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METABOLISMO E AÇÃO DOS HORMÔNIOS TIREOIDIANOS

65741 LIRAGLUTIDE PROMOTES INTRACELLULAR THYROID HORMONE ACTIVATION AND HAS ADDITIVE EFFECTS TO β3-ADRENERGIC SIGNALING IN INDUCING THERMOGENESIS IN BROWN ADIPOSE TISSUE

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Background: Liraglutide is a long-acting glucagon-like peptide 1 (GLP-1) receptor agonist used as an anti-hyperglycemiant agent in type 2 diabetes and recently approved as an anti-obesity agent. Weight loss is mainly attributed to induction of satiety, but recent studies indicate it may increase energy expenditure by activating brown and beige adipocytes. We therefore aimed to investigate the effects of liraglutide on thermogenic adipocytes in obese mice. **Methods:** Male C57Bl/6 mice with high fat diet-induced obesity were assigned into 4 groups and treated with saline (control), the β3-adrenergic agonist CL316,243, liraglutide or liraglutide and CL316,243. Liraglutide was administered intraperitoneally for 21 days (200 µg/kg, twice daily) and CL316,243 was administered intraperitoneally from day 17 to day 21 (1 mg/kg/d, once daily). WAT (inguinal and epididymal, scWAT and visWAT) and the interscapular brown adipose tissue (iBAT) depots were excised for determination of adiposity, histological analysis, oxygen consumption rates (OCR), type 2 deiodinase (D2) activity and relative expression of Ucp-1, Dio2, Scl16a2 (MCT8), Scl16a10 (MCT10), Thra and Thrb, by RT-qPCR. **Results:** ($p < 0.05$, ~ 6 mice/group): Liraglutide treatment reduced body weight gain, energy intake, caloric efficiency, and WAT mass, when compared with control. In iBAT, liraglutide induced UCP1 protein expression and OCR when compared with saline, and these effects were additive to those of CL316,243. Moreover, liraglutide significantly induced D2 mRNA expression and D2 activity in iBAT, and increased Scl16a2 levels. In scWAT and epiWAT, liraglutide significantly induced the expression of Ucp-1 mRNA levels and UCP1 protein when compared with saline, and the effect on Ucp1 induction was additive to that of CL316,243. In addition, liraglutide enhanced CL316,246-induced increase in OCR and significantly induced Scl16a2 in both WAT depots. **Conclusion:** Our findings suggest that liraglutide induces browning of WAT and increases the thermogenic capacity of WAT and BAT, through a mechanism that may involve increased thyroid hormone activation in BAT. In addition, the effects of liraglutide on Ucp1 expression and oxygen consumption were additive to those of β3-adrenergic signaling, a classical pathway of adaptive thermogenesis activation. This suggests that GLP-1 receptor agonists may increase energy expenditure by activating thermogenic adipocytes, and opens new horizons to treat obesity.