

Trigeminal ganglion neurons lack detectable GLP-1 receptor expression: a cross-species single-cell transcriptomic study

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ABSTRACT

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are accumulating signals of potential benefit in headache disorders, but the cellular locus of any anti-cephalgic action is unknown. A direct effect on the trigeminovascular system would require *GLP1R* to be expressed by cells of the trigeminal ganglion (TG), and we therefore investigated whether *GLP1R* is expressed by TG neurons or non-neuronal cells.

Methods: We reanalysed public single-cell/single-nucleus transcriptomic data from mouse and human TG, quantifying *GLP1R* detection per cell type with exact binomial 95% confidence intervals (CIs). *GLP1R* and the second incretin receptor *GIPR* were benchmarked against validated G protein-coupled receptor (GPCR) drug targets and nociceptor markers, and *GLP1R* detection was verified in pancreatic islets, where it is expressed.

Results: *GLP1R* was detected in 0.09% of mouse and 0.05% of human trigeminal neurons, whereas validated GPCR drug targets were robustly detected in the same cells. *GLP1R* was undetected in the peptidergic subtype and $\leq 0.17\%$ across the other mouse neuronal subtypes, was at the limit of detection in human neurons, and was at or below the limit of detection in all human non-neuronal compartments, while GPCRs and compartment markers labelled their expected populations. The same pipeline detected *GLP1R* in pancreatic beta cells, confirming assay sensitivity.

Conclusions: Across both mouse and human TG, *GLP1R* transcripts were not detectably expressed by neurons or non-neuronal cells. The anti-headache signals of GLP-1 RAs are therefore unlikely to be initiated by *GLP1R* within TG cell bodies and more plausibly reflect extra-ganglionic mechanisms.

Key words: glucagon-like peptide-1; headache; idiopathic intracranial hypertension; migraine; pain.

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are metabolic drugs that are increasingly implicated in neurological and headache conditions. (1) In idiopathic intracranial hypertension, the GLP-1 RA exenatide lowered intracranial pressure and reduced monthly headache days in a randomised controlled trial, (2) with the choroid plexus proposed as the site of action through reduced cerebrospinal fluid secretion. (3) In a prospective pilot study, add-on liraglutide, a once-daily GLP-1 RA, reduced monthly headache days in patients with obesity and high-frequency or chronic migraine, an effect reported as independent of weight change. (4) At the population level, a nationwide interrupted-time-series analysis found that initiation of weight-loss semaglutide, a once-weekly GLP-1 RA widely used for weight loss, was followed by a modest, gradual reduction in triptan consumption, most marked in women and in people with prior migraine prophylaxis. (5) Whether such effects are central/indirect or reflect a direct action on the trigeminovascular system is unresolved. A direct trigeminal mechanism has a clear, testable prerequisite: expression of *GLP1R* by cells of the trigeminal ganglion (TG). *GLP1R* is well-documented in vagal (nodose) afferents, the area postrema, the hypothalamus, the choroid plexus, pancreatic islets, and heart, (6,7) but its expression in trigeminal ganglia is understudied. We therefore tested whether the *GLP1R* transcript is detectable in any cell of the TG, benchmarking against G protein-coupled receptors (GPCRs) that are validated drug targets.

Results

GLP1R transcript is undetectable in trigeminal nociceptors.

In the mouse TG, *GLP1R* was undetectable in nociceptors, being found in only 13 of 14,057 nociceptive-lineage cells (0.09%; 95% confidence interval [CI]: 0.05–0.16%). Canonical nociceptor transcripts were captured (*CALCA* 61.8%, *SCN10A* 53.7%, *TRPV1* 35.9%), as were the drug targets used as positive controls, such as *HTR1D* (6.0%), *HTR1F* (5.1%), *HTR1B* (1.8%), *OPRM1* (9.5%), *OPRK1* (2.0%), *CNR1* (17.8%), and *ADCYAP1R1* (0.9%) (Table 1). *GLP1R* showed no enrichment for co-detection with *CALCA*. Across neuronal subtypes, it was undetected in the peptidergic (CGRP) class (0 of 2,163 cells) and did not exceed 0.17% in any other normal subtype.

The negative finding is confirmed in human trigeminal neurons.

Reanalysed from the primary human dataset, *GLP1R* was detected in 0.05% of human trigeminal neurons (2/3,873; 95% CI: 0.01–0.19) and was undetectable in every neuronal subtype apart from isolated single cells. In the same cells the validated drug targets *OPRM1* (34.0%), *CNR1* (18.4%), *HTR1D* (10.9%), and *HTR1F* (5.1%), and the markers *CALCA* (44.9%) and *SCN10A* (39.6%), were robustly detected, whereas *GLP1R* and the related receptors, *GIPR* (0.54%) and *GCGR* (0.77%), were at the limit of detection (Figure 1). *GLP1R*-positive cells showed no enrichment for *CALCA* co-detection (two double-positive cells observed vs. approximately 171 expected under independence).

The absence extends to human non-neuronal cells. *GLP1R* was at or below the limit of detection in most non-neuronal compartments of the human TG, with the exception of fibroblasts, where a low but non-zero signal was detected. Across 34,155 non-neuronal cells it was detected in 0.00% of vascular cells (0/2,328; 95% CI: 0-0.16), 0.11% of satellite glia (11/10,293; 95% CI: 0.05-0.19), 0.12% of Schwann cells (4/3,338; 95% CI: 0.03-0.31), 0.06% of immune cells (1/1,804; 95% CI: 0-0.31) and, at most, 0.83% of fibroblasts (136/16,392; 95% CI: 0.70-0.98) (**Figure 2**). Cell-type identities were confirmed by canonical markers (*CLDN5/PECAM1* in vascular cells, *FABP7/APOE* in

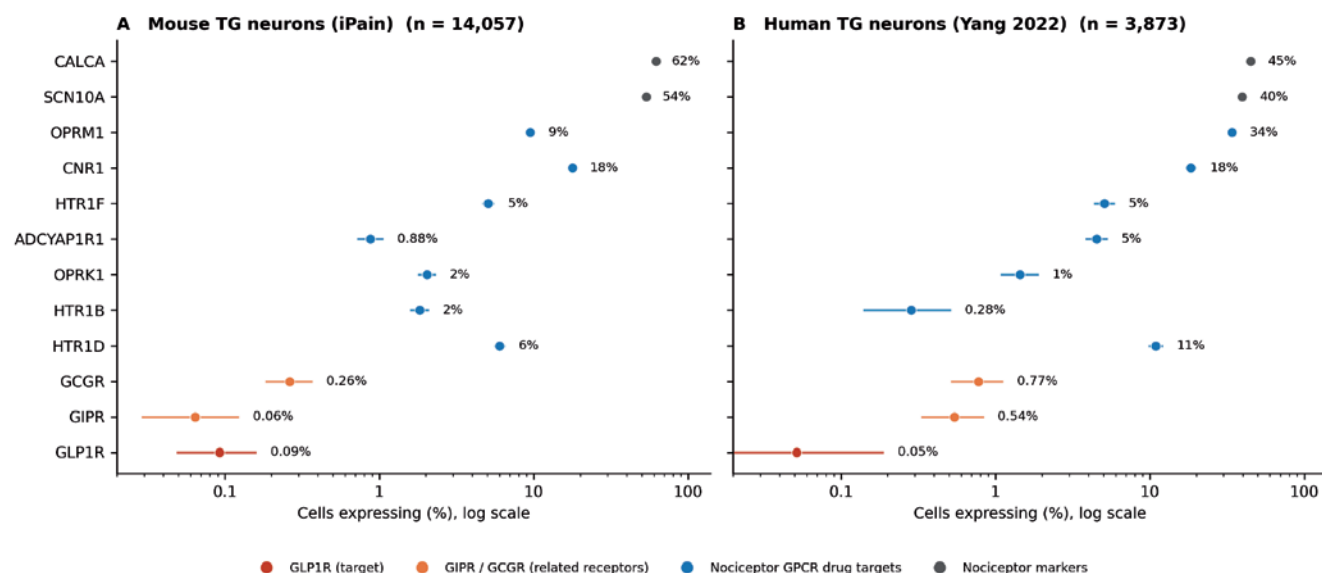
satellite glia, *MPZ* in Schwann cells, *DCN* in fibroblasts, and *PTPRC* in immune cells).

***GLP1R* transcript is detected in pancreatic islet cells.** Applied unchanged to pancreatic islets, the pipeline detected *GLP1R* in endocrine cells (**Figure 3**). In human islets, 29.9% of beta cells and 15.0% of delta cells were *GLP1R*-positive, against $\leq 2.3\%$ of exocrine and other cells. In mouse islets, *GLP1R* detection was lower in absolute terms but retained the same specificity, being highest in beta cells (3.1%) and at the limit of detection in exocrine cells (acinar 0.0%, ductal 0.3%). For reference, the more abundant incretin receptor *GIPR* reached 26.6% in the same beta cells.

Table 1. Percentage of positive cells (GLP-1R vs. controls).

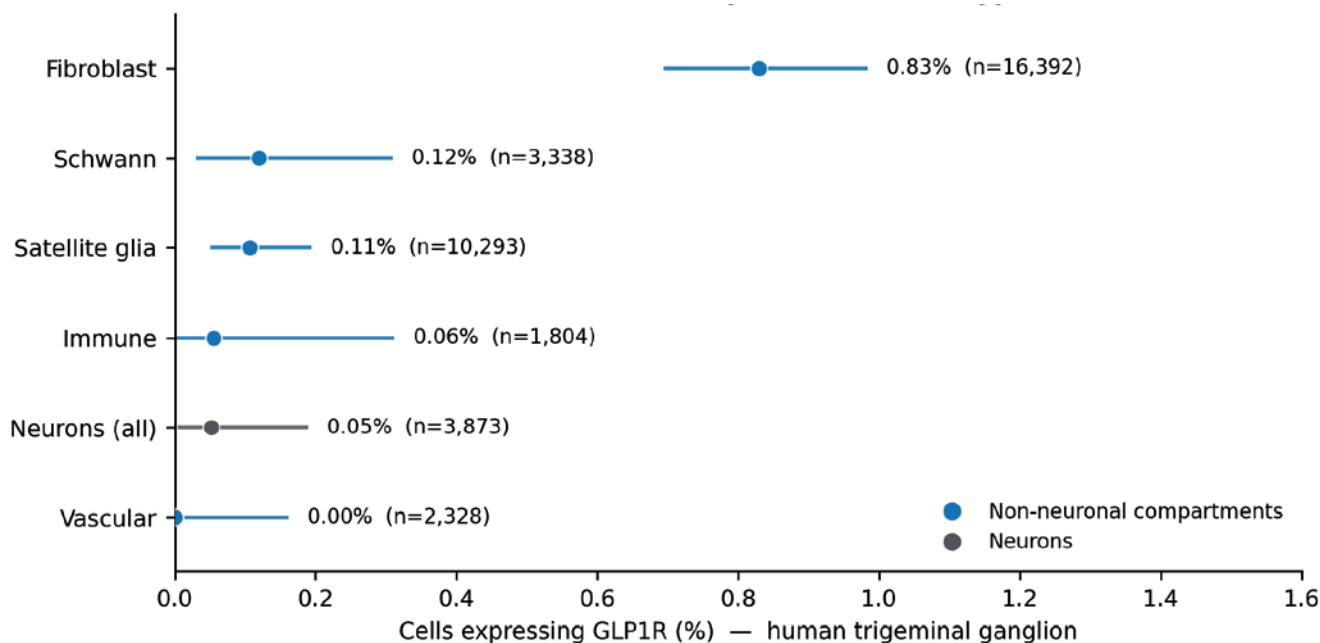
Gene	Role	Mouse TG % (95% CI)	Human TG % (95% CI)
<i>GLP1R</i>	Target (GLP-1)	0.09 (0.05-0.16)	0.05 (0.01-0.19)
<i>GIPR</i>	Target (GIP)	0.06 (0.03-0.12)	0.54 (0.34-0.83)
<i>HTR1D</i>	Triptan target	6.00 (5.62-6.41)	10.90 (9.93-11.92)
<i>HTR1F</i>	Ditan target	5.07 (4.71-5.44)	5.09 (4.42-5.83)
<i>HTR1B</i>	Triptan target	1.82 (1.61-2.06)	0.28 (0.14-0.51)
<i>OPRM1</i>	Analgesic GPCR	9.49 (9.01-9.99)	34.03 (32.54-35.55)
<i>OPRK1</i>	Analgesic GPCR	2.03 (1.81-2.28)	1.45 (1.09-1.87)
<i>CNR1</i>	Analgesic GPCR	17.81 (17.18-18.46)	18.44 (17.23-19.69)
<i>ADCYAP1R1</i>	PACAP (migraine)	0.88 (0.73-1.04)	4.52 (3.89-5.22)
<i>CALCA</i>	Nociceptor marker	61.82 (61.01-62.62)	44.90 (43.33-46.48)

TG, trigeminal ganglion; CI, confidence interval; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; GPCR, G protein-coupled receptor; PACAP, pituitary adenylate cyclase-activating polypeptide. Values are the percentage of cells with detected expression. Mouse values are from the iPain dataset (n=14,057; direct reanalysis, raw counts). Human values are from Yang et al., 2022 (9) (GEO GSE197289; n=3,873 neurons), all with exact binomial 95% CIs.



TG, trigeminal ganglion.

Figure 1. *GLP1R* is at the limit of detection in trigeminal neurons of both species. Percentage of cells expressing each receptor/marker in mouse (A; iPain dataset) and human (B; Yang et al., 2022) trigeminal neurons, from direct reanalysis of the count matrices (raw counts >0; log scale; dots = point estimate, bars = exact binomial 95% CIs). *GLP1R* and the related receptors *GIPR/GCGR* are at the limit of detection in both species, whereas the drug targets *OPRM1*, *CNR1*, *HTR1D*, and *HTR1F*, and the markers *CALCA* and *SCN10A* are robustly detected in the same cells.



TG, trigeminal ganglion.

Figure 2. *GLP1R* is at the limit of detection in every non-neuronal compartment of the human TG. Percentage of cells expressing *GLP1R* (raw counts >0) by cell type. (9) Dots = point estimate, bars = exact binomial 95% CIs. *GLP1R* is at or near zero in vascular, satellite-glia, Schwann, and immune cells and reaches at most 0.83% in fibroblasts, comparable to neurons. Compartment identities were confirmed by their canonical markers.

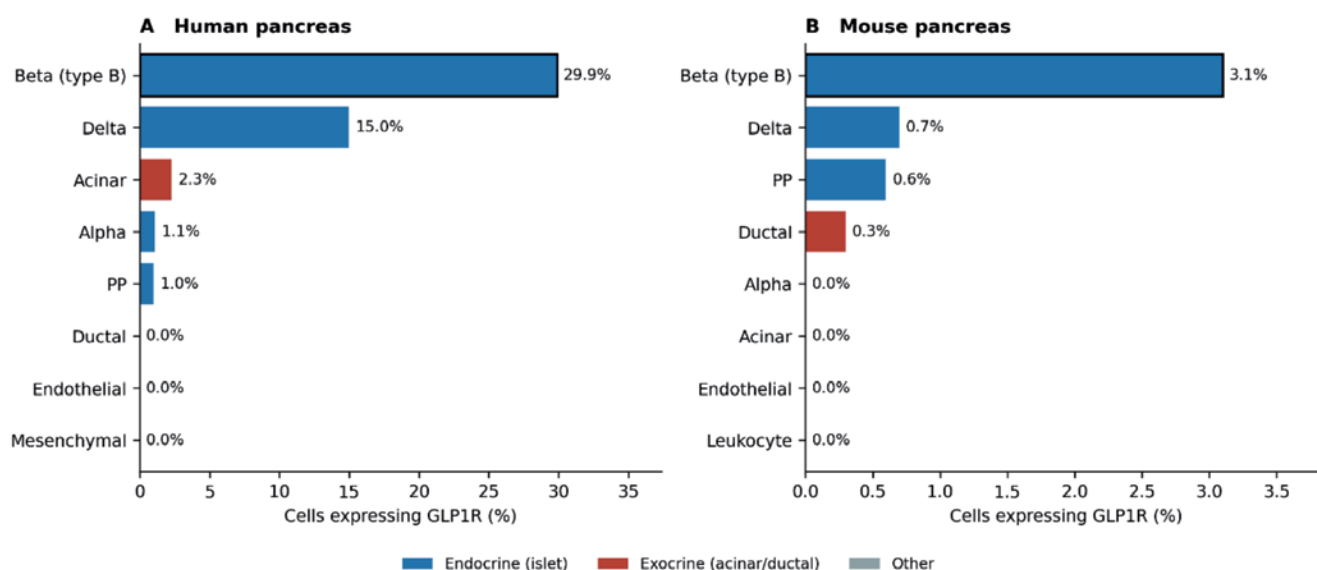


Figure 3. *GLP1R* is detected in pancreatic islet cells. Percentage of cells expressing *GLP1R* (raw counts >0) across annotated cell types of human (A) and mouse (B) pancreatic islets, analysed with the identical pipeline used for the TG. *GLP1R* is detected specifically in endocrine cells and at the floor in exocrine (acinar, ductal) and other cell types. Note the different x-axis scales between panels. The lower absolute values in the mouse dataset reflect its shallower 10x 3' sequencing chemistry.

Discussion

The *GLP1R* transcript is not detectably expressed within trigeminal nociceptors, and is at or below the limit of detection in most non-neuronal compartments of the human TG (vascular, satellite glia, Schwann, immune), with the exception of a low-level but statistically non-zero signal in fibroblasts. These find-

ings derive from ganglion tissue obtained under baseline, non-migraine conditions, and therefore characterize constitutive *GLP1R* expression in the physiology of the TG. Because single-cell atlases sample transcripts in the neuronal cell body, these data speak to the ganglionic soma. Receptor protein trafficked to peripheral (dural) or central (trigeminal nucleus caudalis) afferent terminals is not excluded by our approach and would require

complementary protein-level methods (e.g., immunohistochemistry) to address directly. With that caveat, the emerging anti-headache signals of GLP-1 RAs are unlikely to be mediated by *GLP1R* expressed in TG cell bodies. This does not weaken the clinical signals: *GLP1R* is expressed at several extra-ganglionic sites relevant to headache. (6–8) Two mechanistic routes have experimental support, and both are extra-ganglionic: a cerebrospinal route, in which GLP-1 RAs reduce cerebrospinal fluid secretion and intracranial pressure via the choroid plexus, (3) and a neuro-immune route, in which microglial *GLP1R* in the trigeminal nucleus caudalis dampens central sensitization. (9)

For migraine specifically, the hypothalamus is an attractive candidate node. Functional imaging places hypothalamic activity and its coupling to the brainstem at the origin of the migraine cycle, with changes detectable in the 24 hours preceding pain onset and stronger hypothalamic engagement in chronic migraine. (10,11) The hypothalamus has been proposed as the source of the premonitory symptoms of migraine, several of which fall within the appetite-regulating circuitry on which GLP-1 RAs act. A hypothalamic interface between GLP-1 signalling and migraine physiology is biologically plausible, although it remains to be demonstrated.

A second, related route is metabolic. Obesity is an established risk factor for migraine and, in particular, for its progression to chronic migraine, an association attributed partly to adipose-tissue-derived inflammation and to adipokine signalling that intersects with *CGRP* and trigeminovascular biology. (12,13) Because GLP-1 RAs produce substantial weight loss, part of any anti-migraine benefit could be weight-mediated and thus indirect. An open-label pilot study with liraglutide reported reductions in headache days that appeared independent of measured weight change in individuals with chronic migraine, (4) but whether the effect is weight-dependent, weight-independent, or both remains unresolved.

These mechanistic possibilities should not obscure how preliminary the clinical evidence still is. In migraine there is, to date, no placebo-controlled randomised trial, whereas in idiopathic intracranial hypertension the evidence is stronger but still rests on a single small, randomised trial. (2) Adequately powered, placebo-controlled trials are needed before an anti-migraine effect of GLP-1 RAs can be regarded as established. Against this uncertain background, our transcriptomic result supplies a concrete anatomical constraint: whatever the outcome of such trials, the effect is unlikely to be initiated by *GLP1R* within the trigeminovascular system. Neither incretin receptor targeted by current drugs is detectable in any ganglionic cell type, arguing against a peripheral target for this drug class.

Study limitations. This study has limitations. Single-cell RNA sequencing undercounts low-abundance transcripts, and *GLP1R* mRNA is intrinsically low even where the receptor is functional. Accordingly, low-level or protein-only *GLP1R* expression below the RNA detection threshold cannot be formally excluded. However, the same pipeline detected validated GPCR targets and correctly localised compartment markers, and it recovered *GLP1R* in pancreatic beta cells, demonstrating sensitivity for *GLP1R* where it is expressed. The absolute detection rate is nonetheless platform-dependent, so we interpret our findings as the absence of detectable *GLP1R* transcript rather than proof of absent receptor protein, and we frame the ganglion result as expression at or below the limit of detection. Because single-cell/nucleus data profile cell bodies, receptor proteins trafficked to peripheral or central afferent terminals would not be captured. The human evidence derives from a single study, (14) reflecting the current scarcity of human trigeminal single-cell data. Although 3,873 neurons afford reasonable per-subtype resolution, replication in additional human datasets would further strengthen the cross-species claim. Functional (protein/pharmacological) confirmation in human

ganglion tissue would further strengthen the conclusion of our study. Additionally, both the mouse and human datasets were derived from tissue obtained under baseline conditions rather than from individuals with active migraine or other headache disorders. Our findings therefore characterize constitutive *GLP1R* expression and cannot exclude disease-related or activity-dependent transcriptional changes, such as those potentially induced by neurogenic inflammation or trigeminal sensitization during a migraine attack.

Conclusions

Across mouse and human sensory ganglia, *GLP1R* was not detected in trigeminal nociceptors or in any other neuronal or non-neuronal ganglionic cell type. The reported anti-cephalgic effects of GLP-1 RAs are therefore unlikely to be mediated by *GLP1R* within the trigeminovascular system. This anatomical constraint should inform future mechanistic investigation and temper expectations regarding these agents in headache disorders until their efficacy is established in adequately powered, placebo-controlled trials.

Materials and Methods

We reanalysed a mouse TG atlas, specifically the nociceptive-lineage subset of the iPain sensory-ganglion atlas (14,057 cells), obtained through CZ CELLxGENE Discover. (15) This subset aggregates data from five independently published mouse TG datasets. Sample sizes at the animal level are reported in the respective original publications. Human TG cells were analysed from Yang *et al.* (38,028 nuclei from three donors), (14) using the author-provided cell-type annotations. Detection (raw counts >0) was quantified per cell type for neuronal subtypes and non-neuronal compartments with exact binomial 95% CIs, using the same criterion applied to the mouse data. The full receptor/marker panel was quantified in the same cells as a within-dataset sensitivity control. As positive controls for *GLP1R* detection, we analysed single-cell datasets of human and mouse pancreatic islets obtained through CZ CELLxGENE Discover. (16,17) The identical detection pipeline was applied to these datasets.

Gene panel. The primary targets were the incretin receptors *GLP1R* and *GIPR*, with *GCGR* included as an additional receptor control. Nociceptor identity was assessed using *CALCA* (which encodes the calcitonin gene-related peptide) and *SCN10A* (a sodium channel specifically expressed in sensory pain neurons). In the mouse atlas, *TAC1* (which encodes substance P, another pain mediator), *TRPV1* (the capsaicin receptor, sensitive to heat and painful stimuli) and *SCN11A* (another sodium channel associated with nociceptors) were also assessed. To control for the undersampling of low-abundance transcripts in single-cell data, we benchmarked *GLP1R* against a panel of G-protein-coupled receptors that are validated drug targets: the triptan and ditan receptors *HTR1D*, *HTR1B* and *HTR1F*, the μ - and κ -opioid receptors *OPRM1* and *OPRK1*, the cannabinoid receptor *CNR1* and the pituitary adenylate cyclase-activating polypeptide (PACAP) receptor *ADCYAP1R1*. Non-neuronal identity was defined with endothelial markers (*CLDN5*, *PECAM1*) and satellite-glia markers (*FABP7*, *APOE*).

Statistical analysis. In the mouse atlas, analyses were performed on raw counts because *GLP1R* was flagged as feature-filtered in the normalised matrix. A gene was considered detected in a given cell when its count exceeded zero. For each gene, we computed the proportion of positive cells across the whole dataset and within each neuronal subtype, together with an exact binomial 95% CI for the *GLP1R*-positive fraction and

the percentile rank of *GLP1R* among all genes ranked by the number of cells in which they were detected. For the human TG, (9) detection (raw counts >0) was quantified per cell type across neuronal subtypes and non-neuronal compartments with exact binomial 95% CIs, using the same criterion and the author-provided annotations. The full receptor/marker panel was quantified in the same cells as a within-dataset sensitivity control. Co-detection of *GLP1R* with *CALCA* was compared against the proportion expected under independence. The rationale for the positive-control panel was that an assay that robustly detects validated GPCR drug targets and that correctly localizes compartment markers but fails to detect *GLP1R* indicates low *GLP1R* expression. For the pancreatic datasets, *GLP1R* detection (raw counts >0) was quantified per annotated cell type using the same criterion as for the ganglion data. Analyses were performed in Python (v3.14) using Scanpy, NumPy, and SciPy packages. (18-20)

References

- Halloum W, Duhem YA, Beier D, Pellesi L. Glucagon-like peptide-1 (GLP-1) receptor agonists for headache and pain disorders: a systematic review. *J Headache Pain* 2024; 25:112.
- Mitchell JL, Lyons HS, Walker JK, Yiangou A, Grech O, Alimajstorovic A, et al. The effect of GLP-1RA exenatide on idiopathic intracranial hypertension: a randomized clinical trial. *Brain* 2023;146:1821-30.
- Botfield HF, Uldall MS, Westgate CSJ, Mitchell JL, Hagen SM, Gonzalez AM, et al. A glucagon-like peptide-1 receptor agonist reduces intracranial pressure in a rat model of hydrocephalus. *Sci Transl Med* 2017;9:eaan0972.
- Braca S, Russo CV, Stornaiuolo A, Cretella G, Miele A, Giannini C, De Simone R. Effectiveness and tolerability of liraglutide as add-on treatment in patients with obesity and high-frequency or chronic migraine: A prospective pilot study. *Headache* 2025;65:1831-8.
- Roland N, Sonne H, Pellesi L, Bramming M, Cardél LG, Pottegård A, Kildegaard H. Impact of semaglutide introduction on the use of triptans: an interrupted-time series. *J Headache Pain* 2026;27:199.
- Kabahizi A, Wallace B, Lieu L, Chau D, Dong Y, Hwang ES, Williams KW. Glucagon-like peptide-1 (GLP-1) signalling in the brain: From neural circuits and metabolism to therapeutics. *Br J Pharmacol* 2022;179:600-24.
- Kopp KO, Glotfelty EJ, Li Y, Greig NH. Glucagon-like peptide-1 (GLP-1) receptor agonists and neuroinflammation: Implications for neurodegenerative disease treatment. *Pharmacol Res* 2022;186:106550.
- Alvarez E, Martínez MD, Roncero I, Chowen JA, García-Cuartero B, Gisbert JD, et al. The expression of GLP-1 receptor mRNA and protein allows the effect of GLP-1 on glucose metabolism in the human hypothalamus and brainstem. *J Neurochem* 2005;92:798-806.
- Jing F, Zou Q, Wang Y, Cai Z, Tang Y. Activation of microglial GLP-1R in the trigeminal nucleus caudalis suppresses central sensitization of chronic migraine after recurrent nitroglycerin stimulation. *J Headache Pain* 2021;22:86.
- Schulte LH, May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. *Brain* 2016;139:1987-93.
- Schulte LH, Allers A, May A. Hypothalamus as a mediator of chronic migraine: evidence from high-resolution fMRI. *Neurology* 2017;88:2011-6.
- Bigal ME, Lipton RB, Holland PR, Goadsby PJ. Obesity, migraine, and chronic migraine: possible mechanisms of interaction. *Neurology* 2007;68:1851-61.
- Westgate CSJ, Israelsen IME, Jensen RH, Eftekhari S. Understanding the link between obesity and headache- with focus on migraine and idiopathic intracranial hypertension. *J Headache Pain* 2021;22:123.
- Yang L, Xu M, Bhuiyan SA, Li J, Zhao J, Cohrs RJ, et al. Human and mouse trigeminal ganglia cell atlas implicates multiple cell types in migraine. *Neuron* 2022;110:1806-21.e8.
- Techameena P, Feng X, Zhang K, Hadjab S. The single-cell transcriptomic atlas iPain identifies senescence of nociceptors as a therapeutic target for chronic pain treatment. *Nat Commun* 2024;15:8585.
- The Tabula Muris Consortium. A single-cell transcriptomic atlas characterizes ageing tissues in the mouse. *Nature* 2020;583:590-5.
- Muraro MJ, Dharmadhikari G, Grün D, Groen N, Dielen T, Jansen E, et al. A Single-Cell Transcriptome Atlas of the Human Pancreas. *Cell Syst* 2016;3:385-94.e3.
- Wolf FA, Angerer P, Theis FJ. SCANPY: large-scale single-cell gene expression data analysis. *Genome Biol* 2018; 19:15.
- Harris CR, Millman KJ, van der Walt SJ, Gommers R, Virtanen P, Cournapeau D, et al. Array programming with NumPy. *Nature* 2020;585:357-62.
- Virtanen P, Gommers R, Oliphant TE, Haberland M, Reddy T, Cournapeau D, et al; SciPy 1.0 Contributors. SciPy 1.0: fundamental algorithms for scientific computing in Python. *Nat Methods* 2020;17:261-72. Erratum in: *Nat Methods* 2020;17:352.

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Ethics approval and consent to participate: this study is a secondary analysis of previously published, publicly available, and de-identified single-cell/single-nucleus transcriptomic datasets. No new human participants, human tissue, or animals were recruited or used, and no new data were collected by the authors.

Availability of data and materials: all data analysed in this study are publicly available.

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