Gut feelings about depression

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The perspective that eating and obesity are linked to depressive disorders has gained considerable purchase, in part, because of the attention devoted to obesity in general, the finding that obesity is accompanied by a 25% increase of anxiety and depressive disorders, and because of reports linking obesity and depression to heart disease[1] as well as other conditions that involve inflammatory factors.[2] There has long been the view that some individuals use food consumption, particularly comfort foods high in carbohydrates and fat, as a method of coping with or diminishing stressor-induced negative emotions. Yet another link between eating and depressive disorders and comorbid anxiety has come from the findings that pharmacological treatments to reduce anxiety (e.g., benzodiazepines) have the propensity to increase eating and that agents that reduce eating (e.g., neuromedin B, gastrin-releasing peptide, corticotropin-releasing hormone) promote anxiety.[3] In light of such findings, there has been interest in determining whether key hormones associated with eating processes might also contribute to anxiety and depressive disorders and potentially serve as targets in the treatments of depression or as potential biomarkers for illness subtypes.[4] We suggest that several hormones act additively or interactively in determining eating responses to stressors as well as depressive mood and that these hormones, or the genes associated with them, can serve as biomarkers and potential therapeutic targets in the treatment of depressive disorders.

Besides being a fundamental player in eating processes and in hypothalamic regulation of energy balance, the adipose-derived hormone leptin had been implicated in the etiology of mood disorders.[5,6] Obesity and metabolic syndrome, and the mechanisms underlying these processes, have been linked to depression and comorbid heart disease through the release of cytokines, such as leptin, from adipose tissue. Indeed, in humans, the onset of depression was associated with a combination of high leptin levels coupled with high visceral fat,[7] and the link between leptin levels and severity of depressive symptoms was mediated by adiposity.[8] Likewise, resistance to antidepressant treatment in humans was elevated in the presence of a polymorphism in the leptin gene (*LEP*).[9] It was suggested that leptin might influence depression by acting on leptin receptors present on serotonin neurons within the raphe nuclei and dopamine neurons of the ventral tegmentum (VTA)[10] and, thus, might influence reward processes.[11] Consistent with this supposition, when leptin receptors in the rat hippocampus were genetically deleted, a stressor-induced depressive profile was apparent,[12] and deletion of leptin receptors on midbrain dopamine neurons in mice elicited elevated anxiety.[13] As impressive as these findings were, however, data from clinical studies linking leptin to depression have been inconsistent.[6] A resolution for the diverse findings seemed to be in the offing with reports that atypical depression, characterized by increased eating and other neurovegetative symptoms, was accompanied by elevated serum leptin levels, whereas this did not occur in nonatypical depression,[14] although these findings were countered by the report that elevated circulating leptin levels were present in both melancholia and atypical depression.[15]

Although several factors could potentially account for some of the divergent findings that have been reported, key among these is that like most complex behavioural disturbances, it is unlikely that the link between eating/energy processes and comorbid depression are limited to the actions of leptin. The gut peptide ghrelin also plays a fundamental role in eating and energy regulation, acting in a fashion opposite to that of leptin; although it has not received the attention that leptin has, there have been indications that ghrelin functioning might contribute to depressive illness.[5] Like leptin, ghrelin receptors have been reported in the VTA and the dorsal raphe nucleus[16] and have been associated with reward processes[17] as well as stressor-induced depressive-like symptoms, such as anhedonia.[18] Moreover, it seems that ghrelin may be neuroprotective[19] and may increase neurogenesis in the hippocampus, and drugs that increase neurogenesis make ghrelin receptor knockout mice more resilient to social defeat.[20] In line with a role for ghrelin in stressor-elicited depression,

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negative events promote an increase of circulating ghrelin levels,[21] and in emotionally reactive individuals the normalization of ghrelin levels after stress may be attenuated.[22] Moreover, ghrelin was elevated among depressed patients and declined following pharmacotherapy,[23] and among patients who did not respond to treatment, ghrelin levels were higher than among patients who responded positively.[24]

While not discounting a role for leptin in the provocation or maintenance of depressive disorders, it may be propitious to consider that as it acts in synchrony with ghrelin in relation to eating, energy processes, obesity and metabolic disorders, these hormones might similarly operate in tandem in relation to depressive illnesses. Together, these peptides might underlie the neurovegetative features that differentiate typical and atypical depression. In this regard, interleukin-6 (IL-6), a cytokine that frequently accompanies changes of leptin, is differentially expressed in typical and atypical depression.[25] As well, with stressor-induced obesity, IL-6 increases markedly along with leptin, but this outcome is not apparent in mice with the ghrelin receptor deleted,[5] pointing to the coordination that exists between these systems. Beyond these neurovegetative features, it seems that ghrelin and leptin, by virtue of their effects on dopamine-mediated reward processes,[10,11] might also contribute to the anhedonia characteristic of depressive disorders.

Identifying the linkages between eating-related hormones and the occurrence of depressive disorders is difficult. In particular, it is hardly likely that these hormones act alone in promoting mood disorders, and thus studies that are limited to assessment of plasma leptin or ghrelin might not offer a sufficiently broad perspective of processes associated with depressive disorders. By example, other hormones that affect eating and energy regulation, including bombesin and glucagon-like peptide-1 (GLP-1), the latter also affecting glucose regulation in type 2 diabetes, have also been implicated in mood disorders.[3,26] At the moment, the causal link between depressive disorders and obesity, and the peptides associated with energy balance, is still uncertain, as they could be etiologically involved in depressive disorders or simply be markers of illness. Ultimately, prospective studies assessing specific attributes of the depressive and metabolic profiles will be needed to clarify the nature of the associations. Assuming that a causal connection exists between these hormones and depressive disorders, or specific symptoms or subtypes of these disorders, ghrelin or leptin may serve as targets for adjunctive treatments to diminish the symptoms of illness. At the same time, as in the case of psychoactive drugs, it is possible that treating depression through ghrelin manipulations may promote metabolic alterations that could potentially favour obesity. Nevertheless, low doses of analogues of ghrelin or of leptin antagonists could be used to complement the effects of other antidepressant treatments. Finally, it ought to be considered that inflammatory and anti-inflammatory factors, such as leptin and ghrelin, respectively, may play a fundamental role in mediating syndromes comorbid with depression, including obesity, immune-related disorders, cardiovascular disease and neurodegenerative disorders,[27] making it that much more important to determine the associations between these metabolic hormones and the emergence of stressor-related pathologies.

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