

Leptin dysregulation is specifically associated with major depression with atypical features: evidence for a mechanism connecting obesity and depression

Depression and obesity tend to co-occur and have a bi-directional relationship. Shared mechanisms between depression pathophysiology and obesity-related metabolic dysregulations may explain this relationship. In this context, it has been hypothesized that high levels of leptin (the peptide hormone secreted by white adipose tissue that exerts a primary homeostatic function by suppressing nutritional intake and allowing energy expenditure) due to functional resistance in obese persons (a process comparable to insulin resistance in type 2 diabetes) may represent a phenotype risk for depression. Conflicting findings from previous studies may be attributable to depression clinical heterogeneity. In the current study we compared circulating concentrations of leptin across patients with current (N=1062) and remitted (N=711) major depressive disorder (MDD) and healthy controls (N=497) from the Netherlands Study of Depression and Anxiety (NESDA). Moreover, we examined whether the relationship between leptin and MDD differed across two common clinical subtypes, typical and atypical. Finally, we explored whether leptin was associated with specific depressive symptoms. Higher leptin was associated, as compared to controls, with the atypical MDD subtype both for remitted and current cases. This association was stronger for increasing adiposity levels, strengthening the hypothesis of the involvement of leptin resistance. No association with leptin was found for overall MDD or the typical subtype. Among currently depressed patients, higher leptin was associated with key symptoms identifying the atypical subtype, such as hyperphagia, increased weight, and leaden paralysis. Leptin dysregulation (resistance) may represent an underlying mechanism connecting obesity and MDD with atypical features. Development of treatment effectively targeting leptin resistance may benefit patients with atypical depression characterized by obesity-related metabolic alterations.