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REGULATION OF THE MESOLIMBIC DOPAMINE CIRCUIT BY FEEDING PEPTIDES

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Abstract—Polypeptides produced in the gastrointestinal tract, stomach, adipocytes, pancreas and brain that influence food intake are referred to as 'feeding-related' peptides. Most peptides that influence feeding exert an inhibitory effect (anorexigenic peptides). In contrast, only a few exert a stimulating effect (orexigenic peptides), such as ghrelin. Homeostatic feeding refers to when food consumed matches energy deficits. However, in western society where access to palatable energy-dense food is nearly unlimited, food is mostly consumed for non-homeostatic reasons. Emerging evidence implicates the mesocorticolimbic circuitry, including dopamine neurons of the ventral tegmental area (VTA), as a key substrate for non-homeostatic feeding. VTA dopamine neurons encode cues that predict rewards and phasic release of dopamine in the ventral striatum motivates animals to forage for food. To elucidate how feeding-related peptides regulate reward pathways is of importance to reveal the mechanisms underlying non-homeostatic or hedonic feeding. Here, we review the current knowledge of how anorexigenic peptides and orexigenic peptides act within the VTA.

Key words: feeding peptides, ventral tegmental area, dopamine, anorectic, orexigenic, ingestive behavior.

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Abbreviations: α-MSH, α-Melanocyte-stimulating hormone; AgRP, Agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; CCK, cholecystokinin; CGRP, calcitonin gene-related peptide; CPP, conditioned place preference; CRF, corticotropin-releasing factor; DAT, dopamine transporter; DAMGO, [D-Ala2, N-MePhe4, Gly-ol]-enkephalin; DPDPE, [D-Pen^{2,5}]Enkephalin, [D-Pen^{2},D-Pen^{5}]Enkephalin; FSCV, fast-scan cyclic voltammetry; GHSR, growth hormone secretagogue receptor; GLP-1, glucagon-like peptide 1; icv, intracerebroventricular; ip, intraperitoneal; iv, intravenous; KO, knockout; LDTg, lateral dorsal tegmentum; LepRb, long-form signaling receptors; LTD, Long-term depression; MCH, melanin-concentrating hormone; MTII, (Ac-Nle4, Asp5, DPhe7, Lys10)-Cyclo-a-MSH (4-10) amide; NAc, nucleus accumbens; NMDA, N-methyl-D-aspartate; NPY, neuropeptide Y; NTS, nucleus tractus solitarius; OLETF, otsuka long-evans Tokushima fatty; PI3K, phosphoinsitol 3 kinase; PLC, phospholipase C; PVT, paraventricular thalamic nucleus; sCT, salmon calcitonin; TH, tyrosine hydroxylase; VTA, ventral tegmental area.

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INTRODUCTION

Confucius said, ''The desire for food is a part of human nature''. Desire is elicited by the enjoyment or thoughts of the wanted item, such that individuals will take action to obtain their goal. In an environment rich in easily accessible palatable foods, the signals to eat or to stop

eating are very complex and extend beyond the control of the homeostatic system that responds to metabolic and satiety signals from the gut. A current theory is that the brain's mesolimbic dopaminergic system responds to the sight, smell and taste of food in addition to cues that predict food and overrides homeostatic, metabolism-driven food intake to promote ingestive behavior (Palmiter, 2007). Dopamine neurons originating in the ventral tegmental area (VTA) send projections to forebrain regions including the nucleus accumbens (NAc) and the prefrontal cortex (PFC). Mesolimbic dopamine neurons reinforce learning of cues that predict reward (Schultz et al., 1997) and can engage animals in effortful behavior to obtain them (Salamone and Correa, 2012).

The role of dopamine promoting ingestive behavior was originally described using 6-hydroxydopamine (6-OHDA) lesions into the lateral hypothalamus of midbrain dopamine neurons (Ungerstedt, 1971; Fibiger et al., 1973). Later studies developed this concept by demonstrating that transgenic dopamine-deficient mice do not engage in goal-directed motivated behavior and do not eat or drink (Zhou and Palmiter, 1995). Paradoxically, stimulant agents that increase dopamine concentration, such as amphetamine or cocaine, are typically anorectic (Booth, 1968; Balopole et al., 1979; Bedford et al., 1980) likely due to increased locomotor activity and an increase in hypothalamic norepinephrine levels, both of which are known to decrease food intake (Booth, 1968; Hoebel et al., 1989). Dopaminergic neurons are not required for the motoric action of food intake, as upon startle, or when placed in water, animals will engage in feeding behavior (Zhou and Palmiter, 1995). Therefore, dopamine neurons appear to be critical for the reinforcement and/or salience of food-related cues and motivation to obtain food.

The motivation to eat is regulated by a variety of intrinsic and extrinsic factors. Metabolic signals, including neuronal or circulating peptides released in response to internal states, such as hunger or satiety, can promote or inhibit food intake respectively. Dopamine transmission may provide one mechanism that bridges internal states with motivated behavior as the peptides that govern these internal states can also exert their effects on feeding via dopaminergic mechanisms (Wilson et al., 1995). Therefore, examination of brain areas, such as the VTA, that are implicated in the salience and motivation for rewards is necessary for better understanding the neurobiology of ingestive behavior. In this review, we outline the evidence for receptors and signaling of feeding-related peptides within the VTA and characterize the effects of feeding-related peptides on VTA dopamine neuronal excitability, synaptic transmission, modulation of dopamine concentration as well as behavioral outputs. Important variables that can influence how peptides modulate the mesolimbic circuit include the diet the animals are fed (chow vs. high fat), the satiety state of the animal (fed or fasted), the metabolic state of the animal (lean or obese) and how activity of the mesolimbic circuit is assayed (multiple methods of detection of dopamine concentration, electrophysiological or biochemical measurements of cellular activity). Therefore, we have highlighted these factors throughout the review and in the tables (see Table 1).

Table 1. Effects of intra-VTA feeding peptides on ingestive behaviors

Peptide	Behavioral effects	Mode of administration/concentration	References
Anorexigenic			
Insulin	Decreased food intake for 24 h	Intra-VTA 0.005–5 mU/side	Bruijnzeel et al. (2011)
	Elevated brain reward thresholds	Intra-VTA 0.005 mU/side	Bruijnzeel et al. (2011)
	Reduced sucrose preference; attenuated cocaine-induced locomotor activity under food-restricted conditions	Insulin receptor KO in TH-expressing neurons	Könner et al. (2011)
	Reduced sated high-fat feeding	Intra-VTA 0.3 μg/side	Mebel et al. (2012)
	Inhibited CPP for food	Intra-VTA 63 nmol or 2 μmol	Labouèbe et al. (2013)
	Reduced food anticipatory behaviors	Intra-VTA 5 mU/side	Labouèbe et al. (2013)
Leptin	Decreased food intake (72 h) and body weight (48 h)	Intra-VTA 15–500 ng/side	Bruijnzeel et al. (2011, 2013)
	Elevated brain reward thresholds	Intra-VTA 15 ng/side	Bruijnzeel et al. (2011)
	Suppressed hyperactivity in an animal model for anorexia nervosa	Intra-VTA 0.1–1 μg/side	Verhagen et al. (2011)
	Increased food intake, locomotor activity, and sensitivity to highly palatable food	Selective leptin receptor knockdown by RNAi in the VTA	Hommel et al. (2006)
	Augmented progressive ratio responding for sucrose	Selective leptin receptor knockdown by RNAi in the VTA	Davis et al. (2011a,b)
	Elevated anxiogenic-like behaviors	Selective deletion of leptin receptor in dopamine neurons	Liu et al. (2011)
	Tempered high fat-induced obesity	Leptin over expression in VTA	Scarpace et al. (2013)
Glucagon (GLP-1 or Exendin-4)	Suppressed progressive ratio operant responding for food	Intra-VTA 0.03–0.1 μg exendin-4	Dickson et al. (2012)
	Reduced the reinforcing properties of cocaine or alcohol	Intra-VTA: 0.1 μg exendin-4 or 1.0 μg GLP-1	Shirazi et al. (2013), Egecioglu et al. (2013)