

THEMED ISSUE REVIEW

Brain GLP-1 and the regulation of food intake: GLP-1 action in the brain and its implications for GLP-1 receptor agonists in obesity treatment

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This review considers the similarities and differences between the physiological systems regulated by gut-derived and neuronally produced glucagon-like peptide 1 (GLP-1). It addresses the questions of whether peripheral and central GLP-1 sources constitute separate, linked or redundant systems and whether the brain GLP-1 system consists of disparate sections or is a homogenous entity. This review also explores the implications of the answers to these questions for the use of GLP-1 receptor agonists as anti-obesity drugs.

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1 | INTRODUCTION

Glucagon-like peptide 1 (GLP-1) receptor agonists are a hot topic in obesity. They are successfully used as a second-line treatment for Type 2 diabetes mellitus, and their major additional effect of body weight loss has put them on centre stage as anti-obesity drugs (Knudsen, 2019). **Liraglutide** and, more recently, **semaglutide** are the most efficacious weight loss drugs in clinical trials (O'Neil et al., 2018; Pi-Sunyer et al., 2015; Wilding et al., 2021), and the observation that postprandial rises in endogenous GLP-1 are small in people living with obesity, but significantly increased after bariatric surgery, seems to suggest that elevation of circulating GLP-1 levels is a promising strategy for substantial weight loss (Holst, 2013; Holst et al., 1983, 2018;

le Roux et al., 2006). The major side effect of nausea (also associated with bariatric surgery) at the start of treatment induces some patients to stop therapy, but most battle through this phase. Additionally, **GLP-1 receptor** agonists seem to have beneficial effects on other organs including the brain, with potential neuroprotective effects, even in Alzheimer's and in Parkinson's disease (Athauda et al., 2017; During et al., 2003; Foltynie & Athauda, 2020; Gault & Holscher, 2008; McClean et al., 2011). However, there are various gaps in our understanding of how and why these agonists achieve these effects. This review is aimed at understanding the biology underlying these effects, particularly those involving the CNS.

Because GLP-1 originates from at least two separate locations within our body, the enteroendocrine L cells of the intestine and the preproglucagon (PPG) neurons of the brain (Holst, 2007; Muller et al., 2019), we will first address the question of whether GLP-1 really is a hormone that circulates throughout the entire body,

Abbreviations: BBB, blood-brain barrier; DPP-4, **dipeptidyl peptidase 4**; Ex-4, **exendin-4**; Ex-9, **exendin-(9-39)**; GLP-1, glucagon-like peptide 1; IRT, intermediate reticular nucleus; NTS, nucleus tractus solitarius; PPG, preproglucagon.

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including the CNS. Or is its action more locally restricted, so its release in specific places determines its function, akin to neurotransmitters and neuromodulators within the brain? Glutamate, for instance, has vastly different effects dependent on where exactly it is released within the CNS. After discussing whether the peripheral (gut-produced) and central (PPG neuron-produced) GLP-1 systems are linked or not, we will concentrate on the central GLP-1 system. We will ask the question: Is GLP-1 involved in the physiological regulation of food intake? GLP-1 clearly *reduces* food intake, but does it *regulate* food intake? Administration of a general anaesthetic will substantially *reduce* food intake, because the subject is asleep, but this does not mean that it *regulates* intake or would be a sensible drug to reduce obesity. Where does GLP-1 sit on a spectrum of drugs that reduce intake? And finally, after addressing this question, we will consider the various other functions of brain-derived GLP-1. Exogenous GLP-1 injected into the CNS has been implicated in a wide array of roles ranging from the suppression of food intake, to effects on energy expenditure, to cardiovascular effects and neuroprotective actions (Barragan et al., 1999; During et al., 2003; Kanoski et al., 2016; Lee et al., 2018; Tang-Christensen et al., 1996; Turton et al., 1996). We will discuss whether these seemingly diverse functions are manifestations of a single overarching function of GLP-1 within the brain or whether they reflect an array of functions that are activated individually and independently by the appropriate activation of subsets of PPG neurons.

2 | ARE THE PERIPHERAL AND THE CENTRAL GLP-1 SYSTEMS ENTIRELY DIFFERENT ENTITIES?

Environmental pressures coupled with millions of years of evolution have made biological systems rather frugal. Many signalling molecules found in the periphery are also used within the brain. Investigating and understanding the function of these peptides both in the periphery and in the CNS presents us with technical as well as intellectual challenges. A number of peptides seem to be produced in the periphery only (**insulin**, **leptin** and **amylin**) and then access (part of) the CNS to elicit central functions (Hayes et al., 2014; Kullmann et al., 2020; Pandit et al., 2017). Others, such as **cholecystokinin** (CCK) or GLP-1, are released both in the periphery and centrally (Chaudhri et al., 2006; D'Agostino et al., 2016; Steinert et al., 2017), and it is not immediately obvious whether the peripherally and centrally derived peptides act at distinct sites or whether the same receptor populations can be accessed by both.

Currently, there is one molecularly defined **receptor for GLP-1** (Thorens, 1992), and this receptor is expressed throughout the body in most major organ systems, including the digestive and cardiovascular systems, as well as the peripheral and central nervous systems (Baggio et al., 2018; Campos et al., 1994; Cork et al., 2015; Merchenthaler et al., 1999; Richards et al., 2014; Shughrue et al., 1996; Ussher et al., 2014). From a teleological point of view, we are tempted to argue that there is one GLP-1 molecule and there is one receptor, and consequently, we are looking at one single biological system with functions that are directly linked and all serve the maintenance of energy homeostasis. The canonical view has been:

GLP-1 is released postprandially from the gut into the circulation, to (i) enhance the release of insulin from the endocrine pancreas to lower blood glucose—the incretin effect, and (ii) to act on vagal afferents and/or directly enter the brain, in order to suppress appetite, and thus act as a satiation signal. This all sounds like a rather sensible arrangement. Unfortunately, nature threw a spanner in the works by also using GLP-1 as a neuropeptide within the CNS. In the CNS, GLP-1 is synthesised by a relatively small population of a few thousand neurons primarily located within the lower brainstem of vertebrates, in the nucleus tractus solitarii (NTS) and in the adjacent intermediate reticular nucleus (IRT) (Larsen et al., 1997; Llewellyn-Smith et al., 2011; Merchenthaler et al., 1999). These neurons are typically referred to as GLP-1 neurons in rat (where they are solely defined by immunoreactivity) and as PPG neurons (named after the transcript) or GCG neurons (named after the gene) in mice (Gaykema et al., 2017; Hisadome et al., 2010; Rinaman, 1999b). Additionally, GLP-1 is produced and acts within the olfactory bulb (Merchenthaler et al., 1999; Thiebaud et al., 2016, 2019). At present, this is considered as a ‘local circuit’ and has only been described in rodents, but knowledge is limited, and it is unclear if it has a role to play in food intake and body weight control or whether this circuit exists in humans. This olfactory population will not be discussed any further in this review.

Although we are talking about the same GLP-1 molecule, and the same receptor it acts upon, we are potentially considering two substantially different modes of action. Neuronally produced GLP-1 is transported to the axon terminals of the producing cells and is there stored in synaptic vesicles until its eventual release into the synaptic cleft, or in case of extrasynaptic release, into the brain parenchyma (Zheng et al., 2014). This means that the largest quantities of GLP-1 within the CNS are found in the hypothalamus and in the spinal cord, and not in the brainstem where it is produced (Holt, Richards, et al., 2019; Jin et al., 1988). Considering that PPG neurons are projecting neurons that have axons containing GLP-1 vesicles in many distinct regions of the brain (Figure 1), it seems likely that GLP-1 release and action within the brain is locally restricted and regulated like that of other neurotransmitters and modulators. In contrast, GLP-1 derived from enteroendocrine L cells of the intestine is released into the interstitial space at the site of its synthesis and then diffuses locally to act on, for example, vagal nerve endings embedded into the gut mucosa (Berthoud et al., 2021), or enters the bloodstream or lymphatic system, and is transported freely to sites of action anywhere in the body accessible from the circulation, limited only by inactivation by blood-borne **dipeptidyl peptidase 4** (DPP-4) (Holst, 2007; Kieffer et al., 1995; Mentlein et al., 1993). Although a neuropod configuration has been proposed for some enteroendocrine cells (Liddle, 2018), it is unclear whether such structures play any role in the action of gut-derived GLP-1.

This principal difference in organisation between hormonal and neuronal signalling has important implications. Although release of GLP-1 from any L cell in the gut can potentially act throughout the entire body and consequently must have a related, concerted action on different GLP-1 receptors in different locations, GLP-1 released from a specific neuron only acts at the defined site of its release; that is, activation of each PPG neuron can potentially have a distinct local

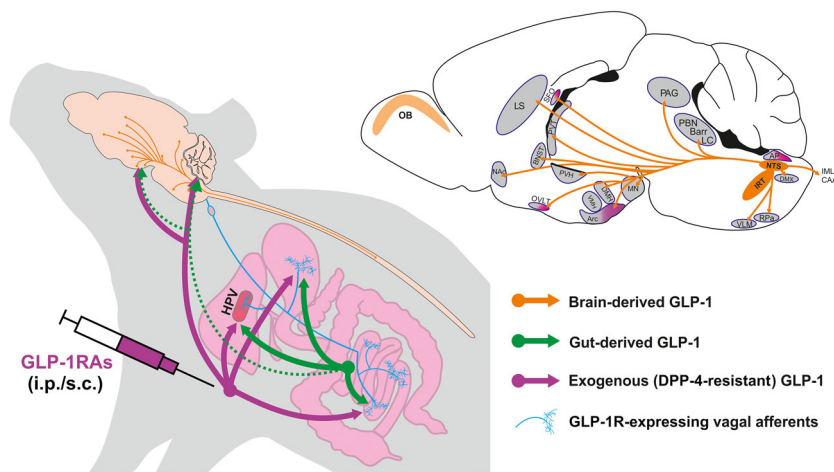


FIGURE 1 Similarities and differences between the proposed pathways of action for brain-derived, gut-derived and exogenous glucagon-like peptide 1 (GLP-1). The action of brain-derived GLP-1 (orange) is limited to the CNS and determined by the projection pattern of the preproglucagon (PPG) neurons throughout the brain and the spinal cord. Gut-derived GLP-1 (green) is released into the bloodstream and acts locally within the gastrointestinal system and potentially (dotted lines) might reach circumventricular organs of the brain. Degradation-resistant, peripherally administered, GLP-1 receptor (GLP-1R) agonists (GLP-IRAs) act within the gastrointestinal system and reach the circumventricular organs but are unlikely to penetrate significantly through the blood–brain barrier. Within the gastrointestinal tract, GLP-1 and **GLP-1 receptor** agonists can act on vagal afferents that project to the brain to elicit satiation. AP, area postrema; Arc, arcuate nucleus; Barr, Barrington's nucleus; BNST, bed nucleus of the stria terminalis; CAA, central autonomic area; DMH, dorsomedial hypothalamus; DMV, dorsal motor nucleus; DPP-4, dipeptidyl peptidase 4; HPV, hepatic portal vein; IML, intermediolateral nucleus; IRT, intermediate reticular nucleus; LC, locus coeruleus; LS, lateral septum; MN, mammillary nucleus; NAc, nucleus accumbens; NTS, nucleus tractus solitarius; OB, olfactory bulb; OVLT, organum vasculosum of the lamina terminalis; PAG, periaqueductal grey; PBN, parabrachial nucleus; PVH, paraventricular nucleus of the hypothalamus; PVT, paraventricular thalamus; RPa, raphe pallidus; SFO, subfornical organ; VLM, ventrolateral medulla; VMH, ventromedial hypothalamus

effect that is entirely independent of that elicited by GLP-1 release from a different PPG neuron projecting to a different CNS area. Given these principally different modes of action, is it actually plausible that gut-derived GLP-1 should physiologically activate receptors within the CNS? GLP-1 is rapidly inactivated by DPP-4 within the bloodstream. In fact, some studies in rats have suggested that postprandial rises in (presumably gut-derived) active GLP-1 are not detectable in the bloodstream beyond the liver, although in humans, postprandial rises in venous GLP-1 have been measured (Kreymann et al., 1987; Punjabi et al., 2014; Steinert et al., 2016). On the other hand, peripheral administration of pharmacological doses of exogenous radiolabelled GLP-1 leads to detectable amounts found in the circumventricular organs of the brain, which are characterised by a leaky blood–brain barrier (BBB) (Orskov et al., 1996). These seemingly conflicting findings illustrate the difference between ‘physiologically relevant’ and ‘principally possible’ pathways. That is, no physical barrier exists for gut-derived GLP-1 to reach the cranial circulation, but the combination of physiologically released ‘doses’ and DPP-4 inactivation might make it unlikely that postprandially released GLP-1 reaches even the circumventricular organs of the brain. This raises the question of what is the physiological role of GLP-1 receptors in the circumventricular organs? We will return to this question later in this review. However, an unphysiologically large postprandial release of GLP-1, for example, after gastric bypass surgery (Korner et al., 2007), might reach the circumventricular organs, and DPP-4-resistant **GLP-1 receptor** agonists clearly have central actions, though whether this includes action on GLP-1 receptors inside the BBB or is limited to direct activation of GLP-1 receptors in the circumventricular organs outside the BBB, is less clear (Adams

et al., 2018; Gabery et al., 2020; Gu et al., 2013; Salinas et al., 2018; Secher et al., 2014). Adams et al. (2018) analysed what proportion of cells showing c-Fos activation upon systemic liraglutide actually express GLP-1 receptors, in five different brain regions. The only circumventricular organ analysed was the area postrema, and this was the only region where the majority of c-Fos-positive cells expressed GLP-1 receptors.

Nevertheless, insofar as the physiological, postprandial GLP-1 release from L cells is concerned, gut-derived GLP-1 might not reach the CNS at all, but primarily acts ‘locally’ in a paracrine fashion, activating GLP-1 receptors in the vicinity of the intestinal system (Richards et al., 2014). It is important to note, however, that this does not mean that it cannot produce an indirect central signal. It might act on GLP-1 receptors located on the nerve endings of subdiaphragmatic vagal afferents within the intestine (Bai et al., 2019; Krieger, 2020; Williams et al., 2016; see also review by Brierley & de Lartigue, 2021), or even elsewhere close to the circulation, which in turn release glutamate and peptide co-transmitters within the lower brainstem to convey postprandial satiation signals to the CNS (Figure 1).

3 | HOW SEPARATED ARE THE TARGETS FOR GUT-DERIVED AND BRAIN-DERIVED GLP-1?

Accepting the premise that circulating GLP-1 does not enter the CNS beyond the circumventricular organs is a prerequisite to assuming that

GLP-1 is released from PPG neurons as a neurotransmitter or neuro-modulator with locally restricted and potentially disparate actions. Only if circulating GLP-1 cannot activate these different GLP-1 receptor populations is it sensible to employ GLP-1 as a neurotransmitter/modulator to mediate disparate actions. However, given that it is the same molecule that is released from gut L cells and PPG neurons, it is experimentally difficult to prove that peripheral GLP-1 does not act on receptors in the CNS. In fact, particularly the circumventricular organs with their GLP-1 receptors present some conundrum. These brain regions, with their lack of BBB, are classical entry portals for blood-borne factors into the brain. The circumventricular organs actually express high levels of GLP-1 receptors (Cork et al., 2015; Jensen et al., 2018; Merchenthaler et al., 1999), and studies injecting large doses of radiolabelled GLP-1, or fluorescently labelled **GLP-1 receptor** agonists or antagonists, into the periphery (i.p./i.v./s.c.) have demonstrated that circulating GLP-1 can access these structures (Ast et al., 2020; Gabery et al., 2020; Orskov et al., 1996; Salinas et al., 2018; Secher et al., 2014). In contrast, it is less clear whether the circumventricular organs are projection targets for PPG neurons. Projections to the area postrema and the other circumventricular organs such as the median eminence or the subfornical organ are very sparse (Llewellyn-Smith et al., 2011), so one might argue that these receptors are targets for gut-derived GLP-1, but not brain-derived GLP-1, leaving the separation between the peripheral and central GLP-1 system intact. However, the observations that knockout of gut-derived GLP-1 affects glucose handling, but not food intake or body weight (Song et al., 2019), and that the GLP-1 receptor antagonist **exendin-(9-39)** (Ex-9) did not affect food intake in human volunteers (Melhorn et al., 2014; Steinert et al., 2014) would suggest that a substantial number of receptors are left without a native ligand accessing them in physiological (postprandial) situations. Although that might intuitively sound unlikely, hypophagia and weight loss are not effects reported for DPP-4 inhibitors, such as **sitagliptin** or **vildagliptin** (Gilbert & Pratley, 2020; Rosenstock et al., 2008), suggesting that indeed even prolonging the availability of postprandial, circulating, active GLP-1 seems insufficient to elicit those responses. This lack of effect would include GLP-1 receptors in the arcuate nucleus, part of which is freely accessible from the general circulation together with the median eminence. as shown for both **GLP-1 receptor** agonists and the antagonist LUXendin645 (Ast et al., 2020; Gabery et al., 2020; Secher et al., 2014).

Interestingly, the arcuate nucleus has been identified as the prime mediator for the hypophagic action of liraglutide (Secher et al., 2014; Sisley et al., 2014), reinforcing the point that postprandial and even prolonged postprandial GLP-1 rises are unable to activate these GLP-1 receptors. However, compared with, for example, the area postrema, the arcuate nucleus receives stronger innervation from PPG neurons (Gu et al., 2013; Llewellyn-Smith et al., 2011) and thus might be a target for central GLP-1 under physiological conditions as well as for truly supraphysiological amounts of circulating GLP-1 and **GLP-1 receptor** agonists. In support of this notion, subcutaneously administered LUXendin645, an Ex-9-based GLP-1 receptor antagonist, has been demonstrated to have an overlapping

distribution with PPG axons in the arcuate nucleus (Ast et al., 2020).

GLP-1 receptors are found in many regions throughout the CNS (Cork et al., 2015; Jensen et al., 2018; Merchenthaler et al., 1999), and PPG neurons send axonal projections to numerous regions of the brain and spinal cord (Card et al., 2018; Larsen et al., 1997; Llewellyn-Smith et al., 2011, 2013, 2015; Vrang et al., 2007). With a few notable exceptions, such as the ventral hippocampus, this projection pattern largely matches the distribution pattern of GLP-1 receptor-expressing cells (Trapp & Cork, 2015), which might be indicative of these receptors throughout the CNS mainly being exposed to brain-derived GLP-1. In contrast, the distribution pattern of fluorescently labelled **GLP-1 receptor** agonists found within the CNS after systemic administration is substantially more limited (Gabery et al., 2020; Salinas et al., 2018; Secher et al., 2014). Additionally, Williams et al. (2009) demonstrated that the intake-suppressing effects of peripherally administered GLP-1 can only be prevented by peripheral, but not central, Ex-9, and the effects of centrally administered GLP-1 can only be antagonised by central Ex-9, but not peripheral Ex-9. Collectively, these data might indicate that access to GLP-1 receptors behind the BBB for peripherally administered **GLP-1 receptor** agonists (and antagonists; Ast et al., 2020) is considerably less than anticipated and would be in line with the notion that endogenous activation of GLP-1 receptors inside the BBB is solely the consequence of brain GLP-1 release.

However, particularly after chronic treatment, fluorescent **GLP-1 receptor** agonists are found in selective areas in the vicinity of the third ventricle behind the BBB (Secher et al., 2014). This CNS access appears to be GLP-1 receptor-dependent, because it was not observed in GLP-1R-KO mice (Secher et al., 2014). GLP-1 receptor-dependent internalisation and transcellular transport of the ligand have been suggested for **GLP-1 receptor** agonists, but not antagonists (Ast et al., 2020; Secher et al., 2014). Interestingly, even acute exposure to a single dose of the **GLP-1 receptor** agonist or antagonist leads to the detection of the molecule within parts of the ventricular system of the brain. This is not dependent on GLP-1 receptor-mediated cellular uptake because it is observed with the antagonist (Ast et al., 2020; Secher et al., 2014). Whether this does or does not involve the choroid plexus (Lun et al., 2015) is currently unclear. On first sight, this could indicate that there is no principal barrier for endogenous GLP-1 to reach at least this part of the brain, though it would require a large enough 'dose' to overcome the physiological inactivation of the native, gut-derived GLP-1 in the circulation. Additionally, it seems surprising that Ast et al. (2020) did not observe fluorescent antagonist labelling in areas adjacent to the ventricles, other than that seen in the circumventricular organs. This is particularly surprising given that i.c.v administration is a standard route to test central effects of drugs in animal studies, and a large number of studies have injected GLP-1 or **GLP-1 receptor** agonists and antagonists into the ventricular system in order to explore direct effects of GLP-1 receptor activation within the CNS (Meeran et al., 1999; Tang-Christensen et al., 1996; Turton et al., 1996; van Dijk et al., 1996, 1997). In fact, revisiting the raw data from Ast et al. (2020) reveals that the

fluorescent signal inside the ventricles of a cleared mouse brain after i.p. administration of luxendin does not fill the entire ventricles, nor is it localised to the ependymal cells lining the ventricles, but rather is limited to distinct structures within the ventricles—presumably parts of the choroid plexus (Figure 2). Additionally, a clinical study assessed CSF from Type 2 diabetes patients treated with liraglutide for 5 months or more. This study reported an average CSF concentration of 6.5 pM with a plasma concentration of 31 nM, suggesting there is minimal penetration of liraglutide into the ventricles even following chronic treatment (Christensen et al., 2015). Thus, access to the brain parenchyma for peripherally administered **GLP-1 receptor** agonists via the ventricular system seems unlikely, though probably deserves further detailed experimental attention in order to produce an unequivocal answer. Interestingly, release of GLP-1 specifically into the ventricles has been suggested as a means of reaching hippocampal GLP-1 receptors in the hippocampus, an area that lacks PPG neuron axon terminals (Hsu et al., 2015; Llewellyn-Smith et al., 2011).

In summary, proving a complete separation and a ‘hard’ border between the peripheral and central GLP-1 system encounters a variety of difficulties, which prevent us from coming to watertight conclusions. Consequently, it might be prudent to ask the ‘opposite’ question and explore whether there are clearly defined links between these two systems. Therefore, the next section addresses specifically the question whether peripheral GLP-1 can activate PPG neurons.

4 | ARE PERIPHERAL AND CENTRAL GLP-1 LINKED?

On balance, the data and arguments presented above suggest some separation between those receptors accessible to gut-derived hormonal GLP-1 and brain-derived neuromodulatory GLP-1, but fail to deliver unequivocal proof. Furthermore, the intake-suppressive effects of neuronal GLP-1 are so suggestive of postprandial effects,

that our mind wants to combine the postprandial release of GLP-1 from the gut with the food intake suppression produced by central GLP-1—after all, they are the same molecules. Consequently, we wonder how gut-derived GLP-1 activates GLP-1 release from the brainstem PPG neurons. Attempting to answer this question, the first surprising finding was that the PPG neurons do not express GLP-1 receptors (Card et al., 2018; Hisadome et al., 2010). This finding was surprising in two ways: first, it is common for neurons to express receptors for their transmitter as a means to provide local negative feedback, but second, it also meant that the idea of peripheral GLP-1 directly activating PPG neurons in order to convert a peripheral GLP-1 signal into a central one was no longer tenable. Additionally, GLP-1 applied to ex vivo brainstem slices containing both the area postrema and PPG neurons failed to affect synaptic inputs to the PPG neurons (Hisadome et al., 2010). This suggests that another possible link between peripheral GLP-1 release and central GLP-1 release, that is, GLP-1 receptor activation on area postrema neurons leading to a synaptic signal onto PPG neurons, is also unlikely (Yamamoto et al., 2002, 2003). This of course might be seen as less surprising in light of the previously mentioned studies in rats that failed to detect any postprandial increase in blood GLP-1 concentrations beyond the liver (Punjabi et al., 2014). Another major hypothetical link is the possibility that vagal afferents that express GLP-1 receptors subdiaphragmatically project (either directly or indirectly) to the PPG neurons in the NTS. Currently, there is clear evidence that a subset of vagal afferents express GLP-1 receptors per se (Bai et al., 2019; Vahl et al., 2007; Williams et al., 2016), that PPG neurons receive both monosynaptic and polysynaptic inputs from vagal afferents (Hisadome et al., 2010) and that PPG neurons are activated by gastric distention (Kreisler et al., 2014; Vrang et al., 2003), which is signalled via vagal afferents. Intriguingly, however, peripheral application of the **GLP-1 receptor** agonist, **exendin-4** (Ex-4), which should reach all GLP-1 receptors accessible for endogenous gut-derived GLP-1, failed to induce c-Fos immunoreactivity in PPG neurons (Holt et al., 2020).

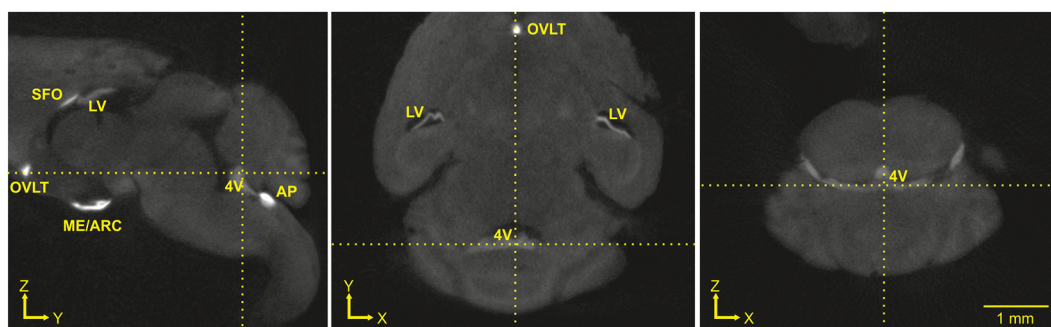


FIGURE 2 The fluorescent glucagon-like peptide 1 receptor (GLP-1R) antagonist LUXendin645 labels the circumventricular organs and selected structures within the lateral (LV) and fourth ventricles (4V). Shown are sagittal, horizontal and coronal optical sections (left to right) along the planes indicated (dotted lines) from a complete, cleared mouse brain; as presented in Ast et al. (2020). Mapping of LUXendin645 distribution in cleared brains showed labelling of the median eminence/arcuate nucleus (ME/ARC), area postrema (AP), subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT). Note that structures inside the ventricle, but not the lining of the ventricle, show fluorescent labelling. These structures within the LV and 4V are likely to be parts of the choroid plexus, but this has not been confirmed in intact brains. Mounted sections of cryostat-cut brain showed clear staining of the choroid plexus (Ast et al., 2020). LUXendin645 was injected subcutaneously at 100-pmol·g⁻¹ body weight. Images courtesy of Ben Jones and Maria A. Lucey, Imperial College London

This suggests that there may not be a functional link between peripheral GLP-1 and central GLP-1 release, as that would require an excitatory effect on PPG neurons that should induce c-Fos expression. To what extent there exists functional or even anatomical connectivity between the peripheral and central GLP-1 systems was comprehensively addressed in a very recent series of experiments in mice (Brierley et al., 2021). These confirmed that PPG neurons receive substantial input from vagal afferents per se, including some that encode gastrointestinal distension, but almost none from the GLP-1 receptor-expressing vagal population. Similarly, virtually, none of the GLP-1 receptor-expressing area postrema neurons innervate PPG neurons. PPG neurons were found not to be necessary for the intake-suppressing effects of the **GLP-1 receptor** agonists liraglutide or semaglutide, and semaglutide did not induce c-Fos in PPG neurons, confirming a lack of functionally relevant input from any GLP-1 receptor-expressing neuron populations. This study concluded that the peripheral and the central GLP-1 systems are therefore separate entities, which independently act to reduce food intake. Further studies are needed to determine the level of any signal convergence downstream of PPG neurons, such as at the level of the arcuate nucleus, which is both accessible for systemically administered GLP-1RAs and contains axon terminals from PPG neurons (Ast et al., 2020).

5 | WHAT ARE THE ROLES OF BRAIN-DERIVED GLP-1, AND IS IT A FEASIBLE TARGET FOR THE TREATMENT OF OBESITY?

In view of these thoughts, it might be worth revisiting the question ‘Is brain GLP-1 involved in the *physiological regulation* of food intake?’. GLP-1 or **GLP-1 receptor** agonists used at pharmacological doses clearly reduce food intake. This occurs in human patients as well as in animal models (Flint et al., 1998; Wilding et al., 2021; Williams et al., 2009). From animal models, we also know that this effect is seen both with systemic application of **GLP-1 receptor** agonists and with direct injection into the CNS (see Kanoski et al., 2016; Trapp & Cork, 2015; Williams, 2021). Again, from animal studies, we know that there is both a central component and a peripheral component to the reduction in food intake induced by GLP-1 or its receptor agonists (Williams et al., 2009). However, when it comes to the assessment of whether native brain GLP-1 has a role in regulating food intake, studies are much thinner on the ground. The earliest studies of GLP-1 receptor antagonists already placed caveats on their use dependent on the physiological conditions the animals were in; for example, Turton et al. (1996) stated that Ex-9, given i.c.v., would increase intake in satiated, but not hungry, rats. Some researchers also found that in order to get a response to Ex-9, animals had to be on a restricted feeding paradigm (Meeran et al., 1999). In further support of a possibly limited role of native GLP-1 in the control of ad libitum food intake, a number of studies have shown that GLP-1-producing PPG neurons are far less responsive to moderate food intake or gastric

distension than neighbouring catecholaminergic neurons in the lower brainstem (Kreisler et al., 2014).

The development of mouse strains expressing Cre recombinase under the GCG promoter enabled a much more comprehensive analysis of brain-derived GLP-1 or, more precisely, of the role that PPG neurons play. Several studies have demonstrated that chemogenetic activation of the PPG neurons in the NTS significantly reduces food intake (Brierley et al., 2021; Gaykema et al., 2017; Holt, Richards, et al., 2019; Liu et al., 2017). Additionally, ablation of these neurons markedly reduces the amount of GLP-1 that is detected in brain and spinal cord, demonstrating that these neurons are the major source of GLP-1 in the CNS (Holt, Richards, et al., 2019). However, the same study also showed that ablation of NTS PPG neurons had no effect on body weight or ad libitum food intake, suggesting that indeed these neurons are not important for the control of food intake in ad libitum fed mice. This finding was confirmed and extended by a comprehensive metabolic phenotyping study, which showed that ablation of NTS PPG neurons did not affect meal patterns or energy expenditure in ad libitum feeding mice (Brierley et al., 2021). Similarly, chemogenetic activation of the NTS PPG neurons induced a modest level of tachycardia in experimental mice, but inhibition of these neurons did not reveal a tonic drive from PPG neurons to modulate heart rate under standard holding conditions (Holt et al., 2020). These experiments leave us with the knowledge that activation of these neurons has the capacity to significantly reduce food intake and influence the function of the cardiovascular system, but currently, we have a very limited idea under which physiological conditions this occurs. Holt, Richards, et al. (2019) gave us some insight by demonstrating that PPG neurons are essential for the hypophagic response to restraint stress and that they limit overeating. This places PPG neurons into a secondary satiation role but suggests they are dispensable for primary meal termination in ad libitum fed laboratory mice. However, this is unlikely to reflect the physiological situation under which the central GLP-1 system evolved, and thus, it will be important to determine whether PPG neurons are indeed ‘only’ a secondary satiation system under more naturalistic feeding conditions in rodents and humans.

The next question to consider is the one of whether PPG neurons are a homogenous cell population, specifically activated by various forms of stress (including abnormally large meals), which then orchestrates the various responses of the body, including hypophagia and tachycardia. This would imply that the diverging projection pattern of PPG neurons simply reflects the diverse responses to a stressor. Such a model is supported by the finding that increasing levels of overeating elicit c-Fos in an increasing proportion of PPG neurons (Kreisler & Rinaman, 2016). This has implications for the assumed architecture of the central GLP-1 system. In its simplest version, all PPG neurons would be functionally equivalent, and each cell would send branched axons to all projection targets. The strength of the stimulus would be encoded in the percentage of PPG neurons recruited. This clearly is not the case, because a number of retrograde tracing studies have shown that for each projection target, only a subset of PPG neurons are labelled (Alhadeff et al., 2012; Dossat et al., 2011; Larsen

et al., 1997; Vrang et al., 2007). For instance, approximately 50% of PPG neurons project to the spinal cord, whereas the remaining 50% do not (Llewellyn-Smith et al., 2015). Thus, there is clearly some level of segregation related to the projection pattern of individual PPG neurons. Although it is not essential that there is a difference to the inputs received by these PPG neurons projecting to different targets, a divergence between inputs received by individual PPGs seems highly likely. Various studies that functionally investigated such inputs found that certain percentages of PPGs, but not all of them, responded to a given stimulus (De Jonghe et al., 2016; Elias et al., 2000; Lachey et al., 2005; Rinaman, 1999b; Terrill et al., 2019; Vrang et al., 2003). Additionally, recent studies mapping specific inputs to PPG neurons demonstrated that only subgroups of PPG neurons received individual inputs (Brierley et al., 2021; Holt, Pomeranz, et al., 2019). Similarly, studies investigating the role of GLP-1 receptor activation in specific brain regions suggested that region-specific functional segregation exists. For example, microinjection of GLP-1 into the central nucleus of the amygdala has been shown to elicit conditioned taste aversion but not hypophagia, whereas targeting of the lower brainstem with fourth ventricular GLP-1 injection resulted in hypophagia, but not conditioned taste aversion (Kinzig et al., 2002), and similarly, anxiety responses were preferentially elicited by GLP-1 injected into the central nucleus of the amygdala, whereas ACTH and corticosterone levels were increased by administration in the paraventricular nucleus of the hypothalamus (Kinzig et al., 2003).

Although these different lines of evidence suggest that at least some level of functional segregation exists between GLP-1 receptors in different brain regions, and consequently hint at functionally defined subpopulations, substantially more data will need to be gathered before any therapeutic advantage might be gained from selective targeting of any specific PPG subpopulations in order to reduce food intake or body weight.

6 | LOOSE ENDS: WHAT IS THE PURPOSE OF GLP-1 RECEPTORS EXPRESSED IN THE CIRCUMVENTRICULAR ORGANS?

The area postrema is a circumventricular organ located in the lower brainstem. It has fenestrated capillaries, that is, a leaky BBB, and it is situated at the caudal end of the fourth ventricle. The area postrema is traditionally seen as a part of the brain that senses hormonal and homeostatic signals in the general circulation and conveys these to the CNS. The area postrema is also specifically implicated as an important input to the NTS for emesis and nausea responses (Horn, 2008; Miller & Leslie, 1994; Zhang et al., 2020). Like the other circumventricular organs—the median eminence, the subfornical organ and the vascular organ of the lamina terminalis, the area postrema contains many cells that express GLP-1 receptors (Cork et al., 2015). Although this suggests that the circumventricular organs are equipped to respond to GLP-1, it is less clear whether this would be GLP-1 in the circulation or GLP-1 released from the PPG neurons. As

mentioned above, the area postrema and the other circumventricular organs receive sparse innervation by PPG axons (Llewellyn-Smith et al., 2011, 2013). Additionally, results from experiments using fluorescently tagged GLP-1 receptor agonists and antagonists have confirmed that these areas are readily accessible from the circulation, and one study has reported that most of the liraglutide-activated cells in the area postrema express GLP-1 receptors (Adams et al., 2018). However, there is currently no data on whether the GLP-1 receptor-expressing cells within these organs are activated by PPG-derived GLP-1 or native gut-derived GLP-1.

Although access from the circulation to the circumventricular organs is indisputable, the question remains whether relevant amounts of endogenous postprandial gut-derived GLP-1 can reach these areas of the brain. As discussed previously, even postprandial GLP-1 levels boosted by the administration of DPP-4 inhibitors do not elicit reductions in food intake or nausea. In contrast, the fact that nausea and vomiting are symptoms experienced by a minority of patients after Roux-en-Y gastric bypass surgery (Scarpellini et al., 2020) might suggest that in situations of strongly increased GLP-1 release, such as observed after Roux-en-Y gastric bypass surgery, circulating GLP-1 levels can become sufficient to elicit nausea and food intake effects. Additionally, it has been suggested that visceral illness, for example, induced by LPS, or inflammation might increase GLP-1 levels (Ellingsgaard et al., 2011; Kahles et al., 2014; Nguyen et al., 2014), though it remains to be determined whether those circulating levels would be sufficient to engage area postrema GLP-1 receptors. If this was the case, activation of the area postrema GLP-1 receptors might constitute a mechanism to signal metabolic stress or disease states. This would imply that such a hormonal gut-brain route for GLP-1 is real but only engaged in situations outside ‘normal’ postprandial activation. If we take the area postrema as an example and consider the established role of the area postrema in nausea and emesis, together with what we know about the role of GLP-1 receptor signalling in nausea and emesis, we could postulate that these receptors in the area postrema signal nausea in response to an unusually large release of GLP-1 from the gut that signals intestinal discomfort/malaise. It would remain to be seen whether, for example, activation of the large population of colonic L cells, for which it is difficult to assign a clear postprandial role, might occur under such conditions. It also would provide an explanation for the nausea experienced by some patients upon treatment with [GLP-1 receptor](#) agonists (Wilding et al., 2021), as these clearly reach the area postrema (Adams et al., 2018; Gabery et al., 2020; Salinas et al., 2018).

Alternatively, it could be assumed that even increased levels of gut GLP-1 do not reach these areas under physiological conditions and, although innervation from PPGs might be sparse, it might be sufficient to provide synaptic/local GLP-1 signalling physiologically or pathophysiologically. Possibly, again, these projections are linked to nausea and reflect the activation of a small subset of PPG neurons that are wired to signal nausea. Under this assumption, [GLP-1 receptor](#) agonists activating the area postrema would mimic the therapeutically undesired effect of activating a subset of PPG neurons

that signal nausea. This would explain their nausea/emesis side effects and also support the previous experimental findings that **GLP-1 receptor** agonists in the arcuate nucleus, rather than the area postrema, are most important for the intake-suppressive effects of these agonists (Secher et al., 2014).

As a third possibility, it could be considered whether, although direct innervation from PPGs is insufficient or irrelevant, GLP-1 is released from PPGs into the ventricular system in some sort of volume transmission route, such that the area postrema receives a (presumably) long-acting tonic signal under physiological conditions, a similar version of which is somewhat coincidentally elicited by **GLP-1 receptor** agonists.

7 | LOOSE ENDS: IS THERE A ROLE FOR VOLUME TRANSMISSION THROUGH THE CSF?

In a few brain areas, there is an apparent mismatch between GLP-1 receptor expression and PPG neuron projections. For example, cells expressing these receptors are found within the hippocampus, but PPG neurons do not project to this brain structure (Cork et al., 2015; Llewellyn-Smith et al., 2011; Merchenthaler et al., 1999). Particularly, if most of the brain is not accessible to GLP-1 or **GLP-1 receptor** agonists from the circulation as discussed earlier, this raises the question of which source of GLP-1 might reach these receptors. Interestingly, PPG axons are found in high density in the vicinity of the brain ventricles, and the idea has been posited that PPG neurons might release GLP-1 into the ventricles and that receptors away from PPG projections might be reached by some type of volume transmission (Hsu et al., 2015).

The first question to ask would be: Do GLP-1 receptor-expressing cells in the hippocampus exhibit c-Fos after systemic application of a **GLP-1 receptor** agonist and/or after activation of PPG neurons? However, the observation that GLP-1 can inhibit, rather than activate, some of these neurons (Cork et al., 2015) raises the question of whether c-Fos immunoreactivity is actually the most appropriate indicator for determining activation of GLP-1 receptors on neurons.

8 | ARE THERE CONSEQUENCES FOR THE USE OF **GLP-1 RECEPTOR** AGONISTS?

The main suggestions made by this review can be summarised as follows:

- There is most likely no direct link between the actions of postprandial GLP-1 released from enteroendocrine L cells and the action of GLP-1 released from PPG neurons.
- Inactivation-resistant **GLP-1 receptor** agonists are not able to freely penetrate the brain parenchyma when administered systemically.

This has implications for the understanding of the clinical use of **GLP-1 receptor** agonists. First, **GLP-1 receptor** agonists given systemically can only mimic gut-released GLP-1, but not brain-released GLP-1. The majority of brain GLP-1 receptors is beyond their reach. This might indicate that the PPG neurons actually present a valuable additional drug target that could be utilised in addition to the **GLP-1 receptor** agonists, in order to achieve increased weight loss capacity. This point has been addressed recently by Brierley et al. (2021), who have demonstrated that the ability of the **GLP-1 receptor** agonists, liraglutide and semaglutide, to reduce food intake and body weight is not reduced by the ablation of PPG neurons and that chemogenetic activation of PPG neurons produced hypophagia in addition to that achieved with concurrent systemic administration of semaglutide. Nevertheless, semaglutide is highly efficacious in reducing food intake and body weight both in animal studies and in clinical studies. It activates a distributed network of neurons throughout the CNS (Gabery et al., 2020) with most of these being secondary rather than primary targets expressing GLP-1 receptors.

Second, the side effects of, for example, nausea and tachycardia have to be explained independent of central action of the drugs on GLP-1 receptors inside the BBB and also cannot reflect the activation of PPG neurons.

Finally, there might be consequences for how some of the neuroprotective effects of GLP-1 are achieved. Although this topic is reviewed in detail by another article within this themed issue (Hölscher, 2021), we would like to briefly consider the following points. If **GLP-1 receptor** agonists do not cross the BBB, neuroprotective effects would have to be achieved primarily by these drugs acting on GLP-1 receptors outside the BBB. In fact, that would remove one problem with GLP-1 neuroprotection related to the very sparse expression of GLP-1 receptors on neurons in the cerebral cortex (Cork et al., 2015; Merchenthaler et al., 1999). With the majority of cortical neurons not expressing GLP-1 receptors, it is difficult to envisage neuroprotection via these receptors expressed directly on the affected neurons. This point has also been raised for beneficial effects of **GLP-1 receptor** agonists in Parkinson's disease, due to a lack of expression of GLP-1 receptors by dopaminergic substantia nigra neurons (Knudsen, 2019). One alternative explanation for GLP-1 neuroprotection that has recently received experimental support is that systemic GLP-1 or **GLP-1 receptor** agonists improve cerebrovascular parameters and thus increase glucose and oxygen supply to the brain. Nizari et al. (2021) demonstrated that GLP-1 receptor activation with systemically administered Ex-4 dilated cortical arterioles, increased cerebral blood flow and increased cortical oxygen partial pressure in rat.

9 | SIDE EFFECTS

When thinking about nausea in relation to GLP-1, it might be worth considering the following points. First, there is significant evidence that PPG neurons are activated by nausea-inducing agents, such as LiCl or LPS (Rinaman, 1999a, 1999b). However, that does not mean

that PPG neurons necessarily mediate all aspects of a nausea response. They might mediate a nausea-linked reduction in food intake but might not be involved in mediating the sensation of feeling sick. In support of this idea, two studies that chemogenetically activated PPG neurons in the NTS failed to detect adverse effects, such as conditioned taste aversion (Gaykema et al., 2017) or a disrupted behavioural satiety sequence (Brierley et al., 2021). In contrast, for **GLP-1 receptor** agonists, it is clear that they induce the feeling of nausea in some patients, so clearly nausea can occur as a downstream effect of GLP-1 receptor activation (most likely) outside the BBB. Because systemically administered **GLP-1 receptor** agonists do not elicit c-Fos in PPG neurons (Brierley et al., 2021; Holt et al., 2020), they are likely to employ a different pathway to induce nausea. Although these studies failed to observe sickness upon activation of PPG neurons in the NTS in mice, a study in rat observed conditioned taste aversion upon injection of GLP-1 into the central amygdala, but not into the paraventricular nucleus of the hypothalamus (Kinzig et al., 2003). Currently, it is not clear whether there is a species difference accounting for the absence of conditioned taste aversion when activating all PPGs in mice. However, because intra-amygdala injection cannot be a part of the response to systemic GLP-1, we have to assume that adverse effects seen in response to systemically administered **GLP-1 receptor** agonists are different to those elicited by activation of GLP-1 receptors behind the BBB. Thus, it might be expected that, also in rat, activation of PPG neurons that do not project to the amygdala would not elicit conditioned taste aversion. Therefore, it seems prudent to analyse the distribution of projection targets between different individual PPG neurons, in order to gain a better understanding of how this cell population works physiologically.

Second, although not being able to penetrate into the brain, **GLP-1 receptor** agonists elicit c-Fos immunoreactivity in many parts of the brain behind the BBB, demonstrating that their effects involve substantial downstream neuronal activation (Gabery et al., 2020; Salinas et al., 2018; Secher et al., 2014). It is not known to what extent, if any, signals from PPGs and **GLP-1 receptor** agonists converge on common downstream targets to elicit particular functions. The observation that a high dose of peripherally administered semaglutide and strong chemogenetic activation of PPGs suppress intake in an additive manner (Brierley et al., 2021) argues against highly convergent signalling mediating hypophagia in this context. However, it is possible that, for example, GLP-1 receptor-expressing neurons in the central amygdala, although not directly accessible to systemic **GLP-1 receptor** agonists, are a common downstream target of such agonists (Gabery et al., 2020) and of a subpopulation of PPG neurons involved in conditioned taste aversion.

Third, it is not clear whether **GLP-1 receptor** agonist-induced nausea reflects one specific action of peripheral GLP-1 that is part of its intended spectrum of physiological actions or whether it occurs because **GLP-1 receptor** agonists act somehow qualitatively differently to gut-released native GLP-1. This may produce a 'sensory mismatch' that is physiologically not intended, somewhat equivalent to the situation of motion sickness, when visual information and signals from the vestibular organ cannot produce a

coherent image of the world, leading to nausea. Such a situation could occur because the large dose of **GLP-1 receptor** agonist might be simultaneously activating various (neuronal) pathways that under normal physiological circumstances are separate and possibly even mutually exclusive.

A series of recent studies might provide some clues to this question. The authors used a conjugate of Ex-4 and vitamin B₁₂ to produce a **GLP-1 receptor** agonist without 'brain penetrance' (Borner et al., 2020; Mietlicki-Baase et al., 2018). Lack of 'brain penetrance' in this context meant that the compound was not even detected in the area postrema; that is, it did not even reach those parts of the brain that are not protected by the BBB. Although the reason for this lack of access to 'unrestricted' areas is currently unclear, the findings of these studies were striking. This compound retained its glucose-lowering potential but did not produce nausea nor hypophagia. In contrast, when it was administered into the ventricular system, it did produce emesis, like its unconjugated parent compound Ex-4. The simplest explanation would be that GLP-1 receptors particularly in the area postrema are responsible for the emetic response. These receptors are not activated by normal postprandial levels of native gut-derived GLP-1, and they are probably not a target for PPG neurons. Only once circulating GLP-1 reaches abnormally high levels, as might occur after extreme overeating, in response to visceral malaise, or after gastric bypass surgery, is this pathway activated to produce the sensation of nausea. This situation might be mimicked by clinical doses of stable **GLP-1 receptor** agonists, which also hit these receptors.

These findings also highlight the fact that GLP-1, Ex-4, liraglutide, semaglutide and other **GLP-1 receptor** agonists and antagonists all show slight variations in their physical, as well as pharmacological, properties and that this can in the end have important implications for their precise action. These relatively subtle differences have been ignored for the purpose of this conceptual review. We would like to refer the reader to other articles within this themed issue of *BJP*, as well as the review by Knudsen and Lau (2019) about liraglutide and semaglutide.

10 | CONCLUSIONS

The existing data are strongly suggestive of two separate GLP-1 systems in our body. Gut-released GLP-1 acts as a hormone and binds to receptors outside the BBB, probably primarily within the digestive system, to fulfil its role as an incretin and to act on vagal afferent neurons to inform the brain of the digestive status of a meal. Some of these vagal afferent neurons generate an electrical signal to the CNS that engages satiation and/or satiety pathways. However, these are separate from the pathways engaged by brain-derived GLP-1 that is released locally in a manner more like a neurotransmitter or neuro-modulator. Thus, GLP-1 is both a hormone and a neurotransmitter, but gut-derived GLP-1 is unable to act as a neurotransmitter, because it cannot access the GLP-1 receptors of the CNS. **GLP-1 receptor** agonists, given systemically, mimic the action of postprandial

endogenous gut-derived GLP-1 and additionally access GLP-1 receptors located in the part of the CNS that is not protected by the BBB.

In summary, the findings discussed here make a strong case for a greater mechanistic understanding of central GLP-1 receptor signaling, in the context of both physiological PPG-derived GLP-1 and brain-penetrant **GLP-1 receptor** agonists. Obtaining this insight should provide an opportunity for improved and rational design of pharmacological strategies for GLP-1-based obesity treatments, targeting both GLP-1 systems.

10.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org> and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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