PMCHS RESEARCH NOTE · REFRACTORY OBESITY

Refractory obesity: when chronic inflammation

short-circuits willpower

This is not a question of willpower

Some forms of obesity resist the best-conducted diets, the most rigorous exercise programmes, and even GLP-1 medications that are effective in the majority of cases. In the PMCHS terrain, this resistance has a neurobiological explanation — not a moral one. It involves three mutually reinforcing mechanisms.

Mechanism 1 — Hypothalamic H1 desensitisation

H1 receptors in the hypothalamus directly regulate appetite: their activation by histamine normally suppresses hunger. In the PMCHS terrain, histamine is chronically elevated — which produces, through the classical receptor down-regulation mechanism, progressive desensitisation of hypothalamic H1 receptors. Result: the satiety signal is extinguished. This has been confirmed in mouse models: mice without H1 receptors develop frank obesity with hyperphagia and leptin resistance (Masaki et al., 2004).

The good news: under mast cell stabilisation (quercetin, luteolin, cromoglycate), progressive re-sensitisation of hypothalamic H1 receptors is possible. PMCHS patients following a stabilisation protocol describe the return of clear hunger and functional satiety — an experience often felt as entirely new.

Mechanism 2 — The leptin-mast cell loop

Leptin — the satiety hormone secreted by adipose tissue — directly activates mast cells and triggers histamine release. The more weight gained, the more leptin rises, the more mast cells degranulate, the more histamine desensitises H1 receptors. A positive feedback loop that self-sustains and produces central — not merely peripheral — leptin resistance.

“ In the PMCHS terrain, obesity is not the cause of leptin resistance — it is partly its consequence. The cause is upstream: programmed mast cell hyperreactivity. ”

Mechanism 3 — The TERT/hypothalamus axis

The ANR THALATEL research programme (Geli et al., 2022–2026) demonstrated that TERT — an enzyme known for its role in telomeres — plays in hypothalamic neurons a direct protective role against oxidative stress. Experimental extinction of hypothalamic TERT in normal mice caused massive weight gain within 3 weeks, with dysfunction of satiety neurons.

In the PMCHS terrain, years of mast cell inflammation generate chronic oxidative stress that may progressively deplete hypothalamic TERT — structurally weakening satiety neurons independently of H1 receptor status. This is a second neurobiological pathway to hyperphagia, explaining why some

long-standing cases resist even mast cell stabilisation.

The H1 antihistamine paradox

Classical H1 antihistamines (cetirizine, loratadine, hydroxyzine) — often prescribed first-line in MCAS — pharmacologically replicate the exact obesogenic mechanism described above: AMPK activation, reduced thermogenesis, appetite stimulation. Their chronic use in a PMCHS terrain may worsen weight gain while masking peripheral allergic symptoms.

Mast cell stabilisers (cromoglycate, quercetin, luteolin) address the source of activation without blocking central receptors — preserving the satiety signal while controlling inflammation.

What this means in practice

- Favour **mast cell stabilisers** (quercetin, luteolin, cromoglycate) over H1 antihistamines alone when weight gain is associated.
- **GLP-1 agonists** (semaglutide) are promising: GLP-1 receptors are present on mast cells and their activation inhibits degranulation (89% benefit reported in 47 refractory MCAS cases, Afrin et al., 2025).
- **Antioxidant strategies** (NAC, omega-3, melatonin) to protect the TERT/hypothalamus axis in long-standing resistant cases.
- Do not wait for hunger — it may not come. **Fixed mealtimes and pre-defined portions** bypass the absent internal signal.
