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**“Altered glucose sensitivity of lateral hypothalamic orexin
glucose-inhibited neurons contributes to the inability to
maintain body weight after weight loss”**

By

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ABSTRACT

One of the major problems of obesity treatment is long-term weight loss maintenance. Long-term body weight loss maintenance is successful in fewer than 20% of individuals. This is important since maintenance of even a 10% body weight loss significantly improves cardiovascular health. The difficulty with weight loss maintenance suggests that there are physiological mechanisms driving weight regain. Fasting and diet restriction activate brain regions involved in feeding that is both homeostatic (e.g., response to metabolic need) and non-homeostatic (hedonistic). Homeostatic and non-homeostatic feeding are not mutually exclusive. For example, the metabolically sensitive lateral hypothalamic area (LHA) orexin neurons drive hedonic or “reward-based” feeding since they activate the ventral tegmental area (VTA) dopamine (DA) neurons which stimulate reward-based feeding. LHA orexin neurons are inhibited by glucose (GI neurons). The “hunger” hormone ghrelin directly enhances the activation of orexin-GI neurons in low glucose while the “satiety” hormone leptin does the converse via modulation of upstream neurons. Low glucose persistently increases orexin-dependent excitatory glutamate signaling onto VTA DA neurons. A 24-hr fast (high ghrelin/low leptin) also increases activation of LHA orexin-GI neurons in low glucose and enhances glutamate transmission on VTA DA neurons. Importantly, we showed that increasing LHA glucose in weight restricted animals blunts motivation for food reward. These data suggest that diet-restriction induced changes in the glucose sensitivity of orexin neurons may be a mechanism underlying an inability to maintain weight loss. Based on these data, we hypothesize that ***“the hormonal changes associated with diet restriction and weight loss drive reward-based feeding by regulating the glucose sensitivity of orexin-GI neurons.”***

In testing this hypothesis, we found that low glucose activates the orexin-GI neurons through a G-protein coupled receptor (GPCR) linked to adenylate cyclase-cyclic AMP-protein kinase-A (AC-cAMP-PKA) signaling pathway. We also found that ghrelin converges on the same signaling pathway in a way that it amplifies low glucose signaling on these neurons. Next, we found that diet restriction and weight loss maintenance increased the sensitivity of these neurons to low glucose. Furthermore, we found that diet restriction led to long-term changes in VTA DA neurons as evident from induction of synaptic plasticity on VTA DA neurons. We then determined whether these long-term changes were orexin dependent using cre-dependent designer receptors exclusively activated by designer drugs (DREADDs) which expressed the inhibitory G protein, hM4Di, in orexin-cre mice. As we hypothesized, inhibition of orexin neurons inhibited the induction of synaptic plasticity. Diet restriction also led to an increase in reward-based feeding behavior which was similarly found to be orexin-dependent. Thus, these results demonstrate that diet restriction and weight loss maintenance lead to altered glucose sensitivity of orexin-GI neurons in a way that these neurons are activated by smaller changes in glucose decreases. This altered glucose sensitivity might be leading to long-term changes in VTA DA neurons and an increase in reward-based feeding behavior. This might be one of the mechanisms underlying an inability to maintain long-term weight loss. The results from my thesis will lead to a better understanding of the mechanisms underlying an inability to maintain weight loss after diet restriction. Thus, these data might contribute to developing potential targets for successful long-term weight loss maintenance.