PIVIT

Mechanism of Action

Molecular Basis of Enteroendocrine Chemosensory Signalling and Satiety Hormone Secretion

Prepared for Medical & Scientific Review

Clinical Overview

PIVIT is a novel, food-derived ligand formulation designed to restore physiological enteroendocrine chemosensory signalling. Rather than acting as a direct pharmacological agonist, it provides the molecular inputs required for endogenous secretion of multiple satiety hormones — GLP-1, PYY, GIP, and oxyntomodulin — through coordinated activation of G-protein-coupled receptors (GPCRs), ion channels, and co-transporter proteins expressed on intestinal L- and K-cells.

1. Enteroendocrine Cell Biology and Receptor Expression

The intestinal mucosa contains specialised enteroendocrine cells — principally L-cells (distal small intestine and colon) and K-cells (proximal small intestine) — which function as luminal chemosensors. These cells express a diverse repertoire of apically-oriented receptors that detect ingested nutrients and microbial metabolites, transducing luminal signals into systemic endocrine responses.

Receptor Class	Key Members	Ligand Class	Primary Response
Co-transporter	SGLT1	Glucose, galactose	Membrane depolarisation → GLP-1, GIP
Free Fatty Acid GPCRs	FFAR1 (GPR40) FFAR2 (GPR43) FFAR3 (GPR41) FFAR4 (GPR120)	LC-FAs, SC-FAs SCFAs SCFAs LC-FAs, LCPUFAs	G_q/G_i signalling → GLP-1, PYY, GIP
Olfactory GPCRs	OR51E1, OR51E2 OR1A1, OR2W1	Nonanoic acid Aromatic ligands	cAMP elevation → GLP-1 secretion
TRP Channels	TRPA1, TRPV1 TRPM5	Pungent compounds Sweet tastants	Ca^{2+} influx → exocytosis
Taste Receptors	T1R1/T1R3, T2R family	Amino acids, bitter compounds	PLC-β/IP_3 → GLP-1, CCK

Table 1. Key chemosensory receptors expressed on intestinal L- and K-cells targeted by PIVIT ligands. LC-FA = long-chain fatty acid; SCFA = short-chain fatty acid; LCPUFA = long-chain polyunsaturated fatty acid.

2. Molecular Signal Transduction Cascade

Upon luminal delivery of PIVIT ligands, a defined intracellular signalling cascade is initiated within enteroendocrine cells, culminating in exocytosis of hormone-containing secretory vesicles:

1 **Receptor Binding & Membrane Depolarisation**

SGLT1-mediated glucose co-transport and FFAR1/4 activation by medium- and long-chain fatty acids trigger phospholipase C-β (PLC-β) via G_q coupling, generating inositol trisphosphate (IP_3) and diacylglycerol (DAG). Concurrently, TRPA1 and TRPV1 channel activation by terpene and spice-derived ligands produces direct Na^+/Ca^{2+} influx, contributing to rapid membrane depolarisation.

2	**Intracellular Ca²■ Mobilisation** IP_3-driven release from the endoplasmic reticulum (ER) and voltage-gated Ca^{2+} channel (VGCC) opening produce a bimodal rise in cytosolic [Ca^{2+}]. SCFA stimulation of FFAR2/3 via $G_{i/o}$ modulates adenylyl cyclase activity, tuning cAMP/PKA-mediated amplification of the Ca^{2+} signal.
3	**cAMP–PKA Amplification** Olfactory receptor activation (e.g., OR51E1 by nonanoic acid) couples through $G_{olf/s}$ to adenylyl cyclase, elevating intracellular cAMP. This activates protein kinase A (PKA), which phosphorylates vesicle-associated proteins and potentiates VGCC conductance, amplifying secretory output.
4	**Vesicle Exocytosis** The convergent Ca^{2+} and PKA signals drive SNARE-complex-mediated fusion of hormone-containing dense-core granules with the basolateral plasma membrane. This releases GLP-1, PYY, GIP, and oxyntomodulin into the subepithelial capillary bed and portal circulation.

3. Multi-Hormonal Secretory Profile and Downstream Effects

A key mechanistic distinction of ligand-driven enteroendocrine activation is the simultaneous secretion of multiple gut hormones, reflecting the natural stoichiometry of enteroendocrine vesicle content. This contrasts with pharmacological GLP-1 receptor agonists, which activate only a single downstream pathway.

Hormone	Primary Source	Molecular Targets	Physiological Effects
GLP-1	L-cells (ileum/colon)	GLP-1R on β-cells, vagal afferents, hypothalamus	↑ Insulin secretion, ↓ glucagon, delayed gastric emptying, central satiety
PYY_{3-36}	L-cells (colon)	Y2R on hypothalamic arcuate nucleus neurons	↓ NPY/AgRP signalling → reduced appetite; ↓ gastric motility
GIP	K-cells (duodenum)	GIPR on β-cells, adipocytes	↑ Insulin secretion, lipid partitioning, bone metabolism
Oxyntomodulin	L-cells	GLP-1R and GCGR (dual agonism)	↑ Energy expenditure, ↓ food intake, ↑ gut motility

Table 2. Hormones released in response to PIVIT ligand activation, with molecular targets and downstream physiological effects. NPY = neuropeptide Y; AgRP = agouti-related peptide; GCGR = glucagon receptor.

4. Threshold Kinetics and Additive Receptor Summation

Satiety hormone secretion from L- and K-cells is not a binary event but follows a summation threshold model, in which subthreshold stimulation of individual receptor classes is insufficient to trigger exocytosis, but cumulative activation across multiple receptor types generates a superthreshold intracellular signal. This is the molecular basis of PIVIT's multi-ligand design strategy:

Signal Inputs (Additive)

- SGLT1 co-transport → basal depolarisation
- FFAR2/3 activation by SCFAs → G_i-mediated cAMP modulation
- FFAR1/4 activation by LCFAs → G_q-mediated IP_3/DAG
- OR51E1 activation by nonanoic acid → G_s-mediated cAMP rise
- TRP channel activation by terpenes → direct Ca^{2+} influx

Together these lower the secretion threshold for hormone exocytosis.

Threshold Concept

Ultra-processed diets deplete natural food ligands — particularly SCFAs, plant volatile terpenes, and long-chain fatty acid diversity. This raises the effective secretion threshold, blunting GLP-1 and PYY responses. PIVIT replaces these missing environmental molecular inputs, restoring the additive signalling required to achieve threshold depolarisation and Ca^{2+}-mediated exocytosis. The result is normalisation of postprandial hormone kinetics without exogenous hormone delivery.

5. Pulsatile Secretion Kinetics and Receptor Integrity

Because PIVIT acts upstream at the level of luminal receptor activation rather than at the systemic receptor level, hormone secretion retains its natural pulsatile, meal-linked kinetics. This has important molecular consequences:

Receptor cycling preserved. GLP-1R and Y2R on target organs (pancreas, hypothalamus, vagal afferents) are not subjected to continuous agonist exposure. Normal receptor internalisation and recycling cycles are maintained, preventing downregulation and preserving receptor density and sensitivity.

Physiological hormone ratios. Co-secretion of GLP-1, PYY, GIP, and oxyntomodulin occurs in ratios reflecting endogenous vesicle stoichiometry. This preserves the natural cross-talk between signalling pathways — for example, GIP potentiation of GLP-1 insulinotropic action — which is absent in single-hormone pharmacotherapy.

Self-limiting secretory capacity. Enteroendocrine cell vesicle pools are finite and replenished through regulated biosynthesis. This imposes a physiological ceiling on hormone output, preventing supraphysiological plasma concentrations and associated adverse effects.

6. Gut–Brain Axis: Central Integration of Peripheral Signals

The molecular effects of PIVIT-induced hormone secretion are ultimately integrated at the level of the gut–brain axis via two principal pathways:

Vagal Pathway (Rapid)

GLP-1 and PYY bind receptors on the nodose ganglion of the vagus nerve. This activates nucleus tractus solitarius (NTS) neurons in the brainstem, relaying satiety signals to the hypothalamic arcuate nucleus within minutes of meal onset — suppressing NPY/AgRP orexigenic neurons and activating POMC/CART anorexigenic circuits.

Endocrine Pathway (Sustained)

Circulating GLP-1 crosses the blood–brain barrier (BBB) at circumventricular organs (area postrema, median eminence) to directly engage hypothalamic GLP-1R. PYY_{3-36} acts at the Y2R on arcuate nucleus neurons. Together these produce sustained post-meal anorexia and reductions in meal size and frequency through coordinated neuroendocrine modulation.

7. Mechanistic Comparison: PIVIT vs Pharmacological GLP-1 Receptor Agonists

Parameter	PIVIT (Ligand-Based)	Pharmacological GLP-1 Agonists
Mechanism	**Upstream receptor ligand activation**	Direct receptor agonism

Hormone profile	**GLP-1 + PYY + GIP + oxyntomodulin**	GLP-1 pathway only
Secretion pattern	**Pulsatile, meal-linked**	Continuous (tonic)
Receptor cycling	**Preserved**	Impaired (tachyphylaxis risk)
Physiological ceiling	**Yes — endogenous limits apply**	No — supraphysiological exposure possible
Structural modification	**None — food-derived ligands**	Synthetic analogues with extended half-life

Summary

Molecular Summary

PIVIT engages a physiologically coherent molecular pathway: food-derived ligands activate a suite of GPCRs, ion channels, and co-transporters on intestinal L- and K-cells, initiating calcium-mediated exocytosis of multiple satiety hormones. The resulting multi-hormonal signal engages both vagal and endocrine arms of the gut–brain axis to produce coordinated appetite suppression. By operating upstream of receptor agonism, PIVIT restores the molecular signalling environment that ultra-processed diets have depleted — preserving receptor integrity, maintaining physiological hormone ratios, and avoiding the supraphysiological exposure associated with synthetic analogues.

This document is intended for medical and scientific audiences. The mechanism described reflects current understanding of enteroendocrine physiology and receptor pharmacology. Specific clinical claims are subject to ongoing validation.