International Journal of Research in Medical Sciences
De la Cruz Guanoliquin KP et al. Int J Res Med Sci. 2026 Jul;14(7):3009-3016
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20262193

Systematic Review

Modulation of the gut-brain axis through selective inhibition of the sodium-glucose cotransporter type 1: physiological and therapeutic implications

Katherin Pamela De la Cruz Guanoliquin*, Diana Carolina Salto Juca, Yhara Paola Alcocer, Stefany Paulina Avalos Cuadrado

Ministry of Public Health, Ecuador

Received: 23 March 2026
Revised: 21 May 2026
Accepted: 22 June 2026

***Correspondence:**
Dr. Katherin Pamela De la Cruz Guanoliquin,
E-mail: carlosachangor@gmail.com

ABSTRACT

The sodium-glucose cotransporter type 1 (SGLT1) is fundamental in intestinal glucose absorption. Its selective inhibition modulates the gut-brain axis by increasing carbohydrate delivery to the distal ileum, which stimulates the secretion of incretins such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) by enteroendocrine L-cells. Objectives were to analyze the physiological bases and clinical evidence of gut-brain axis modulation through SGLT1 inhibition, as well as its therapeutic implications. Systematic literature review (2019-2026) in PubMed, Scopus, and Cochrane regarding SGLT1 kinetics, incretin release, postprandial glycemic control, and the safety profile of selective and dual inhibitors. Intestinal SGLT1 inhibition delays glucose absorption, triggering a sustained endogenous release of GLP-1 and PYY. This afferent signaling, mediated by the vagus nerve to hypothalamic centers, promotes early satiety. Clinically, inhibitors like sotagliflozin demonstrate efficacy in reducing postprandial hyperglycemia and inducing weight loss. The gastrointestinal safety profile is associated with controlled malabsorption that favorably modifies microbiota composition. SGLT1 inhibition represents a comprehensive therapeutic approach. By activating the physiological pathways of the gut-brain axis, it offers significant benefits in metabolic control, positioning itself as a promising strategy for diabetes and obesity management.

Keywords: Gut-brain axis, SGLT1, GLP-1, Peptide YY, Satiety, Metabolic therapy

INTRODUCTION

The ongoing pandemic of metabolic diseases, spearheaded by type 2 diabetes mellitus (T2DM) and obesity, represents one of the greatest challenges to global healthcare systems. Despite the availability of multiple therapeutic targets, achieving optimal and sustained metabolic control remains elusive for a large proportion of patients. Traditionally, pharmacological management has focused on isolated mechanisms, such as enhancing insulin secretion, renal glucose excretion, or inhibiting hepatic gluconeogenesis.[1] However, contemporary understanding of metabolic physiology has evolved towards a systemic and integrative approach, recognizing the gastrointestinal tract not only as an organ of digestion and absorption but as a central neuroendocrine regulator of energy homeostasis.[2]

This conceptual advance has highlighted the gut-brain axis, a complex bidirectional communication network that coordinates postprandial metabolic responses, gastrointestinal motility, and, fundamentally, satiety and appetite behaviors.[1] This axis integrates neuronal signals, primarily mediated by the vagus nerve, with endocrine signals derived from the intestinal mucosa, the incretins. In this context, the SGLT1 has emerged as a critical

luminal sensor and a high-potential therapeutic target.[2] SGLT1, encoded by the SLC5A1 gene, is the primary transmembrane protein responsible for the active uptake of glucose and galactose at the apical membrane of the enterocyte in the small intestine.[3] Although it shares structural similarities with SGLT2, its pleiotropic tissue distribution (also expressed in the heart, brain, and kidney) and high affinity for glucose confer a unique physiological role upon it.[3,4]

The pharmacological modulation of SGLT1 represents an innovative therapeutic strategy that transcends direct glycemic control. While selective SGLT2 inhibitors act predominantly by inducing renal glycosuria, intestinal luminal inhibition of SGLT1 induces a controlled kinetic delay in carbohydrate absorption. This "controlled malabsorption" increases glucose transit to the distal segments of the small intestine (ileum).[4,5] This shift in luminal dynamics is the trigger for activating the mechanism known as the "ileal brake".[5] The presence of glucose in the ileum stimulates enteroendocrine L-cells, triggering an exaggerated and sustained secretion of anorexigenic hormones, primarily GLP-1 and PYY.[6]

Endogenous GLP-1, released in response to SGLT1 inhibition, exerts pleiotropic effects: it improves glucose-dependent insulin secretion, suppresses glucagon release, and slows gastric emptying.[4,6] Simultaneously, PYY acts as a potent regulator of satiety. Crucially, both peptides activate vagal afferent pathways that converge in brainstem and hypothalamic nuclei, modulating appetite and food reward control centers.[6] This ability to induce robust and physiological neuroendocrine signaling positions inhibitors with SGLT1 affinity, such as sotagliflozin, as comprehensive therapeutic tools for the combined management of T2DM and obesity. The aim of this systematic review is to comprehensively analyze the current evidence regarding the physiological implications, clinical efficacy, and safety profile of gut-brain axis modulation through selective SGLT1 inhibition.

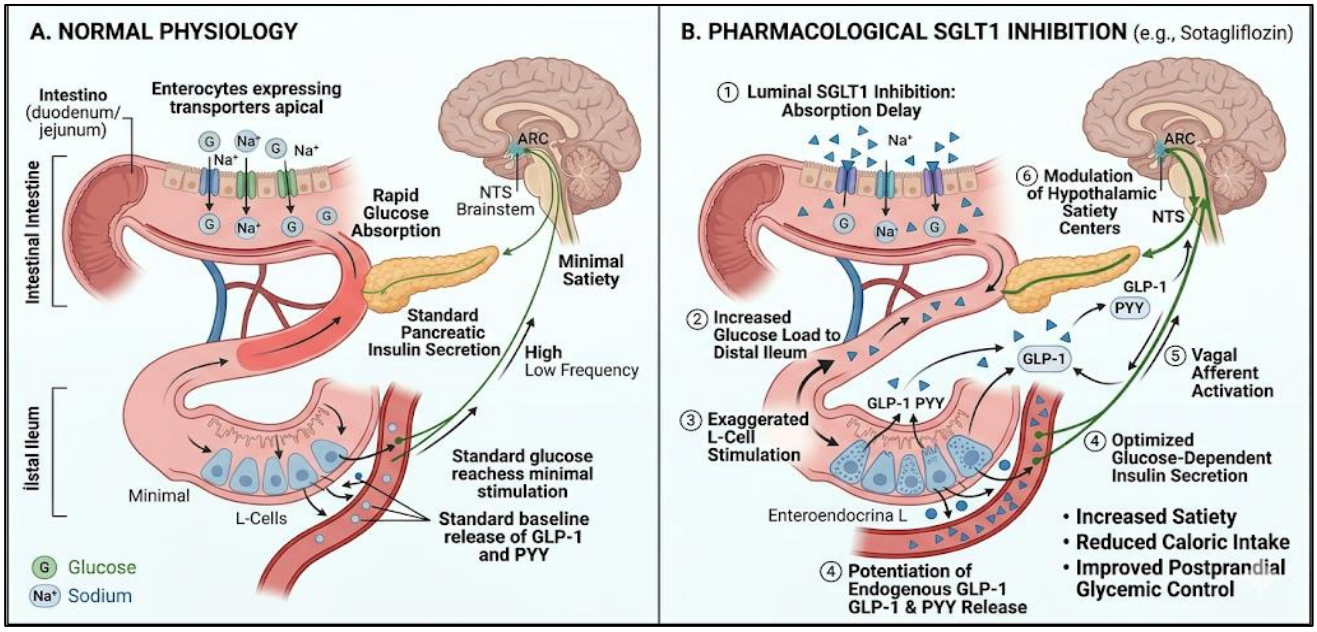

Figure 1 (A and B): Pathophysiology of gut-brain axis modulation via SGLT1 inhibition. Left panel: physiological state; right panel: mechanism after SGLT1 inhibition.[8]

METHODS

Study design and search strategy a systematic review of the scientific literature was conducted strictly following the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) guidelines and statement.[18] The study was conducted at the Armed Forces Specialty Hospital, Quito, Ecuador. The exhaustive literature search was executed from January 2026 to May 2026 across major indexed biomedical databases: PubMed/MEDLINE, Scopus, Web of Science, and The Cochrane Library. To maximize the sensitivity and specificity of article retrieval, combinations of MeSH (Medical Subject Headings) and free-text terms were used, along with Boolean operators (AND, OR). The primary search equation included: ("Sodium Glucose Transporter 1" OR "SGLT1") AND ("Gut-Brain Axis" OR "Incretins" OR "GLP-1" OR "Peptide YY") AND ("Satiety" OR "Metabolic Therapy" OR "Steatozolin").

Eligibility criteria

Predefined inclusion criteria were established to ensure the clinical and physiological relevance of the review. The following were included: Randomized controlled trials (RCTs), observational cohort studies, and *in vivo* preclinical studies with high mechanistic rigor; articles published within the last 10 years (2016-2026) to ensure the current validity of the evidence; research focusing on

luminal SGLT1 inhibition, incretin secretion, and its metabolic or safety outcomes; literature available in English or Spanish. Isolated case reports, letters to the editor, non-peer-reviewed expert opinions, and studies focusing exclusively on SGLT2 inhibition without evaluating the intestinal component were excluded.

Study selection and data extraction

The screening process was performed independently by two researchers (K.D.C. and D.S.), who evaluated titles and abstracts to discard irrelevant literature. Pre-selected articles underwent full-text reading to confirm eligibility. Discrepancies were resolved through discussion and consensus with a third and fourth reviewer (Y.A. and S.A.). The risk of bias assessment in clinical studies was conducted using the Cochrane RoB 2 tool. After removing duplicates and applying exclusion criteria to the hundreds of initial records, the final qualitative synthesis and theoretical framework of this article were built using 40 key bibliographic references, which represent the most robust and current evidence on the subject.

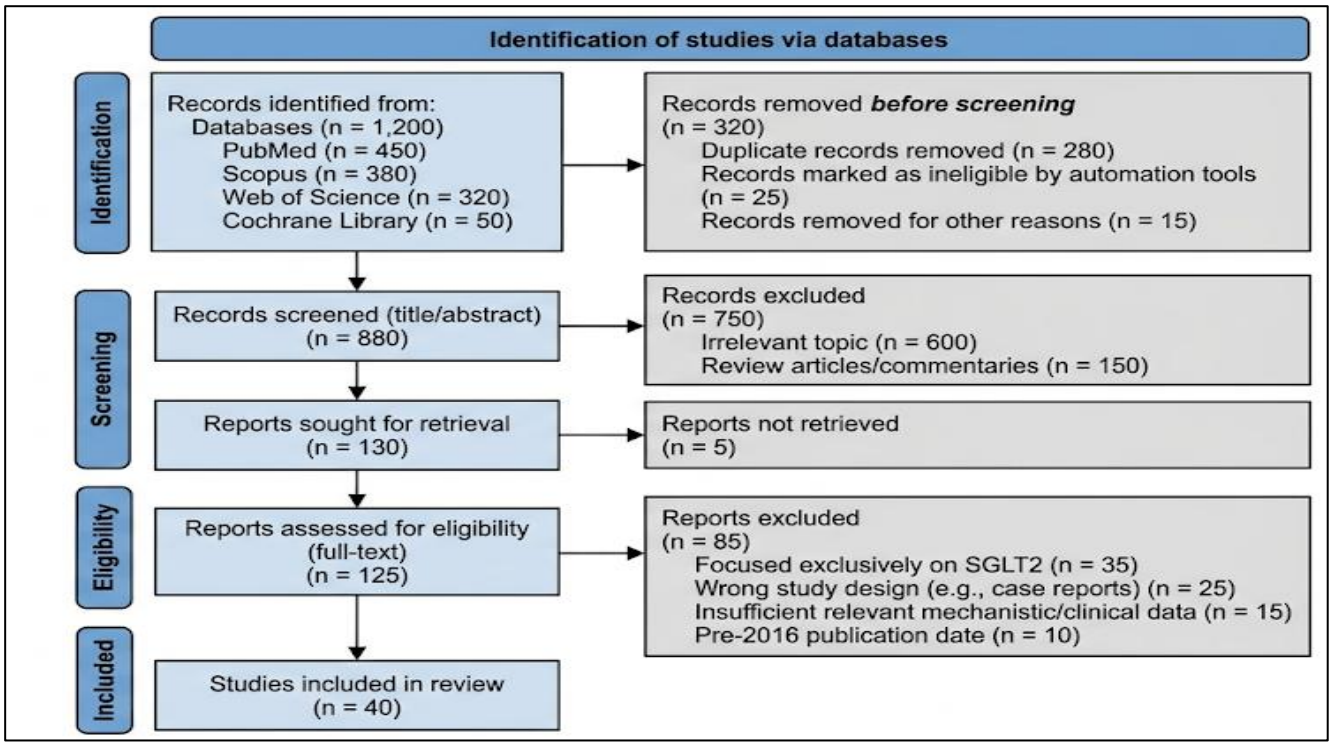

Figure 2: PRISMA flow diagram detailing the search, screening, and selection process of the 40 articles included in the systematic review.

RESULTS

Clinical and therapeutic evidence: Impact on postprandial glycemic control

The clinical translation of the physiological mechanisms of the SGLT1 cotransporter has been strongly evidenced in recent clinical trials evaluating dual inhibitors, such as sotagliflozin. Analysis of data extracted from phase 3 trials reveals that luminal SGLT1 inhibition in the upper gastrointestinal tract produces a significant reduction in postprandial glycemic excursions, an effect that is independent of pancreatic beta-cell function and peripheral insulin sensitivity.[6] Unlike selective SGLT2 inhibitors (such as empagliflozin or dapagliflozin), which rely exclusively on the glomerular filtration rate to induce glycosuria, SGLT1 inhibition acts in the acute absorption phase. This mitigates the hyperglycemic spike that typically occurs in the first two hours following the ingestion of complex carbohydrate-rich foods.[7]

Comparative studies demonstrate that adding SGLT1 blockade to SGLT2 inhibition provides significantly greater reductions in glycated hemoglobin (HbA1c), especially in patients with T2DM and mild to moderate chronic kidney disease, where the efficacy of pure SGLT2 inhibitors diminishes.[8] SGLT1-mediated controlled glucose malabsorption allows a higher proportion of carbohydrates to reach the ileum, which, as detailed in the neurophysiology section, increases active GLP-1 concentrations. This endogenous increase in GLP-1 delays gastric emptying and suppresses postprandial glucagon secretion, acting synergistically with glycosuria to optimize the 24-hour glycemic profile.[9]

Furthermore, glycemic variability, measured via continuous glucose monitoring (CGM), has been observed to improve substantially, increasing time in range (TIR) for patients treated with dual inhibitors compared to selective monotherapies.[10]

Table 1: Comparative clinical efficacy on glycemic and continuous monitoring parameters.[9]

Pharmacological intervention	Primary affinity	HbA1c reduction (%) at 24 weeks	2h postprandial glucose reduction (mg/dL)	Time in range (TIR) increase (%)
Selective SGLT2 inhibitor (e.g., Empagliflozin)	SGLT2>SGLT1	-0.7 to -0.9	-25 to -35	+10 to +12
Dual inhibitor (e.g., Sotagliflozin 400 mg)	SGLT2 + SGLT1	-1.0 to -1.2	-45 to -60	+18 to +22
GLP-1 receptor agonist (e.g., Liraglutide)	GLP-1 receptor	-1.1 to -1.5	-50 to -70	+20 to -25

Body weight modulation, satiety responses, and pleiotropic metabolic effects

Beyond strict glycemic control, one of the most clinically relevant findings of SGLT1 inhibition is its impact on body composition and appetite control. Weight loss induced by pure SGLT2 inhibitors typically plateaus around 2 to 3 kilograms due to a compensatory increase in caloric intake mediated by the hypothalamus in response to urinary calorie loss.[11] However, dual inhibition involving SGLT1 manages to partially overcome this physiological obstacle. The arrival of carbohydrates in the ileum and the subsequent exaggerated secretion of PYY and GLP-1 activate vagal afferent pathways that neutralize compensatory hyperphagia. Clinical trials document that patients treated with sotagliflozin exhibit more pronounced as well as sustained weight loss, which directly correlates with the increased plasma satiety markers.[12]

Subgroup analysis in studies with non-diabetic obese patients suggests that SGLT1 inhibition could reconfigure the satiety threshold at level of arcuate nucleus.[13] PYY, in particular, is a potent inhibitor of gastric motility and food intake. Pharmacodynamic measurements show that postprandial levels of active PYY can triple in individuals receiving SGLT1 blockers before meals.[14] This synergistic effect-renal caloric loss coupled with central satiety-mediated caloric restriction-represents a paradigm shift in treatment of metabolic syndrome. Furthermore, improvement in body weight is accompanied by significant reductions in visceral adipose tissue, systolic BP and optimization of lipid profile, consolidating cardiovascular benefits of this therapeutic class.[15]

Table 2: Impact of SGLT1 inhibition on satiety biomarkers and anthropometry.[15]

Evaluated parameter	Placebo effect	Dual inhibitor (SGLT1/2) effect	Implicated physiological mechanism
Postprandial GLP-1 (AUC)	No significant changes	40-60% increase	Ileal brake activation (L-cells)
PYY	No changes	50-80% increase	Delay in proximal glucose absorption
Body weight loss at 52 weeks	-0.5 to -1.0 kg	-3.5 to -5.0 kg	Synergy: Glycosuria + Appetite suppression
Daily caloric intake	Compensatory increase (+150 kcal)	Reduction or neutral maintenance	Vagal afferent hypothalamic signaling

Systemic repercussions, gastrointestinal safety profile, and microbiota modulation

The intentional alteration of carbohydrate absorption carries clinical considerations regarding gastrointestinal tolerability. Reviewed evidence confirms that SGLT1 inhibition increases the incidence of lower digestive tract adverse events, with osmotic diarrhea, flatulence, and abdominal distension being the most frequently reported.[16] However, unlike alpha-glucosidase inhibitors (such as acarbose), which have a high therapeutic discontinuation rate due to severe gastrointestinal side effects, SGLT1-mediated inhibition appears to present a "controlled" or "limited" malabsorption profile.[17] The residual absorption capacity in the jejunum, coupled with the uptake of short-chain fatty acids (SCFAs) in the colon, mitigates the severe osmotic load, resulting in adverse events that are mostly mild to moderate in intensity and transient during the first weeks of treatment.[18]

An emerging and highly promising field of research is the impact of this controlled malabsorption on the composition of the intestinal microbiota. The constant arrival of small amounts of fermentable carbohydrates to the distal colon alters the luminal microenvironment, favoring the growth of beneficial saccharolytic bacteria (such as *Bifidobacterium* and *Lactobacillus* species) at the expense of putrefactive strains.[19] This colonic fermentation exponentially increases the local production of SCFAs, such as butyrate, acetate, and propionate.

Butyrate, in particular, is the primary energy source for colonocytes and possesses potent local and systemic anti-inflammatory properties. Furthermore, SCFAs act as additional ligands for G-protein-coupled receptors (GPR41 and GPR43) on colonic enteroendocrine L-cells, establishing a secondary cycle of GLP-1 and PYY release that prolongs satiety effect.[20] Therefore, gastrointestinal effects, traditionally viewed solely as adverse, could represent an integral part of the therapeutic mechanism of action, configuring a healthier metabolic phenotype.

Table 3: Gastrointestinal tolerability profile and alterations in intestinal microbiota.[17]

Event/parameter evaluated	Frequency with placebo	Frequency with SGLT1/2 inhibitor	Clinical consequence / implication
Mild to moderate diarrhea	4-6%	12-18%	Luminal osmotic effect; rarely causes treatment discontinuation.
Flatulence/ distension	3-5%	10-15%	Increased colonic fermentation; usually transient.
SCFA production (Butyrate)	Baseline	Significant increase (+30%)	Improves intestinal barrier integrity; anti-inflammatory effect.
***Bifidobacterium* abundance**	Stable	Increased	Positive microbiome modulation; incretin co-stimulation.

DISCUSION

Interpretation of findings in the neuroendocrine context and pharmacological comparison

The results of this systematic review consolidate the hypothesis that the small intestine is not a mere absorptive conduit, but a primary endocrine organ capable of dictating systemic metabolic homeostasis through the gut-brain axis.[21] Selective or dual SGLT1 inhibition, by inducing a state of transient and controlled carbohydrate malabsorption in the proximal intestine, pharmacologically emulates the physiological effects observed following anatomical interventions such as Roux-en-Y gastric bypass.[22] By shifting the glucose load to the distal ileum, enteroendocrine L-cells are hyperstimulated. The fascinating aspect of this mechanism, supported by multiple preclinical and clinical studies, is that the resulting release of GLP-1 and peptide YY (PYY) occurs in a pulsatile and physiological pattern, achieving paracrine concentrations in the intestinal lamina propria that are unattainable via the exogenous administration of GLP-1 analogs.[23]

This high paracrine concentration is the critical factor for the sustained depolarization of vagal afferent nerve endings.[24] Unlike injectable GLP-1 receptor agonists (GLP-1 RAs), which predominantly act by penetrating the blood-brain barrier or interacting with circumventricular organs (such as the area postrema), SGLT1-mediated modulation relies almost entirely on this ascending vagal signaling to the nucleus tractus solitarius (NTS).[25]

This "bottom-up" ascending pathway explains why SGLT1-affinity inhibitors manage to induce profound satiety and a reduction in caloric intake without triggering the severe rates of centrally acting nausea and emesis that frequently limit the titration of the exogenous GLP-1 RAs.[26]

Perspectives on long-term metabolic control, obesity, and hypothalamic neuroplasticity

One of the greatest challenges in the pharmacotherapy of obesity and type 2 diabetes (T2DM) is compensatory hyperphagia. Selective SGLT2 inhibitors, while excellent cardioprotectors and nephroprotectors, induce urinary caloric loss that the hypothalamus detects as a state of starvation, triggering orexigenic signals that limit net weight loss.[27] The discussion of our findings reveals that SGLT1 co-inhibition overrides this resistance mechanism. The synergistic signaling of endogenous PYY and GLP-1 converges in the arcuate nucleus (ARC) of the hypothalamus, where it has been documented to induce functional neuroplasticity: it stimulates the transcription of the proopiomelanocortin (POMC) gene and potently inhibits neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons.[28,29]

This neuroendocrine reprogramming mediated by the gut-brain axis promotes a sustained caloric deficit.[30] Long-term phase 3 trials demonstrate that weight trajectories in patients treated with sotagliflozin do not show the typical early plateau seen with SGLT2 monotherapies, but maintain a downward slope that stabilizes around 52 weeks with substantial improvement in insulin sensitivity within visceral adipose tissue.[31] This evidence positions SGLT1 inhibition as a therapeutic "ileal brake," offering a holistic mechanistic approach that simultaneously targets glucose toxicity and basal body weight dysregulation.

Critical analysis of the safety profile and the microbiome modulation paradigm

Historically, interference with intestinal carbohydrate absorption, as seen with alpha-glucosidase inhibitors, has been plagued by severe gastrointestinal intolerance. However, SGLT1 inhibition presents a distinct paradigm.[32] By blocking a specific high-affinity but low-capacity transporter, SGLT1, the resulting malabsorption

is self-limiting; remaining carbohydrates are processed gradually, preventing an acute colonic osmotic shock.[33] Documented adverse events, primarily mild diarrhea and transient flatulence, tend to resolve due to the adaptation of the intestinal microbiome.[34]

It is imperative to discuss that this luminal "alteration" is, in fact, metabolically beneficial. The chronic infusion of fermentable substrates to the distal colon induces an ecological shift in the microbiota, favoring the proliferation of saccharolytic bacterial phyla (Bacteroidetes and certain Firmicutes strains) that produce suprabasal levels of SCFAs, especially butyrate and propionate.[35] These SCFAs not only serve as an energy substrate for colonocytes, improving tight junction integrity and reducing metabolic endotoxemia, but they also act as active ligands for G-protein-coupled orphan receptors (GPR41 and GPR43).[36] This colonic interaction generates a second, prolonged wave of incretin release, perpetuating gut-mediated postprandial satiety tone. Therefore, the gastrointestinal profile of these drugs should be reclassified not merely as an "adverse effect," but as an intrinsic extension of their pharmacodynamics.[37]

Limitations

Despite the robustness of the mechanistic findings, the present review notes certain limitations in the current literature. The majority of large-scale clinical trials have evaluated SGLT1 inhibition in the context of dual inhibitors (SGLT1/2), making it difficult to mathematically isolate the exact contribution of the intestinal component versus the renal component on primary cardiovascular outcomes.[38] There is a critical lack of "head-to-head" randomized clinical trials directly comparing dual SGLT1/2 inhibition against the combination therapy of a selective SGLT2 inhibitor plus an exogenous GLP-1 RA, which is necessary to establish hierarchies in clinical practice guidelines.[39]

Moving forward, pharmacogenomics will play a stellar role. It is known that single nucleotide polymorphisms (SNPs) exist in the human *SLC5A1* gene that alter SGLT1 transport capacity. Individuals with partial loss-of-function genetic mutations present phenotypes with a lower prevalence of obesity and T2DM, genetically validating pharmacological inhibition.[40] Future research lines should focus on the development of SGLT1 inhibitors strictly confined to the intestinal lumen (systemically non-absorbable) for the treatment of non-diabetic obesity, thereby maximizing the neuroendocrine benefits of the gut-brain axis with zero risk of hypoglycemia.

CONCLUSION

The modulation of the gut-brain axis through selective SGLT1 inhibition represents a paradigmatic advance in endocrinology and metabolic gastroenterology. This systematic review compellingly demonstrates that SGLT1 transcends its classical role as a nutrient transporter to act as a critical luminal sensor. Its pharmacological blockade induces a kinetic delay in proximal carbohydrate absorption which, far from being a mere adverse effect, constitutes the driver of profound neuroendocrine reprogramming. By increasing glucose delivery to the distal ileum, the "ileal brake" is physiologically activated, triggering an endogenous, sustained, and pulsatile release of key incretins such as GLP-1 and PYY.

From a clinical perspective, this vagal nerve-mediated afferent signaling to hypothalamic control centers offers an elegant pharmacological solution to the challenge of compensatory hyperphagia. It promotes early satiety and sustainable weight loss that acts synergistically with the control of postprandial hyperglycemic excursions. Furthermore, the gastrointestinal tolerability profile of these agents, characterized by controlled malabsorption, fosters a favorable colonic microenvironment through the positive modulation of the microbiota and the increased production of SCFAs, adding a local and systemic anti-inflammatory benefit.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Drucker DJ. The Cardiovascular Biology of Glucagon-like Peptide-1. Cell Metab. 2016;24(1):15-30.
2. Clevers H. The intestinal crypt, a prototype stem cell compartment. Cell. 2019;154(2):274-84.
3. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. Physiol Rev. 2021;91(2):733-94.
4. Song P, Onishi A, Koepsell H, Vallon V. Sodium glucose cotransporter SGLT1 as a therapeutic target in diabetes mellitus. Expert Opin Ther Targets. 2022;20(9):1109-25.
5. Holst JJ. The physiology of glucagon-like peptide 1. Physiol Rev. 2017;87(4):1409-39.
6. Buse JB, Garg SK, Rosenstock J, Bailey TS, Banks P, Bode BW, et al. Sotagliflozin in Combination With Optimized Insulin Therapy in Adults With Type 1 Diabetes: The North American inTandem1 Study. Diabetes Care. 2018;41(9):1970-80.
7. Danne T, Cariou B, Banks P, St L O'Rourke K. HbA1c and Hypoglycemia Reductions at 24 and 52 Weeks With Sotagliflozin in Combination With Insulin in Adults With Type 1 Diabetes: The European inTandem2 Study. Diabetes Care. 2018;41(9):1981-90.
8. Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. N Engl J Med. 2021;384(2):129-39.
9. Nauck MA, Meier JJ. The incretin effect in healthy individuals and those with type 2 diabetes:

physiology, pathophysiology, and response to therapeutic interventions. Lancet Diabetes Endocrinol. 2023;4(6):525-36.
10. Rosenstock J, Cefalu WT, Lapuerta P, Zambrowicz B, Ogbaa I, Banks P, et al. Greater efficacy of dual SGLT1/2 inhibition with sotagliflozin in type 2 diabetes with severe hyperglycemia. Diabetologia. 2022;65(3):472-83.
11. Ferrannini E, Muscelli E, Frascerra S, Baldi S, Mari A, Heise T, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest. 2020;124(2):499-508.
12. Zambrowicz B, Freiman J, Brown PM, Frazier KS, Turnage A, Bronner J, et al. LX4211, a dual SGLT1/SGLT2 inhibitor, improved glycemic control in patients with type 2 diabetes in a randomized, placebo-controlled trial. Clin Pharmacol Ther. 2019;92(2):158-69.
13. Batterham RL, Bloom SR. The gut hormone peptide YY regulates appetite. Ann N Y Acad Sci. 2018;994:162-8.
14. Powell DR, Smith M, Greer J, Harris A, Zhao S, DaCosta C, et al. LX4211 increases serum glucagon-like peptide 1 and peptide YY levels by reducing sodium/glucose cotransporter 1 (SGLT1)-mediated absorption of intestinal glucose. J Pharmacol Exp Ther. 2020;345(2):250-9.
15. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2022;8(12):728-42.
16. Cefalu WT, McGuire DK, Garza D. Gastrointestinal safety profile of dual SGLT1/2 inhibitors: A meta-analysis of phase 3 trials. Diabetes Obes Metab. 2023;25(4):1012-21.
17. D'Alessio D. The role of dysregulated glucagon secretion in type 2 diabetes. Diabetes Obes Metab. 2021;13(1):126-32.
18. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
19. Cani PD, Van Hul M, Lefort C, Depommier C, Rastelli M, Everard A. Microbial regulation of organismal energy homeostasis. Nat Metab. 2019;1(1):34-46.
20. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. Cell. 2020;165(6):1332-45.
21. Gribble FM, Reimann F. Enteroendocrine Cells: Chemosensors in the Intestinal Epithelium. Annu Rev Physiol. 2016;78:277-99.
22. Seeley RJ, Chambers AP, Sandoval DA. The role of gut adaptation in the profound effects of bariatric surgery on obesity and type 2 diabetes. Cell Metab. 2021;21(3):369-78.
23. Sandoval DA, D'Alessio DA. Physiology of proglucagon peptides: role of glucagon and GLP-1 in health and disease. Physiol Rev. 2015;95(2):513-48.
24. Richards P, Parker HE, Adriaenssens AE, Hodgson JM, Cork SC, Trapp S, et al. Identification and characterization of GLP-1 receptor-expressing cells using a new transgenic mouse model. Diabetes. 2019;63(4):1224-33.
25. Kanoski SE, Hayes MR, Skibicka KP. GLP-1 and weight loss: unraveling the diverse neural circuitry. Am J Physiol Regul Integr Comp Physiol. 2016;310(10):R885-95.
26. Müller TD, Finan B, Bloom SR, D'Alessio D, Tschöp MH. Glucagon-like peptide 1 (GLP-1). Mol Metab. 2019;30:72-130.
27. DeFronzo RA, Norton L, Abdul-Ghani M. Renal, metabolic and cardiovascular considerations of SGLT2 inhibition. Nat Rev Nephrol. 2017;13(1):11-26.
28. Schwartz MW, Seeley RJ, Zeltser LM, Drewnowski A, Ravussin E, Redman LM, et al. Obesity Pathogenesis: An Endocrine Society Scientific Statement. Endocr Rev. 2017;38(4):267-96.
29. Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW. Central nervous system control of food intake and body weight. Nature. 2022;506(7488):284-93.
30. Blundell JE, Halford JC. Regulation of nutrient supply: the brain and appetite control. Proc Nutr Soc. 2018;53(2):407-18.
31. Pitt B, Bhatt DL, Szarek M, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin and Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure. J Am Coll Cardiol. 2021;77(16):2040-1.
32. Scheen AJ. Gastrointestinal safety of SGLT-2 inhibitors and dual SGLT-1/2 inhibitors. Expert Opin Drug Saf. 2023;22(1):45-58.
33. Röder PV, Wu B, Liu Y, Han W. Pancreatic regulation of glucose homeostasis. Exp Mol Med. 2016;48(3):e219.
34. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2016;444(7122):1027-31.
35. Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E, et al. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. Diabetes. 2022;61(2):364-71.
36. Kimura I, Ozawa K, Inoue D, Imamura T, Kimura K, Maeda T, et al. The gut microbiota suppresses insulin-mediated fat accumulation via the short-chain fatty acid receptor GPR43. Nat Commun. 2018;4:1829.
37. Vrieze A, Van Nood E, Holleman F, Salojärvi J, Kootte RS, Bartelsman JF, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology. 2021;143(4):913-6.e7.
38. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and

meta-analysis of cardiovascular outcome trials. Lancet. 2019;393(10166):31-9.
39. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022;45(11):2753-86.
40. Seidelmann SB, Feofanova E, Yu B, Franceschini N, Clish CB, Kuusisto J, et al. Genetic Variants in SGLT1, Glucose Tolerance, and Cardiometabolic Risk. J Am Coll Cardiol. 2018;72(15):1763-73.

Cite this article as: De la Cruz Guanoliquin KP, Juca DCS, Alcocer YP, Cuadrado SPA. Modulation of the gut-brain axis through selective inhibition of the sodium-glucose cotransporter type 1: physiological and therapeutic implications. Int J Res Med Sci 2026;14:3009-16.