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A Short-Term Tirzepatide Treatment Improves Insulin Sensitivity and Reduces Leptin-Ghrelin Ratio in Diet-Induced Obese Mice

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Tirzepatide (TZP) has achieved significant acclaim for its effectiveness as a glycemic control agent, but the underlying mechanism remains unclear. As a dual GLP-1/GIP agonist, TZP is thought to achieve this effect partly via decreasing appetite and inducing weight loss. Here, we examined the effects of a short-term TZP treatment on metabolic and neuroendocrine parameters. Male C57BL/6 mice were fed a high-fat diet (HFD) for 12 weeks, and during the last 2 weeks of HFD, mice received a once-weekly treatment of TZP (3 nmol/kg) or saline (Controls) (n=6/group) with or without acute bouts of exercise. Acute exercise alone did not significantly affect any of the measured parameters. Metabolic and neuroendocrine parameters were examined before and after a 2-week treatment using metabolic cages, intraperitoneal glucose tolerance tests (GTT), and multiplexed-Luminex analysis. A single dose of TZP treatment modestly reduced body weights (~8%) but dramatically decreased blood glucose levels by 57% in HFD-fed mice (86 mg/dl vs. 200 mg/dl before treatment; $p<0.001$). This was due to improved glucose tolerance in TZP-treated mice where area-under-curve of GTT was reduced by 23% compared to Controls (23,295±1,996 vs. 30,311±2,166 mg/dl x min in Controls; $p=0.076$). Plasma insulin levels were markedly lower in TZP-treated mice (2.5±0.7 vs. 6.9±0.8 ng/ml in Controls; $p=0.012$), indicating improved glucose tolerance was due to increased insulin sensitivity, not elevated insulin secretion. This is further supported by a 63% decrease in plasma C-peptide levels in TZP-treated mice (580±213 vs. 1,580±472 pg/ml; $p=0.12$), consistent with a notion that a short-term TZP treatment lowers endogenous insulin secretion secondary to improved insulin sensitivity. Plasma leptin levels were decreased by 47% whereas plasma ghrelin levels were increased by 2.2-fold in TZP-treated mice compared to Controls (8.7±5.2 vs. 16.3±5.5 ng/ml in Controls for leptin; 40±11 vs. 18±14 pg/ml in Controls for ghrelin). Consequently, a two-dose TZP treatment reduced leptin-ghrelin ratio by 93% compared to Controls (0.3±0.1 vs. 3.4±1.7 in Controls; $p=0.065$). Surprisingly, this change did not impact daily food intake as measured by our metabolic cage analysis (1.4±0.6 vs. 1.6±0.4 g in Controls). Overall, once-weekly treatment of TZP for 2 weeks profoundly improved glycemia and insulin sensitivity without significant alterations in body weight and food intake, thought to be a major component of TZP's mechanism of action, in diet-induced obese mice. Additionally, dramatically lowered leptin-ghrelin ratio following a short-term TZP regimen indicates a potential role of neuroendocrine axis in TZP effects on metabolic health. Even in the acute setting, we can conclude that TZP can deliver significant metabolic health benefit without necessarily altering food intake, showcasing its potential for sustainable therapeutic effect.

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