DOI: 10.1111/bph.15788

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

EDITORIAL

New developments in the prospects for GLP-1 therapy

LINKED ARTICLES: This article is part of a themed issue on GLP1 receptor ligands (BJP 75th Anniversary). To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v179.4/issuetoc

The glucagon-like peptide-1 (GLP-1) receptor agonist, semaglutide, has recently been confirmed as the most efficacious weight-loss drug in clinical use (Wilding et al., 2021), which highlights a major success in the clinical exploitation of the humble 30 amino acid incretin hormone, GLP-1.

An incretin is a hormone, produced by the digestive system, that promotes the lowering of the concentration of glucose in the plasma by stimulating the secretion of pancreatic hormones, particularly insulin. The incretin effect describes the more effective stimulation of insulin release following oral ingestion of glucose, by comparison with that induced by infusion of glucose directly into the bloodstream. Thus, after its identification as an incretin in the 1980s, early interest in GLP-1 focussed on this effect and led to the development of degradation-resistant GLP-1 receptor agonists, such as exenatide, liraglutide, albiglutide and others, which are now used successfully in the clinic as second-line treatments for type 2 diabetes mellitus. Since then, evidence gathered through clinical use of these agonists, as well as intense preclinical research, has increased our understanding of the physiology of GLP-1 appreciably and stimulated the development of novel GLP-1 receptor agonists.

This Themed Issue provides a timely update of its diverse actions, all linked to GLP-1 receptor activation, together with the latest developments in the understanding of the mechanisms of action of their natural and engineered ligands in the nervous system and beyond. There is now a plethora of new research directions in this field, and this Themed Issue has assembled a series of reviews of some of the most exciting and recent developments. These articles outline our current understanding of the importance of GLP-1 receptors, not only in the gut, as a prime source of GLP-1, but also within the central and peripheral nervous systems and other organs.

A key topic is the development of small molecules and peptides for oral administration, the consideration of biased agonism and the development of positive allosteric modulators. The aim of this research effort has been to improve the clinical profile of GLP-1 receptor ligands by enhancing their efficacy, reducing their side-effects and adjusting their pharmacokinetics to enable a more convenient route of administration. This field is covered by a review that considers the therapeutic potential of biased agonism (Jones, 2021), whilst Malik and Li (2021) focus on the scope for small-molecule agonists and positive allosteric modulators of GLP-1 receptors in the treatment of type II diabetes.

Additionally, we are now aware of a much-enhanced scope for GLP-1-mediated therapy. GLP-1 receptor agonists have been confirmed as a highly successful class of treatments for type 2 diabetes, but it has become apparent that there are many additional opportunities to broaden their therapeutic applications. These potential applications extend far beyond GLP-1's classic incretin effect and are reviewed here by Tanday et al. (2021).

The most widely reported clinical side-effect of GLP-1 therapy is the induction of nausea, which is a problem when GLP-1 receptor ligands are used to treat Type 2 diabetes. A number of recent studies have provided more insight into the potential locus for this response; they also suggest potential new pharmacological tools that dissociate nausea from the desired glucose-lowering and food intake suppressing effect of GLP-1R agonists. Borner et al. (2021) review these developments, discussing the implications for their clinical application, and also highlight what we can learn about the GLP-1Rs involved in these different effects.

Arguably, the largest scope for GLP-1R agonists is currently in the treatment of obesity. As injectable peptides, these have proved to be the most efficacious weight-loss drugs to date (Wilding et al., 2021). However, the precise targets of these drugs that mediate this response, within and beyond the brain, are still being determined and are somewhat controversial. This is not least because recent research has raised doubts about some of our preconceptions of how GLP-1 released from the gut is functionally linked to GLP-1 action in the brain (Brierley et al., 2021).

The classic concept has been that GLP-1 is released postprandially from enteroendocrine cells into the bloodstream 'simply' to act as a primary satiation (meal-terminating) signal within the CNS. However, that proposal was difficult to reconcile with the early observation that GLP-1R knockout mice are not obese, which was tentatively explained by proposals for redundant signalling pathways and/or developmental compensatory mechanisms. Lately, this view is being challenged, and this debate is addressed by an article contributed by Trapp and Brierley (2021) and also a reappraisal of the role of the vagus nerve in this process by Brierley and de Lartigue (2021).

Indeed, increasingly sophisticated analysis of GLP-1 action within the CNS has begun to dissect the mechanisms that underly the reduction of food intake after administration of GLP-1, either within the CNS or systemically. These studies, reviewed in this issue by articles from both Williams (2021) and Kabahizi et al. (2021), provide insight into a variety of brain circuits that are modulated by GLP-1. These are involved not only in satiety and satiation but also include circuits that determine the reward value of food and induce nausea or conditioned taste aversion in animal models. Furthermore, a reduction in the reward value of food after GLP-1 administration hints at the potential use of GLP-1 in the treatment of addiction, not only to food but also substances of abuse, more generally. This fascinating area of research is reviewed by Klausen et al. (2021).

GLP-1 action in the brain, as well as activation of GLP-1-producing neurons, has also been associated with the stress response, an increase in heart-rate and a rise of systemic blood pressure. Various rodent studies have associated GLP-1 with hypophagia, induced by restraint stress, and have shown that several forms of stress activate GLP-1 producing neurons in the lower brainstem. Holt and Rinaman (2021) review that evidence and propose that GLP-1 neurons in the brain might be a useful target in the treatment of stress-related disorders. Whilst GLP-1R ligands raise the sympathetic tone, there is also strong evidence that GLP-1R ligands offer cardiovascular protection through actions in the periphery, including anti-inflammatory effects, which is discussed by Helmstädter et al. (2021).

Another important aspect of recent research focussing on the brain is the role of GLP-1 receptor activation in the prevention or treatment of neurodegenerative diseases such as Alzheimer's or Parkinson's disease and also recovery, post-stroke (Augestad et al., 2021). The evidence that GLP-1 has neuroprotective actions is reviewed by Hölscher (2021).

Moving away from a neuron-centric view of the brain, there is now persuasive evidence that certain responses to GLP-1 and GLP-1 receptor agonists, particularly within the brain, are mediated by GLP-1 receptors located on non-neuronal cells, namely, glial cells. The latest research, which has important implications for the whole field, is reviewed by Cui et al. (2021).

Last, but definitely not least, a review by Holst et al. (2021) considers the actions of GLP-1 within the gut. This is an area of GLP-1 research that has received less attention than it deserves, which is somewhat surprising. Given the rapid degradation of GLP-1 within the circulation, a greater understanding of the action of GLP-1 in the vicinity of its release sites should be viewed as a priority when considering the physiology of this system. This review gives this topic due consideration and highlights the significant advances that have been made recently towards understanding the 'local' roles of gut-produced GLP-1.

In summary, this selection of articles, written by some of the current leaders in the field of GLP-1 research, aims to provide a comprehensive update of a highly active and dynamic field of research. Furthermore, we hope that this Themed Issue will also stimulate more ideas on how to develop this exciting field of research, which has immense translational potential for addressing some major challenges to human health, especially in respect of diabetes, obesity, cardiovascular disease, neurodegenerative disorders and addiction.

Stefan Trapp
S. Clare Stanford

Department of Neuroscience, Physiology and Pharmacology, University College London, London, UK

Correspondence
Stefan Trapp, Department of Neuroscience, Physiology and Pharmacology, University College London, Gower Street, London WC1E 6BT, UK.
Email: s.trapp@ucl.ac.uk

REFERENCES

Augestad, I. L., Dekens, D., Karampatsi, D., Elabi, O., Zabala, A., Pintana, H., Larsson, M., Nyström, T., Paul, G., Darsalia, V., & Patrone, C. (2021). Normalisation of glucose metabolism by exendin-4 in the chronic phase after stroke promotes functional recovery in male diabetic mice. *British Journal of Pharmacology*, *179* (4), 677–694. https://doi.org/10.1111/bph.15524

Borner, T., Tinsley, I. C., Doyle, R. P., Hayes, M. R., & De Jonghe, B. C. (2021). Glucagon-like peptide-1 in diabetes care: Can glycaemic control be achieved without nausea and vomiting? *British Journal of Pharmacology*, *179* (4), 542–556. https://doi.org/10.1111/bph.15647

Brierley, D. I., & de Lartigue, G. (2021). Reappraising the role of the vagus nerve in GLP-1-mediated regulation of eating. *British Journal of Pharmacology*, *179* (4), 584–599. https://doi.org/10.1111/bph.15603

Brierley, D. I., Holt, M. K., Singh, A., de Araujo, A., McDougle, M., Vergara, M., Afaghani, M. H., Lee, S. J., Scott, K., Maske, C., Langhans, W., Krause, E., de Kloet, A., Gribble, F. M., Reimann, F., Rinaman, L., de Lartigue, G., & Trapp, S. (2021). Central and peripheral GLP-1 systems independently suppress eating. *Nature Metabolism*, *3*(2), 258–273. https://doi.org/10.1038/s42255-021-00344-4 Epub 2021 Feb 15

Cui, Q. N., Stein, L. N., Fortin, S. M., & Hayes, M. R. (2021). The role of glia in the physiology and pharmacology of GLP-1: Implications for obesity, diabetes, and neurodegenerative processes including glaucoma. *British Journal of Pharmacology*, *179* (4), 715–726. https://doi.org/10.1111/bph.15683

Helmstädter, J., Keppeler, K., Küster, L., Münzel, T., Daiber, A., & Steven, S. (2021). Glucagon-like peptide-1 (GLP-1) receptor agonists and their cardiovascular benefits-the role of the GLP-1 receptor. *British Journal of Pharmacology*, *179* (4), 659–676. https://doi.org/10.1111/bph.15462

Hölscher, C. (2021). Protective properties of GLP-1 and associated peptide hormones in neurodegenerative disorders. *British Journal of Pharmacology*, *179* (4), 695–714. https://doi.org/10.1111/bph.15508

Holst, J. J., Anderson, D. B., & Grunddal, K. V. (2021). Actions of glucagon-like peptide-1 receptor ligands in the gut. *British Journal of Pharmacology*, *179* (4), 727–742. https://doi.org/10.1111/bph.15611 Online ahead of print

Holt, M. K., & Rinaman, L. (2021). The role of nucleus of the solitary tract glucagon-like peptide-1 and prolactin-releasing peptide neurons in stress: Anatomy, physiology and cellular interactions. *British Journal of Pharmacology*, *179* (4), 642–658. https://doi.org/10.1111/bph.15576

Jones, B. (2021). The therapeutic potential of GLP-1 receptor biased agonism. *British Journal of Pharmacology*, *179* (4), 492–510. https://doi.org/10.1111/bph.15497

Kabahizi, A., Wallace, B., Lieu, L., Chau, D., Dong, Y., Hwang, E. S., & Williams, K. W. (2021). Glucagon-like peptide-1 (GLP-1) signaling in the brain: From neural circuits and metabolism to therapeutics. *British Journal of Pharmacology*, *179* (4), 600–624. https://doi.org/10.1111/bph.15682

Klausen, M. K., Thomsen, M., Wortwein, G., & Fink-Jensen, A. (2021). The role of glucagon-like peptide 1 (GLP-1) in addictive disorders. *British Journal of Pharmacology*, *179* (4), 625–641. https://doi.org/10.1111/bph.15677

Malik, F., & Li, Z. (2021). Non-peptide agonists and positive allosteric modulators of glucagon-like peptide-1 receptors: Alternative approaches for treatment of type 2 diabetes. *British Journal of Pharmacology*, *179* (4), 511–525. https://doi.org/10.1111/bph.15446

Tanday, N., Flatt, P. R., & Irwin, N. (2021). Metabolic responses and benefits of glucagon-like peptide-1 (GLP-1) receptor ligands. *British Journal of Pharmacology*, *179* (4), 626–541. https://doi.org/10.1111/bph.15485

Trapp, S., & Brierley, D. I. (2021). 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. *British Journal of Pharmacology*, *179* (4), 557–570. https://doi.org/10.1111/bph.15638

Wilding, J. P. H., Batterham, R. L., Calanna, S., Davies, M., Van Gaal, L. F., Lingvay, I., McGowan, B. M., Rosenstock, J., Tran, M. T., Wadden, T. A., & Wharton, S. (2021). Once-weekly Semaglutide in adults with overweight or obesity. *New England Journal of Medicine*, *384*(989), 1002. https://doi.org/10.1056/NEJMoa2032183

Williams, D. L. (2021). The diverse effects of brain glucagon-like peptide 1 receptors on ingestive behaviour. *British Journal of Pharmacology*, *179* (4), 571–583. https://doi.org/10.1111/bph.15535