COMMENTARY

Ghrelin in Addictive Behaviors: Plenus Venter Non Studet Libenter

Falk Kiefer

The medieval proverb that a full stomach does not like to "study" ("studere" in its original sense—directing one’s efforts or attention to something, or striving after it) may be useful in understanding the work of Leggio et al. published in this issue of Biological Psychiatry (1). It is a fundamental human experience that one’s motivation to pursue—or strive for—stimulation is attenuated during a state of satiety. Fullness, laggardness, and phlegm are associated with a full belly. So what does that mean for addiction research?

People consume food not only in response to an intrinsic sensation of hunger (that ensures energy homeostasis) but also as a result of neuronal processes influenced by the rewarding and positively reinforcing features of food. This "exostatic system" modulates the motivation to ingest food using information on food’s hedonic properties; this information is based on earlier experiences with food and expectations that develop within the context in which food is encountered. This motivation is due to the fact that food, similar to addictive substances, activates the mesolimbic reward system and causes a short-term increase of dopamine in the nucleus accumbens, which acts as a “signature” of reinforcement and reward expectation (2).

However, more recent data suggest that both of these systems —the "endostatic" energy-homeostatic system of the lateral hypothalamus and the motivational, mesolimbic reward system —may operate in dynamic interplay with each other (3). According to these data, the rewarding value of food is reduced in a state of satiety (positive energy balance) and increased in a state of hunger (negative energy balance); this would have evolutionary benefits. The less food is available in the environment (and the hungrier one feels), the more attention is directed to food—signaling stimuli and calorific reinforcers.

There is good evidence that this interplay is mediated at least partly by appetite-regulating peptides such as leptin, orexin, and ghrelin. Receptors of these hormones have been detected in the ventral tegmental area of the midbrain (VTA), where they modulate the activity of dopaminergic neurons projecting to the nucleus accumbens (4). Assuming that these hormones modulate mesolimbic reactivity, is this the case in response only to food cues (5)? Or do these hormones modulate mesolimbic reactivity in response to reward-associated cues in general (including cue related to drugs and alcohol)?

The first study to associate an appetite-regulating peptide with alcohol craving was published in 2001 in Biological Psychiatry (6). This study found leptin to be associated with alcohol craving. Studies on other appetite-regulating signals and their effects on mesolimbic pathways in addictive disorders extended these findings. Taken together, these studies constitute a growing body of evidence suggesting that factors that increase the activity of VTA dopaminergic neurons (or a resistance to factors that reduce such activity, such as leptin) also increase cue reactivity and craving, whereas factors attenuating VTA dopaminergic activity have the opposite effect, attenuating drug cue reactivity and craving (Figure 1).

One of the stimulating factors is ghrelin, a hormone of the gastric fundus to signal a low filling level (7). Ghrelin increases appetite, food intake, and weight gain. Ghrelin receptors have been detected in dopaminergic neurons of the VTA; local administration into the VTA of mice has been shown to increase both locomotor activity and extracellular concentration of dopamine in the nucleus accumbens. Ghrelin receptor antagonism has been shown to suppress intake of rewarding food and to decrease alcohol consumption in mice. Ghrelin knockout mice demonstrate decreased voluntary alcohol intake and reduced ethanol-induced conditioned place preference (8). In humans, the plasma concentration of activated ghrelin was found to be positively associated with alcohol craving in alcohol-dependent subjects during withdrawal from alcohol (9).

Against this background, the present article by Leggio et al. (1) supports and extends our appreciation of the impact of peripherally administered—or released—ghrelin in alcohol-dependent subjects with regard to cue-induced alcohol craving. Using a double-blind human laboratory design, the authors studied heavily drinking alcohol-dependent subjects during cue exposure to alcohol versus neutral stimuli after placebo-controlled administration of ghrelin. Their main result is that administering 3 μg/kg of ghrelin increased subjects’ alcohol craving markedly in response to alcohol cues compared with placebo.

With this finding, Leggio et al. go beyond the aforementioned preclinical and clinical data by showing 1) effects of ghrelin on alcohol craving in the specific context of cue-induced alcohol craving, supporting strongly the involvement of mesolimbic pathways dedicated to reward prediction; 2) that this effect can be achieved by administering ghrelin peripherally (imitating the hormonal signal of the cells of the gastric fundus), supporting the hypothesis that ghrelin has an immediate central effect (currently a controversial issue) (10); and 3) that targeting ghrelin receptor antagonism in alcoholism treatment could help reduce cue-induced craving and relapse. It is not surprising that this study did not find ghrelin to affect food craving because ghrelin, as discussed earlier, is expected to increase food craving by increasing mesolimbic reactivity to food cues. However, the study by Leggio et al. was not designed to test the effects of ghrelin on food craving, which should be tested in a study on food-cue reactivity.

This study sheds light on the interrelatedness of alcohol and food craving, which may be relevant for future cue-reactivity studies in addictive disorders. In particular, cue-exposure studies focusing on alcohol or drug cues should control for a patient’s state of hunger (or satiety) during cue exposure. Future studies should test to what extent both reactivity to drug cues and cue-induced craving are modulated by factors associated with energy...
balance, including ghrelin. However, the authors’ suggestion that ghrelin might serve as a novel biomarker for craving might be challenged. A factor such as ghrelin, which modulates the amplitude of cue reactivity and cue-induced craving in concert with other factors, may not be a marker for craving itself.

In conclusion, this important study supports the general idea that ghrelin’s central effects go beyond the endostatic regulation of energy homeostasis, also involving pathways underlying reward expectation and conditioned response to alcohol-related stimuli. Physiologic factors modulating the reactivity of mesolimbic pathways represent an important research topic for developing pharmacologic treatments for disorders characterized by altered reward-related behaviors, such as substance use disorders and behavioral addictions.

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