

Does brainstem-derived serotonin mediate GLP-1 receptor agonist-induced suppression of appetite and body weight via 5-HT_{2A} receptors?

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Brain serotonin (5-HT) systems have a critical role in the regulation of appetite and body weight. Central serotonin 5-HT_{2C} receptors contribute to the leptin-independent regulation of appetite [1]. On the other hand, central 5-HT_{2B} and 5-HT_{1A} receptors have implicated in the leptin-dependent regulation of appetite [2]. The recent article by Anderberg *et al.* [3] suggested that brain-derived serotonin is a critical mediator of the weight loss induced by GLP-1 receptor activation, and that central 5-HT_{2A} receptors mediate the chronic anorexic and weight loss effects of central injection of exendin-4 (EX4) or of intraperitoneal injection of liraglutide. We question their results and conclusions.

First, can increases in brainstem-derived 5-HT induce body weight reduction and feeding suppression? Brainstem 5-HT content and TPH2 expression are increased in ob/ob mice compared with wild-type mice [2]. Genetic inhibition of 5-HT synthesis in the brainstem decreases food intake and body weight in ob/ob mice and wild-type mice [2]. In addition, pharmacologic inhibition of 5-HT synthesis in the brainstem induced by treatment with a high dose of p-chlorophenylalanine (PCPA) (500 mg/kg) or trans-2 PCPA decreases body weight and food intake in C57BL/6J mice, db/db mice [4], and high-fat-diet-induced obesity [5]. Thus, depletion of brainstem-derived 5-HT leads to decreases in body weight and energy intake in mice. Moreover, treatment with PCPA for 3 days does not permanently deplete brain-derived 5-HT content and it gradually recovers. It is unclear whether depletion of the brainstem 5-HT content induced by treatment with a low dose of PCPA (100 mg/kg) for 3 days can be sustained for 5 days.

Second, can 5-HT_{2A} receptors mediate body weight reduction and feeding suppression induced by GLP-1 analogs? Previous results of pharmacologic and genetic studies do not provide that central 5-HT_{2A} receptors downregulate food intake and body weight.

Anorexic effects of a 5-HT_{2A} receptor agonist, TCB-2, are only observed at the highest dose, and do not appear to be dose-dependent [6]. Thus, these effects of high-dose TCB-2 might be due to toxic or non-specific effects. 5-HT_{2A} receptor-deficient mice do not exhibit altered body weight and food intake, as the authors described in their discussion [3].

Although the authors showed that the 5-HT_{2A} receptor antagonist reversed the decreases in body weight and food intake induced by EX4 and liraglutide, EX4 suppressed the increased expression of hypothalamic 5-HT_{2A} receptors induced by food restriction [3]. Do GLP-1 analogs increase the expression of hypothalamic 5-HT_{2A} receptors in freely-fed rats?

Moreover, the degree of weight loss induced by EX4 alone in the study using R-96544, a 5-HT_{2A} receptor antagonist, was much greater than that in the study using SB242084, a selective 5-HT_{2C} receptor antagonist (3-fold decrease). This difference leads to significant differences in body weight changes between the EX4 group and 5-HT_{2A} receptor antagonist/EX4 group. The effects of the 5-HT_{2A} receptor antagonist on GLP-1 analogs should be re-examined. Thus, the results and conclusions that brain-derived 5-HT mediates the decreases in body weight and food intake induced by GLP-1 analogs via 5-HT_{2A} receptors are questionable, and further studies are needed to ensure the reliability of the reported findings.

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