The Impact of Glucagon-Like Peptide-1 on the Brain-Reward System and Beyond

Akademisk avhandling

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av
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This thesis is based on the following original studies:

I. **The glucagon-like peptide 1 (GLP-1) analogue, exendin-4, decreases the rewarding value of food: a new role for mesolimbic GLP-1 receptors.**
Dickson SL, Shirazi RH, Hansson C, Bergquist F, Nissbrandt H, Skibicka KP. *Journal of Neuroscience. 2012 Apr.*

II. **Dopamine signaling in the amygdala, increased by food ingestion and GLP-1, regulates feeding behavior.**
Anderberg RH, Anefors C, Bergquist F, Nissbrandt H, Skibicka KP. *Physiology of Behavior. 2014 Sep. Epub 2014 Feb 21.*

III. **Gut peptide GLP-1 and its analogue, Exendin-4, decrease alcohol intake and reward.**
Shirazi RH, Dickson SL, Skibicka KP. *PLoS One. 2013 Apr.*

IV. **Glucagon-like peptide 1 receptor induced suppression of food intake, and body weight is mediated by central IL-1 and IL-6.**
Shirazi R, Palsdottir V, Collander J, Anesten F, Vogel H, Langlet F, Jaschke A, Schürmann A, Prévot V, Shao R, Jansson JO, Skibicka KP.
Proc Natl Acad Sci U S A. 2013 Oct.

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ABSTRACT

Glucagon-like peptide-1 (GLP-1), produced in the intestine and the brain, regulates food intake and glucose metabolism. A GLP-1 based treatment is already approved for clinical use in type 2 diabetes patients, and recently in obese patients. GLP-1 fibers also form a circuitry in the brain ascending from the hindbrain, mainly nucleus of solitary tract (NTS), to the key nodes of the mesolimbic reward system (including ventral tegmental area, VTA, and the nucleus accumbens, NAc). The GLP-1 receptor is also expressed in the VTA, NAc, and amygdala. The aim of this thesis was: 1) to investigate the impact of GLP-1 on the food/alcohol oriented behavior, 2) to identify the neuroanatomical substrate underlying the effect of GLP-1 on reward behavior.

Our results demonstrated that GLP-1 and its clinically approved analogue, exendin 4, suppressed the rewarding value of food and alcohol. GLP-1R activation in the VTA was sufficient for this effect. Amygdala has long been implicated in emotional processing, learning and memory but less attention has been given to its role in feeding behavior. Dopamine is a neurotransmitter implicated in reward and motivated behavior. Our results revealed that GLP-1R stimulation elevated the level of dopamine metabolites and dopamine turnover in amygdala. These changes were also associated with a reduction in sucrose-driven food-reward behavior. A potential link between GLP-1 and cytokine signaling outside of the CNS has recently been suggested by a study showing an increase in GLP-1 production and secretion in response to elevated interleukin-6 in the blood. However, the relationship between GLP-1 and central cytokines remained unexplored. To determine if there is an interaction between GLP-1 and interleukin-6 (IL-6) and interleukin-1β (IL-1β) at the level of the CNS, we used both pharmacologic and non-pharmacologic (transgenic mice) models of signaling blockade for both of these cytokines. Our results indicated that IL-6 and IL-1β are mediators of GLP-1 anti-obesity effect. Collectively this thesis revealed a potent impact of GLP-1 and its stable analogues on food and alcohol reward behavior and identified the neurocircuitry and neurochemical mediators involved. Furthermore a surprising link, relevant for the anorexic and weight loss effects of GLP-1, between GLP-1 and cytokines was discovered. Considering that GLP-1 analogues are approved for clinical use, these findings may be of considerable clinical significance.

Keywords: GLP-1, VTA, Dopamine, reward, alcohol, food intake, IL-6, IL-1β

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