al., 2018) and GABAergic

(Fortin et al., 2020) neurons expressing GLP-1Rs are both needed to observe full intake suppression following GLP-1 ligand delivery. The evergrowing body of literature collectively suggests that multiple cell types, including glial subtypes, in multiple nuclei relevant to energy balance express GLP-1Rs and facilitate the anorectic response to GLP-1 ligands. What remains to be determined is the unique mechanisms by which glia modulate neurotransmission to contribute to energy balance control.

Despite the long-standing appreciation that astrocytes are the most abundant cells within the CNS, only recently have scientists begun to embrace the idea that astrocytes serve a critical role in regulating neuronal excitability and synaptic plasticity (Agulhon et al., 2013; Halassa & Haydon, 2010; J. G. Kim et al., 2014). In fact, a single astrocyte may connect thousands of synapses and, along with presynaptic terminals and postsynaptic neurons, form a tripartite synapse (Araque, Parpura, et al., 1999; Araque, Sanzgiri, et al., 1999; Halassa & Haydon, 2010). Like neurons, astrocytes are activated by neurotransmitters released from presynaptic terminals and gliotransmitters released by other astrocytes. Importantly, astrocytes also express receptors for and are activated by other non-GLP-1-circulating signals of energy availability (e.g. leptin and ghrelin) (Chowen et al., 1999; Iwai et al., 2006; J. G. Kim et al., 2014; Kobayashi et al., 2013; Marina et al., 2017; McDougal, Hermann, & Rogers, 2013; Stein et al., 2020). Astrocytic activation increases calcium signalling, stimulating the release of gliotransmitters such as L-glutamic acid, ATP and D-serine (Araque et al., 2001; Coco et al., 2003; Halassa & Haydon, 2010; Mothet et al., 2000; Parpura et al., 1994).

In the case of L-glutamic acid-mediated astrocyte–neuron signalling, astrocytes are predominately responsible for the clearance of glutamate from the synapse by EAAT1 and EAAT2 (Danbolt, 2001; Perego et al., 2000). Interestingly, an increase in cAMP signalling within astrocytes reduces the expression of these glutamate transporters (Lim et al., 2005) and enhances synaptic glutamatergic signalling. Consistent with our previous research examining cAMP/PKA signalling in GLP-1R-expressing neurons (Hayes et al., 2011), GLP-1R activation in rat astrocytes results similarly in a dose-dependent increase in cAMP (Reiner et al., 2016). Likewise, in a coronal brainstem slice preparation, exendin-4 produced a robust and sustained live Ca^{++} signalling response in NTS astrocytes (Reiner et al., 2016). In summary, the collective evidence supports the hypothesis that within the NTS, GLP-1R activation of astrocytes may enhance vagal glutamatergic transmission of GI-derived satiation signals, possibly through a down-regulation of synaptic L-glutamic acid clearance and/or gliotransmission (see Figure 1 for a basic theoretic working model of astrocytic contribution to GLP-1 signalling in the NTS).

In addition to activating classic downstream intracellular signalling pathways to mediate hypophagic effects (e.g. cAMP/PKA, MAPK, AMPK and Akt) (Hayes et al., 2011; Rupprecht et al., 2013), hindbrain GLP-1R activation also increases interleukin (IL) signalling (Shirazi, Palsdottir, et al., 2013). Intriguingly, ILs can block the ability of astrocytes to clear L-glutamic acid from the synapses (Takahashi et al., 2003). Furthermore, cytokine signalling sensitizes vagal afferent signalling (Hermann & Rogers, 2008) and presumably modulates other presynaptic glutamatergic signalling in GLP-1R-expressing astrocytes throughout the CNS. Another glia-specific mechanism that may contribute to GLP-1R-mediated suppression of intake and body weight could be microglia GLP-1R-mediated increase of brain derived neurotrophic factor (BDNF) expression, as seen in human glia cultures (Spielman et al., 2017). Indeed, BDNF activation of the TrkB receptor has been well characterized to suppress food intake and body weight (B. Xu et al., 2003; Nakagawa et al., 2003; Spaeth et al., 2012; Tsao et al., 2008). In short, a concerted effort is underway to uncover the numerous mechanisms by which glia-derived GLP-1R activation could modulate the neuronal excitability in the tripartite synapse to influence energy balance. Discussed in more detail below, it is important

FIGURE 1 The role of astrocytes providing a supportive role to neurons has been investigated heavily over the past 30 years. What we know now in the context of glucagon-like peptide-1 (GLP-1) signalling is that first, astrocytes could theoretically help facilitate the transport of GLP-1 across the blood–brain barrier, due to the internalization of the receptor when bound (1). GLP-1 could modulate synaptic signalling indirectly by regulating astrocytic glutamate transporters GLT-1 and GLAST (2) or through the release of gliotransmitters (3). GLP-1R, glucagon-like peptide-1 receptor; NTS, nucleus tractus solitarius. Abbreviations, Lac, lactate; Gln, glutamine; Glu, glutamate; Ser, serine
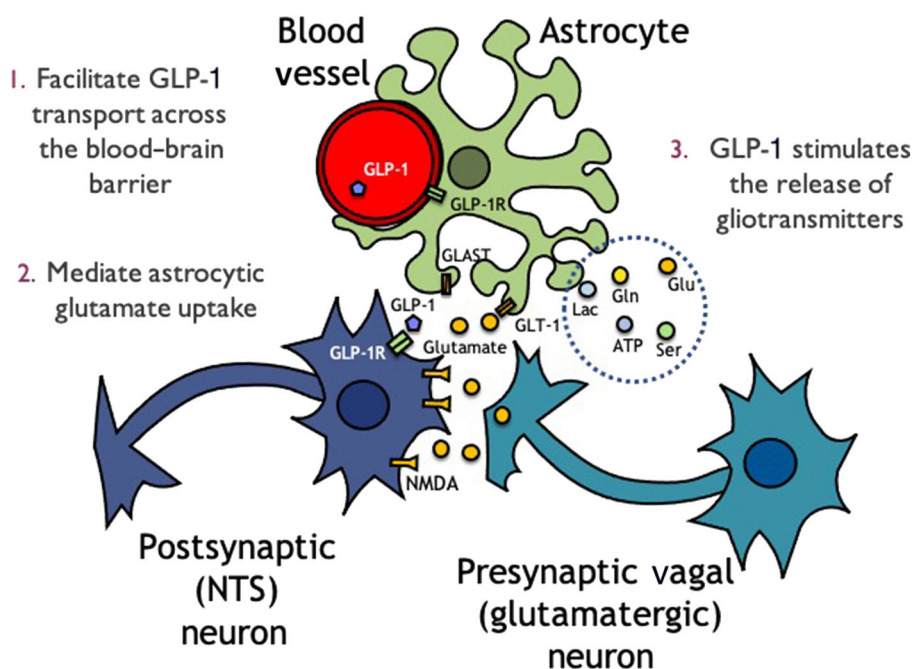
to note that the complexity of GLP-1-glia signalling with relevance to energy balance control is altered in various energy states such as obesity.

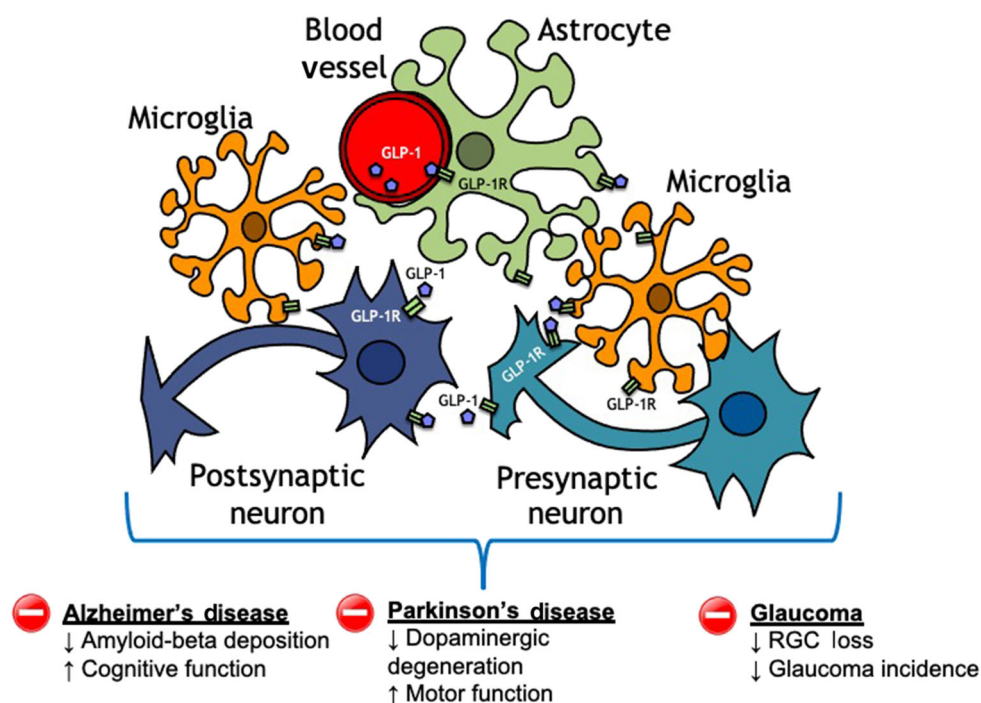# 4 | GLP-1 IN NEURODEGENERATIVE DISEASES AND GLAUCOMA

GLP-1R activation initiates a signalling cascade that inhibits the release of pro-inflammatory cytokines and astrocyte transformation to a neurotoxic (A1) phenotype, both key contributors to the pathogenesis of Parkinson's and Alzheimer's neurodegeneration (Athauda & Foltynie, 2016). Indeed, an evergrowing body of literature shows that GLP-1R agonists exert an assortment of anti-inflammatory effects to induce neuroprotection in multiple *in vitro* and animal models of Parkinson's and Alzheimer's diseases (see Figure 2). Specifically, GLP-1R agonists, such as exenatide (aka exendin-4), liraglutide and lixisenatide, have been shown to prevent dopamine neuronal degeneration in multiple studies utilizing toxin-induced nigrostriatal degeneration, resulting in improved motor function (Bertilsson et al., 2008; Harkavyi et al., 2008; Li et al., 2009; Liu et al., 2015; S. Kim et al., 2009). GLP-1 analogues also reduce amyloid β deposition and improve cognition in animal models (Gengler et al., 2012; Hamilton et al., 2011; Han et al., 2013; Hsu et al., 2018; Li et al., 2010; McClean et al., 2010; McGovern et al., 2012; Perry et al., 2003; Porter et al., 2010; Wang et al., 2010). In human trials, exenatide improved both motor and nonmotor deficits in patients with Parkinson's disease (Athauda et al., 2017) and liraglutide improved amyloid β accumulation (Gejl et al., 2016) and cognitive function in Alzheimer's disease (Femminella et al., 2019).

Recently, a novel GLP-1R agonists, NLY01 (Neuraly, Germantown, MD), prevented neurodegeneration and improved behavioural deficits

in a mouse model of Parkinson's disease (Yun et al., 2018). Indeed, NLY01 is a pegylated form of exendin-4 with a long half-life in both non-human primates (88 h) and mice (38 h), where it can efficiently penetrate the BBB resulting in high concentration in the CNS (Yun et al., 2018). In mouse models of Parkinson's disease and in culture, NLY01 was shown to prevent neuron death by reducing IL-1α, TNF-α and C1q release from microglia, thereby preventing astrocyte conversion to a neurotoxic (A1) phenotype (Yun et al., 2018). Clinical trials examining the safety and efficacy of NLY01 in treating early Parkinson's and Alzheimer's diseases are ongoing (clinical trial identifiers: NCT04154072 and NCT03672604).

The anti-inflammatory and neuroprotective effects of GLP-1R agonists suggest that they may be similarly beneficial in other disease processes with a neurodegenerative component. Glaucoma is an example of such a neurodegenerative disease and is characterized by retinal ganglion cell (RGC) degeneration and optic nerve atrophy, resulting in progressive and permanent loss of vision. It is the leading cause of irreversible blindness worldwide and has been projected to affect more than 100 million people by 2040. Regardless of the glaucoma subtype, all available treatment modalities for glaucoma rely on intraocular pressure (IOP) reduction through either decreased aqueous production or increased outflow. Intraocular pressure lowering, however proves insufficient to prevent disease progression in a significant number of patients and intraocular pressure-independent treatment options are urgently needed for this blinding disease.

In the retina, intraocular pressure elevation stimulates microglia/macrophages (CD11b+ cells) to produce IL-1α, TNF-α and C1q, a trio of pro-inflammatory cytokines necessary and sufficient to induce A1 astrocyte transformation and retinal ganglia cell death (Guttenplan et al., 2020; Liddelow et al., 2017; Sterling et al., 2020a). Knocking out the cytokine genes or neutralizing antibodies to these cytokines

FIGURE 2 A growing body of preclinical evidence is supporting the hypothesis that glucagon-like peptide-1 receptor (GLP-1R) agonism may be a novel therapeutic tool to treat and/or prevent the onset of multiple neurodegenerative diseases. The accumulating evidence is suggestive of a complex putative multicellular anti-inflammatory and neuroprotective action of GLP-1R agonists on neurons, astrocytes and microglia. GLP-1, glucagon-like peptide-1; RGC, retinal ganglion cell

rescued retinal ganglia cells in a microbead-induced mouse model of acute, hypertensive glaucoma (Guttenplan et al., 2020; Sterling et al., 2020a). In a recent study by our group, we showed that treatment with NLY01 reduced production of all three pro-inflammatory cytokines by microglia/macrophages in this mouse model of glaucoma (Sterling et al., 2020a). Further, NLY01 treatment prevented A1 astrocyte transformation and rescued retinal ganglia cells in these animals (Sterling et al., 2020a). GLP-1R agonists reduce blood–retina barrier (BRB) permeability by down-regulating pro-inflammatory cytokines and protect tight junctions in rodent models of diabetes (Simo & Hernandez, 2017). However, it is unknown whether NLY01's ability to rescue retinal ganglia cells involves modulating infiltration of myeloid cells through the blood–retina barrier. In support of this possibility, GLP-1R agonists have been shown to modulate macrophage phenotypes and decrease macrophage infiltration in rodent models of diabetes (Y. S. Lee et al., 2012), atherosclerosis and nephropathy (Y. S. Lee & Jun, 2016), and multiple sclerosis (Chiou et al., 2019). The use of GLP-1R agonists has also been associated with decreased glaucoma risk in diabetic patients (Sterling et al., 2021). However, because diabetes is an independent risk factor for glaucoma, it is not known whether GLP-1R agonists directly alter glaucoma progression and/or if this is a secondary outcome of improved glycaemic control following GLP-1R agonist administration.

In addition to macrophage and microglia, Müller cells are another important class of glia that spans the entire thickness of the retina to provide structural support, establish cellular homeostasis and maintain the blood–retina barrier. Increased glial fibrillary acidic protein (GFAP) expression, signalling Müller activation and gliosis have been demonstrated in animal models of glaucoma and human glaucomatous retinas (Lam et al., 2003; Tezel et al., 2003), whereas decreased L-glutamic acid uptake by Müller cells resulting in excitotoxicity has been postulated in glaucoma pathogenesis (Kawasaki et al., 2000). Pertinent to this review, GLP-1R agonists have been shown to exert a beneficial effect in animal models of diabetic retinopathy by limiting Müller reactivity and promoting survival resulting in improved blood–retina barrier integrity (Fan et al., 2014a, 2014b; Ren et al., 2020). Although direct evidence of reduced Müller reactivity following GLP-1R agonist treatment has not been similarly demonstrated in glaucoma, given the potential pathogenic role of Müller activation in glaucoma pathogenesis, this may be another area in which GLP-1R agonists are of benefit.

Notably, it remains to be seen whether GLP-1R agonists are beneficial in models of other forms of glaucoma, either those with chronic and progressive intraocular pressure elevation or for so-called normotensive glaucoma, where optic degeneration occurs without elevated intraocular pressure. Our group is presently working to answer one of these questions by evaluating the effect of NLY01 in the DBA/2J mouse model of pigmentary glaucoma and chronic, progressive intraocular pressure elevation. Collectively, existing data clearly highlight GLP-1R agonists as promising drug targets for treating neurodegenerative diseases such as Alzheimer's and hypertensive glaucoma through putative GLP-1-glia/macrophage-mediated mechanisms.

5 | THE CHALLENGES IN MOVING THE GLP-1 FIELD FORWARD IN GLIA RESEARCH

The concept that astrocytes, tanycytes and microglia, in addition to neurons, facilitate the effects mediated by GLP-1R activation is rapidly gaining traction. We believe that multidisciplinary evaluation of this idea portends widespread implications beyond improving treatments for diabetes and obesity, but must overcome a number of unique challenges, a few of which are highlighted below.

5.1 | Multiple neuroscience disciplines have embraced glia as a focus in their research; the obesity and diabetes fields are just joining the fray

The bulk of research on GLP-1 has focused on the metabolic diseases of obesity and diabetes. To the average diabetologist or obesity expert, the idea that glia contributes to normal glycaemic control or energy balance regulation is likely a foreign concept or, at best, one that is understood as being under investigation. Although the therapeutic potential of GLP-1's activity on glia has been predominately investigated in non-metabolic diseases, similar studies are desperately needed in the metabolic field. Investigation into the contribution of glia in modulating neuronal processing of satiety signals is essential, as is investigating glia-mediated synaptic pruning with regard to neural pathways of relevance to ingestive behaviour. Although GLP-1 and GLP-1R ligands clearly act on glia, it is also clear that the obesity and diabetes field has not yet devoted a wealth of resources to the study of these interactions. Nonetheless, investigating the cellular substrates that mediate GLP-1's latent potential to treat neurological and metabolic diseases through glia-mediated mechanisms is likely to uncover additional therapeutic targets that can be martialled to treat these same diseases. Although historically the tools have been lacking for interrogating glia *in vivo*, multiple recent advancements are likely to be of interest to the GLP-1 research community and should be utilized (Yu et al., 2020).

5.2 | Rat versus mouse and possible glia-specific difficulties with transgenic reporter lines

In the GLP-1 field, there are notable differences between species in both GLP-1 physiology and behavioural and metabolic effects produced by GLP-1 pharmacology (Huo et al., 2008; Lachey et al., 2005; Perez-Tilve, 2010). Of relevance to this review, GLP-1R expression on astrocytes may differ between mice (Cork et al., 2015) and rats (Kobayashi et al., 2013; Marina et al., 2017; Mora et al., 1992; Reiner et al., 2016). In light of these differences, a logical follow-up question would be - which species is the appropriate model(s) for understanding GLP-1 physiology in humans? Although primary human microglia and astrocytes have been shown to express GLP-1Rs in culture (Spielman et al., 2017), we believe that these data will require confirmation using additional methods for reasons described in detail below. It is also worth stating that because no reliable or validated antibody

for the GLP-1R is commercially available, progress in basic anatomical approaches has been limited. Instead, as bulk single-nuclei transcriptomic analyses with 10× technology in human post-mortem brain tissue become more widely available, we believe this technique will shed light on the question of which animal model best recapitulates human GLP-1 physiology. At present, however, existing single-nuclei transcriptomic data throughout the human brain are not available to answer this question.

In the near term, the notion of species differences between mice and rats for CNS GLP-1R cellular expression may not be as marked as once thought. This is supported by mounting evidence in both mice and rats showing that a subset of glia, including astrocytes, express GLP-1Rs and/or are responsive to GLP-1 pharmacology (C. H. Lee et al., 2018; Gong et al., 2014; Reiner et al., 2016; Sterling et al., 2020b; Yun et al., 2018). The confusion in the literature regarding this difference may be traced back to an initial reliance on a Cre recombinase-based reporter mouse for the GLP-1R (Cork et al., 2015). Importantly, and not limited to the GLP-1R-Cre mouse, a reliance on Cre recombinase can produce false-positive and false-negative expressions (Song & Palmiter, 2018). Indeed, in the initial creation of the GLP-1R–Cre founder strains, Richards et al. (2014) reported that although one founder strain displayed expected GLP-1R expression, the other strain showed sparse expression in pancreatic islets. This is a clear example of a false-negative scenario for GLP-1R–Cre in one of the two founder strains. In the report by Cork et al. (2015), the fact that the heterozygote mouse expressing Cre recombinase under the *Glp1r* promoter did not show expression of GLP-1R on GFAP-positive cells may be the result of such an unintended false-negative scenario. Another important consideration when using heterozygote mice is that one cannot rule out possible unknown haploinsufficiency for the CNS GLP-1R expression. Further, GFAP is only expressed by a subset of astrocytes and should not be relied upon as a ubiquitous marker for astrocytes (Bushong et al., 2002; J. Xu, 2018; Walz & Lang, 1998; Zhang et al., 2019). Collectively, and in line with a growing body of literature in not only rats, but also in mice showing GLP-1R expression and/or GLP-1R agonism in glia (C. H. Lee et al., 2018; Gong et al., 2014; Sterling et al., 2020b; Yun et al., 2018), reliance on the Cre reporter line may have lead the field to mistakenly conclude that absence of evidence is equal to evidence of absence with respect to GLP-1R–glia expression. For each CNS nucleus of interest, a triangulation of analyses in mice, rats and human tissue using immunohistochemistry, in situ hybridization and bulk single-nuclei RNAseq 10× transcriptomic may be necessary to better delineate GLP-1R expression and understand putative direct actions of GLP-1 on glia.

5.3 | The potential implications of intraparenchymal injections on macrophage recruitment

Microglia are resident macrophages of the CNS and are unique among macrophages in that they self-renew from their original yolk sac lineage in adulthood (Ajami et al., 2007; Bruttger et al., 2015; Elmore

et al., 2014; Epelman et al., 2014; Ginhoux et al., 2010; Hoeffel et al., 2015; Mildner et al., 2007; Sheng et al., 2015). Peripheral macrophages, in contrast, derive not only from the primordial yolk sac (Alliot et al., 1999; Ginhoux & Merad, 2011) but also from foetal monocytes and haematopoietic stem cells (Epelman et al., 2014; Hoeffel et al., 2015; Sheng et al., 2015). After infiltrating the CNS in response to injury, disease and microglia depletion, peripheral macrophages demonstrate morphology and expression profiles similar to resident microglia (Ajami et al., 2011; Bennett et al., 2018; Varvel et al., 2012). Yolk sac-derived macrophages, in particular, were shown to express many microglia signature genes including *Tmem119*, *Fcrls*, *Hexb* and *Olfml3* when injected into the brain of microglia-deficient mice, complicating efforts to differentiate resident microglia from infiltrating macrophages (Bennett et al., 2018). Nevertheless, peripheral infiltration versus local activation implicates important differences in disease pathogenesis and necessitates accurate characterization. Similarities between macrophages and microglia are of particular concern to the study of GLP-1 action on glia. The neuroscience field relies heavily on stereotaxically guided intraparenchymal implantation of electrodes, fibre optics, adeno-associated viruse (AAV)-mediated transfections and indwelling cannula. All techniques that begin with an experimenter-induced brain injury in their execution and may potentiate macrophage infiltration. Because GLP-1Rs are expressed on infiltrating macrophages (Shiraishi et al., 2012), a challenge for the GLP-1 field will be to differentiate between macrophage-mediated and glia-mediated GLP-1 function when using these approaches.

5.4 | In vitro, in situ, in vivo … the devil is in the details when studying GLP-1-glia signalling

As research efforts examining GLP-1 action on astrocytes and microglia intensify, and with respect to experiments looking at the contribution of glia to energy balance control, it is important to remember that glia are an unique and dynamic group of cells in constant states of transcriptomic and morphological flux. In the context of energy balance, study results have clearly shown that perturbations to diet and/or energy states can influence the *in situ* cytoarchitecture of hypothalamic and brainstem DVC astrocytes, as well as microglia morphology and activity (Fuente-Martin et al., 2012; Garcia-Caceres et al., 2011; J. G. Kim et al., 2014; Liberini et al., 2020; MacDonald et al., 2020; Stein et al., 2020). Interpretation of GLP-1 action on glia is therefore affected by multiple factors that include, but are not limited to, age, diet and energy states (i.e. fasted, fed, overfed and obese) of the animal model or humans under investigation. Further, glia are 'supporting cells' of the CNS, and it is necessary to appreciate that when cultured in isolation, their transcriptomes and functions change (Bohlen et al., 2019; Collins & Bohlen, 2018; Gosselin et al., 2017), thus making it difficult to interpret physiological or pharmacological GLP-1 signalling on glia *in vitro*. The best approaches for studying the role of glia in mediating GLP-1 function will be ones that involve various assays to include in situ analyses and, when possible, *in vivo* physiological and behavioural assessments in addition to *in vitro* assays.

6 | CONCLUSIONS

The old saying 'less is more' does not apply to GLP-1. Indeed, GLP-1 is a hormonal axis that keeps on giving when it comes to combating not only diabetes and obesity but also potentially other diseases such as neurodegenerative diseases and substance abuse. The more the neuroscience community as a whole investigates GLP-1 physiology and pharmacology, the more we are likely to be rewarded with insights into the innerworkings of both the peripheral and central GLP-1 systems. Highlighted here is the emerging literature showing a complex role for glia in putatively trafficking GLP-1 ligands into the CNS, as well as mediating beneficial effects of GLP-1R signalling in neuroprotection, reducing oxidative stress and leading to food intake and weight loss suppression. Additional research is needed to interrogate the details through which each of these glia-mediated mechanisms is targeted and influenced by GLP-1 pharmacology and to understand how metabolic and neurodegenerative diseases impact the overall glia-GLP-1 landscape.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22 (Alexander et al., 2021).

AUTHOR CONTRIBUTIONS

All the authors prepared, edited and approved the final version of the manuscript.

CONFLICT OF INTEREST

M.R.H. receives research funding from Boehringer Ingelheim and Eli Lilly and Company that was not used in support of these studies. M.R.H. is an owner of Cantius Therapeutics, LLC that pursues biological work unrelated to the current study. All other authors have no conflicts of interest to report.

DATA AVAILABILITY STATEMENT

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

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