



Potential modulators of retatrutide-associated hyperesthesia and allodynia: pharmacological mechanisms and exploratory observations

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Abstract. Retatrutide, a novel triple agonist of glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and glucagon receptors, has emerged as a promising pharmacological intervention for obesity and metabolic disease. Clinical trials have consistently demonstrated substantial reductions in body weight and improvements in cardiometabolic parameters. Gastrointestinal symptoms predominate in the adverse-event profiles reported in most clinical studies, whereas neurological and sensory effects have received comparatively little attention. However, emerging evidence suggests that cutaneous sensory disturbances, such as hyperesthesia and allodynia, may occur in certain contexts. This review summarizes current knowledge regarding the pharmacology and safety profile of retatrutide and discusses mechanistic explanations for possible nociceptive sensitization. Particular attention is given to potential synergistic interactions between retatrutide and commonly used stimulatory or metabolic supplements. Additionally, we present preliminary observational data from an exploratory survey of recreational athletes who reported sensory disturbances during retatrutide exposure before formal human approval. The data suggest a possible interaction between retatrutide and substances such as caffeine, pyridoxine, and thyroid hormones, which may amplify nociceptive sensitivity. These findings suggest that hyperesthesia and allodynia may be underreported in clinical trials due to differences in supplement and stimulant use compared to athletic populations

Key Words: retatrutide, hyperesthesia, allodynia, incretin receptor agonists, nociceptive sensitization, caffeine, pyridoxine, thyroid hormones, pharmacological synergy, recreational athletes.

Introduction. Retatrutide (LY-3437943) represents a new generation of incretin-based therapeutics designed to simultaneously activate three metabolic receptors: glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and the glucagon receptor (Jastreboff et al 2023; Rosenstock et al 2023; Alfaris et al 2024; Sanyal et al 2024; Goldney et al 2025; Katsi et al 2025). Through this tri-agonist mechanism, the molecule produces combined effects on appetite regulation, insulin secretion, lipid mobilization, and energy expenditure. These integrated pathways lead to pronounced reductions in body weight and improvements in metabolic control in individuals with obesity or type 2 diabetes (Abdrabou Abouelmagd et al 2025).

Clinical trials have demonstrated that weekly administration of retatrutide can produce substantial decreases in body weight, body mass index, and cardiometabolic risk markers while generally maintaining a safety profile comparable to other incretin-based therapies (Abdrabou Abouelmagd et al 2025). The most frequently reported adverse effects

include nausea, vomiting, diarrhea, and other gastrointestinal symptoms typical of the incretin drug class.

Nevertheless, anecdotal observations and emerging case reports on incretin-based therapies have described sensory disturbances such as dysesthesia or allodynia, suggesting that central or peripheral sensory modulation may occur in certain individuals exposed to these compounds (Ahern 2025; Katsi et al 2025). These findings raise the possibility that similar phenomena may occur with retatrutide but remain underrecognized.

Current evidence on retatrutide safety profile. Available clinical trials and systematic reviews of retatrutide have primarily focused on metabolic efficacy and classical incretin-related adverse events. Across randomized controlled trials involving obese or diabetic populations, gastrointestinal symptoms remain the dominant adverse effects reported, while neurological or dermatological sensory symptoms are rarely emphasized.

Systematic analyses of trial data have therefore concluded that retatrutide demonstrates a tolerable safety profile with dose-dependent gastrointestinal reactions but without major neurological toxicity signals. In these analyses, reports of cutaneous sensory disturbances, such as hyperesthesia, are rare and generally not considered clinically relevant adverse reactions (Jastreboff et al 2023; Rosenstock et al 2023; Alfaris et al 2024; Sanyal et al 2024; Goldney et al 2025; Katsi et al 2025).

However, the absence of frequent reporting does not necessarily imply the absence of the phenomenon. Instead, several factors may contribute to underrecognition, including differences in patient populations, concurrent medications, and lifestyle factors between clinical trial participants and other populations using metabolic peptides.

Mechanistic basis for hyperesthesia and allodynia associated with retatrutide. A recent mechanistic study has highlighted the biological plausibility of sensory disturbances associated with retatrutide exposure. The study emphasizes that the tri-agonist pharmacology of retatrutide interacts with neuroendocrine signaling pathways that extend beyond metabolic regulation (Petrescu-Mag 2025).

According to the analysis, incretin receptors and glucagon receptors are expressed not only in metabolic tissues but also within the central and peripheral nervous systems. Activation of these receptors may influence neuronal excitability and neuropeptide signaling pathways involved in pain perception. Petrescu-Mag (2025) proposes several potential mechanisms:

Central sensitization mechanisms. GLP-1 receptor signaling within the central nervous system may influence neuronal plasticity and synaptic transmission in regions associated with nociception.

Peripheral sensory nerve modulation. Peptide hormones and their analogues can affect peripheral nerve endings and neurogenic inflammation, potentially lowering the threshold for mechanical or thermal stimulation.

cAMP-dependent neuronal signaling. Retatrutide signaling via incretin and glucagon receptors increases intracellular cAMP levels, which can influence neuronal excitability and synaptic transmission.

Metabolic-neuroendocrine cross-talk. Rapid metabolic shifts induced by powerful incretin agonists may indirectly affect sensory processing via autonomic or inflammatory mediators. Based on these mechanisms, the study argues that hyperesthesia and allodynia are biologically plausible adverse effects even if they remain uncommon or underreported in formal clinical trials (Petrescu-Mag 2025).

Observational survey of recreational athletes using retatrutide. To further explore potential modulators of sensory disturbances associated with retatrutide, we conducted an exploratory observational survey of recreational athletes who reported using retatrutide before its regulatory approval for human therapeutic use.

Methodological overview. Anonymous statements were collected from five recreational athletes who reported experiencing symptoms compatible with hyperesthesia or allodynia during retatrutide exposure. The aim of the survey was not to estimate prevalence but to identify potential co-administered substances with known or suspected nociceptive-sensitizing properties.

Given the wide variety of supplements typically used by recreational athletes, the survey intentionally focused only on substances with plausible neuro-sensory modulatory potential (Table 1).

Table 1
Observed co-exposures among the five individuals reporting sensory disturbances

<i>Supplement or drug</i>	<i>Athlete no 1</i>	<i>Athlete no 2</i>	<i>Athlete no 3</i>	<i>Athlete no 4</i>	<i>Athlete no 5</i>
Caffeine-containing supplements	Yes	Yes	Yes	Yes	Yes
Pyridoxine (B6)	Yes	Only by food	Yes	Yes	Yes
Levothyroxine and/or Liothyronine	No	Yes	Yes	Yes	No
Guarana extract	Yes	No	No	No	Not sure (most probably no)

Observed co-exposures. Among the five individuals reporting sensory disturbances:

- 5/5 reported the use of caffeine-containing supplements
- 4/5 reported pyridoxine (vitamin B6) supplementation
- 3/5 reported use of thyroid hormones (levothyroxine and/or liothyronine)
- 1/5 reported supplementation with guarana extract.

Other commonly used sports supplements were excluded from the analysis because they are not known to affect nociceptive thresholds or sensory hypersensitivity significantly.

Although the number of observations is extremely limited, the clustering of substances with known neuromodulatory properties suggests that contextual pharmacological interactions could represent a plausible explanatory factor deserving further investigation.

Potential synergistic mechanisms

Caffeine. Caffeine is a central nervous system stimulant and adenosine receptor antagonist known to increase neuronal excitability and modulate pain perception pathways (Nehlig et al 1992; Rivera-Oliver & Díaz-Ríos 2014; Kerkhofs et al 2018; Lopes et al 2019; Daly et al 2020; Martins et al 2020; Israelsen et al 2023). Through increased catecholaminergic signaling and altered sensory processing, caffeine could theoretically enhance susceptibility to hyperesthesia when combined with agents that affect neuronal signaling pathways (Ferré 2008; Ferré 2016; Kerkhofs et al 2018; Martins et al 2020; Fox et al 2020) (Table 2).

Caffeine, neuronal excitability, and pain

<i>Claim element</i>	<i>Supporting evidence</i>	<i>References</i>
CNS stimulant, widely used	Described as most widely consumed CNS/psychostimulant	Nehlig et al 1992; Rivera-Oliver & Díaz-Ríos 2014; Kerkhofs et al 2018; Daly et al 2020; Israelsen et al 2023
Adenosine receptor antagonist (A1, A2A etc.)	Non-selective adenosine receptor blockade as main mechanism	Nehlig et al 1992; Rivera-Oliver & Díaz-Ríos 2014; Kerkhofs et al 2018; Lopes et al 2019; Daly et al 2020; Martins et al 2020; Israelsen et al 2023; Bhardwaj et al 2024
Increases neuronal/cortical excitability	Human neocortical pyramidal neuron excitability and synaptic transmission increased by realistic caffeine doses	Kerkhofs et al 2018; Lopes et al 2019; Martins et al 2020
Modulates pain perception / nociception	Reviews of caffeine in pain modulation, TRP channels, neuropathic pain, hyperalgesia/allodynia models	Rivera-Oliver & Díaz-Ríos 2014; Piekarska et al 2021; Israelsen et al 2023; Puthumana et al 2024; Tehrani et al 2024
Alters catecholaminergic (dopaminergic, noradrenergic) signaling	Caffeine disinhibits dopaminergic transmission and activates noradrenergic systems	Nehlig et al 1992; Ferré 2008; Rivera-Oliver & Díaz-Ríos 2014; Ferré 2016; Israelsen et al 2023

Pyridoxine. High doses of pyridoxine have been associated with sensory neuropathy and altered peripheral nerve function in susceptible individuals (Schaumburg et al 1983; Albin et al 1987; Xu et al 1989; Ghavanini & Kimpinski 2014; Kulkantrakorn 2014; Hadtstein & Vrolijk 2021; Muhamad et al 2023; Ko & Kang 2024). Even at moderate doses, vitamin B6 plays a role in neurotransmitter metabolism and neuronal signaling, which may influence nociceptive sensitivity (Jurna et al 1990; Vrolijk et al 2017; Wilson et al 2019; He et al 2020; Hadtstein & Vrolijk 2021; Ghavidel-Parsa et al 2022; Páez-Hurtado et al 2022).

Thyroid hormones. Exogenous thyroid hormones increase basal metabolic rate and may alter peripheral nerve excitability, sympathetic tone, and thermosensory perception (Kim 2008; Yerdelen et al 2010; Dietzel et al 2012; Mcaninch & Bianco 2014; Mullur et al 2014; Iwen et al 2018; Milanese & Brent, 2024). These changes may contribute to altered sensory thresholds (Dietzel et al 2012; Mcaninch & Bianco 2014; Iwen et al 2018; Afarinesh et al 2019).

Combined effects. When combined with a pharmacological agent capable of modifying neuronal signaling via incretin and glucagon receptors, these substances may create a synergistic environment that promotes nociceptive hypersensitivity (Gong et al 2014; Bannister et al 2017; Koivisto et al 2018; Kopp et al 2022; De Sousa et al 2025; Kuthati et al 2025).

Interpretation and implications. The discrepancy between the rarity of hyperesthesia reports in clinical trials and the informal reports in athletic populations may reflect differences in concurrent exposures.

Participants enrolled in controlled clinical trials typically follow strict medication protocols and may avoid high doses of stimulants or metabolic supplements. In contrast, recreational athletes often consume combinations of ergogenic supplements, stimulants, and metabolic modulators.

Therefore, the observed sensory disturbances may not arise from retatrutide alone but from pharmacological synergy between retatrutide and other neuroactive compounds.

Limitations. This review has several limitations. The observational component described here is based on a very small number of self-reported cases and therefore does not allow any estimation of prevalence or causal inference. These observations are presented solely to highlight potential patterns of concomitant exposure that may warrant further investigation.

In addition, the individuals considered in these exploratory observations represent a specific population of recreational athletes whose supplement use differs substantially from that of typical clinical trial participants. Consequently, the observations cannot be generalized to broader patient populations.

Finally, the proposed mechanisms linking retatrutide exposure to sensory disturbances remain largely hypothetical and are based mainly on indirect evidence from neurophysiological and pharmacological studies. Further experimental and clinical investigations will be required to clarify these potential interactions.

Conclusions. Current evidence suggests that hyperesthesia and allodynia associated with retatrutide exposure are biologically plausible but remain insufficiently characterized. Clinical trials have primarily focused on metabolic efficacy and gastrointestinal tolerability, while potential sensory disturbances have received comparatively limited attention.

The exploratory observations discussed in this review indicate that concomitant use of substances with neuromodulatory properties, particularly caffeine and pyridoxine, may represent a potential contextual factor that could enhance nociceptive sensitivity in some individuals. Thyroid hormones may represent an additional modulatory influence through their effects on metabolic rate and peripheral nerve excitability.

Although these observations are preliminary and based on a very limited number of reports, they suggest that pharmacological interactions between retatrutide and commonly used stimulatory or metabolic supplements may deserve further investigation. Future experimental and clinical studies should examine these potential interactions to better understand the mechanisms underlying retatrutide-associated sensory disturbances.

Conflict of interest. The authors declare that there is no conflict of interest.

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