Review

Feelings about food: the ventral tegmental area in food reward and emotional eating

Frank J. Meye[1,2,3] and Roger A.H. Adan[4]

[1] Institut du Fer à Moulin, Paris, France
[2] Inserm, UMR-S839, Paris, France
[3] Université Pierre et Marie Curie 75005 Paris, France
[4] Brain Center Rudolf Magnus Department of Translational Neuroscience, University Medical Center Utrecht, Universiteitsweg 100, 3584 CG Utrecht, The Netherlands

Overconsumption of high caloric food plays an important role in the etiology of obesity. Several factors drive such hedonic feeding. High caloric food is often palatable. In addition, when an individual is sated, stress and food-related cues can serve as potent feeding triggers. A better understanding of the neurobiological underpinnings of food palatability and environmentally triggered overconsumption would aid the development of new treatment strategies. In the current review we address the pivotal role of the mesolimbic dopamine reward system in the drive towards high caloric palatable food and its relation to stress- and cue-induced feeding. We also discuss how this system may be affected by both established and potential anti-obesity drug targets.

Drivers of hedonic feeding

Feeding helps maintain energy balance, but is also pleasurable, especially when it concerns high caloric food. 'Hedonic' feeding occurs when a sated individual consumes food mainly because of its palatability (meaning it is a tasty reward), rather than for nutritional need. This behavior can be triggered by environmental factors such as food cues (e.g., advertisements) or by stressors that lead to negative emotions (i.e., stress-eating). In healthy individuals, emotions and food cues are triggers for initiation of feeding, but this is especially so in obese individuals [1,2]. Therefore, a better understanding of the neural networks that encode the drive to overeat is required for adequate obesity treatment. In the current review we describe the extensive role of the ventral tegmental area (VTA) in hedonic feeding. The VTA is an integrator of peripheral, hypothalamic, mid/hindbrain, limbic, and cortical information [3]. Functionally it encodes motivation for palatable food, and stress- and cue-induced feeding. These three factors, mediated by distinct, but partly overlapping neural circuits in which the VTA is embedded, contribute to the difficulty of an individual to adequately limit food intake.

Energy balance and reinforcing properties of food

The midbrain dopamine system consists of subpopulations of dopamine neurons, each playing specific roles. Dopamine neurons in the substantia nigra have been implicated in motor control and project to the (dorsal) striatum. More medial in the VTA, a subgroup of heterogeneous dopamine neurons are implicated in motivation, reward, and aversion and project to the nucleus accumbens (NAc), ventral pallidum (VP), prefrontal cortex (PFC), amygdala, and hippocampus [4].

Although the VTA also has GABAergic and glutamatergic projections [5–7], the most studied output in relation to feeding is dopamine. Dopamine signaling does not mediate the pleasurable sensation of food *per se* [8]; instead, it is especially involved in the expenditure of effort to obtain desired food, as well as in the detection of unexpected food reward and its coupling to predictive cues [8–12]. We now further address how different inputs and transmitter systems in the mesolimbic dopamine systems can encode information pertaining to some of these facets.

Signals from the gastrointestinal tract act on the VTA

The VTA receives direct information from the gastrointestinal tract (Figure 1). Most notable, the stomach peptide ghrelin acts on the VTA, where ghrelin receptors (GHSRs) are expressed both on dopamine and non-dopamine neurons [13,14]. Ghrelin directly increases the firing rate of dopamine neurons in the VTA in a GHSR-dependent manner [13] and leads to elevated dopamine levels in the NAc [15]. Ghrelin also elevates cholinergic input from the laterodorsal tegmental nucleus (LTDg) to the VTA [15], presumably to dopamine neurons that project to the NAc shell [16]. This ghrelin-modulated LDTg input is indeed important for ghrelin-induced accumbal dopamine release.

Ghrelin signaling in the VTA increases intake of palatable food (peanut butter) more than chow in sated animals [17], but also enhances motivation for lever presses for palatable sucrose [18]. Interestingly, the effects of intra-VTA ghrelin on chow intake and motivation for sucrose

Corresponding author: Adan, R.A.H. (r.a.h.adan@umcutrecht.nl).

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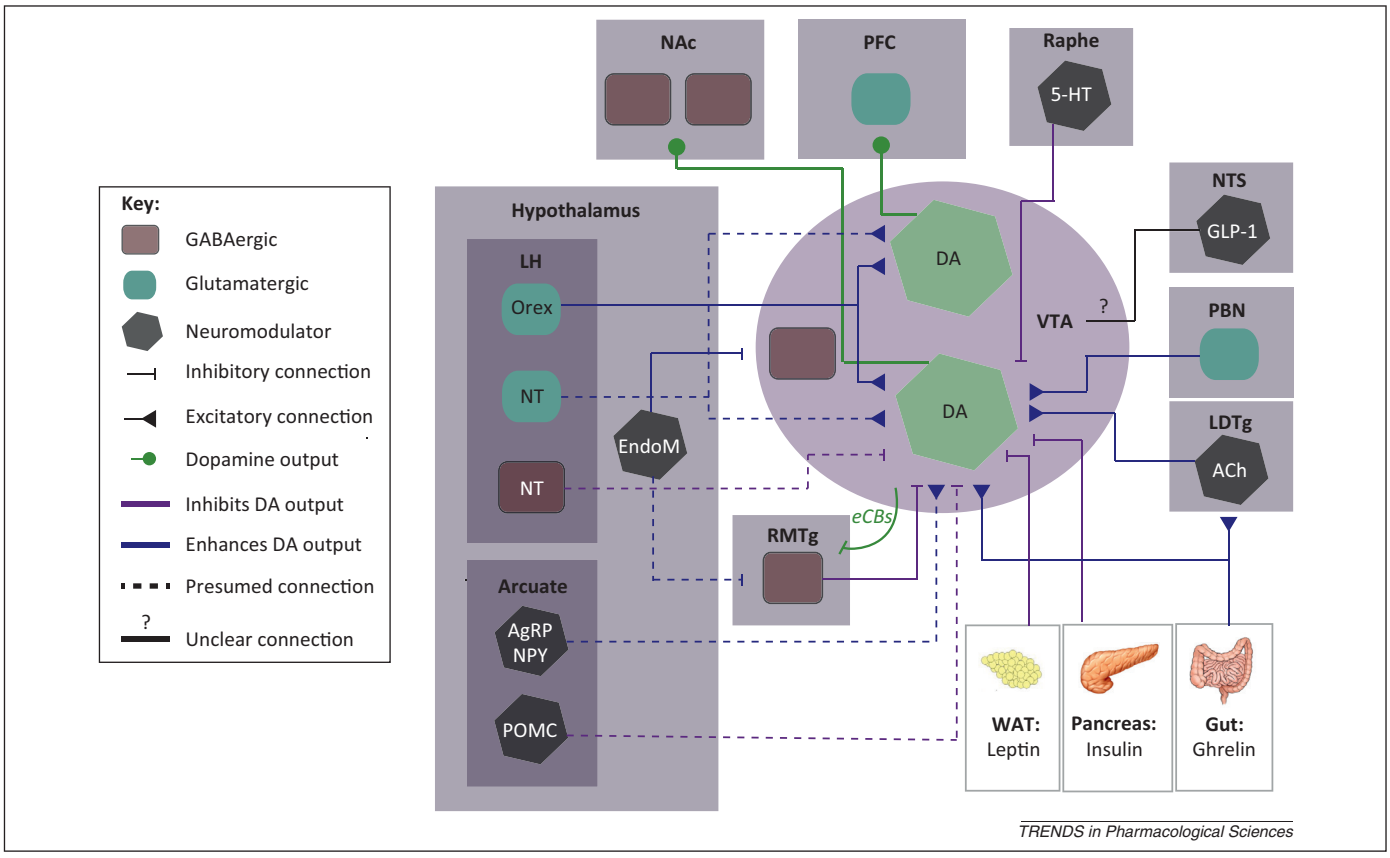

Figure 1. Encoding of drive for palatable food by the mesolimbic dopamine system. Different subsets of ventral tegmental area (VTA) neurons receive multiple inputs that allow it to encode motivation for palatable food. Information on energy balance comes from white adipose tissue (WAT), the pancreas, and the gut. From the lateral hypothalamus (LH) orexin and neurotensin (NT) are sent, and from the arcuate nucleus, presumably agouti-related peptide (AgRP), neuropeptide Y (NPY), and melanocortins (MCs) from proopiomelanocortin (POMC) neurons. Endomorphin (EndoM) comes from other hypothalamic regions. In the mid/hindbrain, the nucleus of tractus solitarius (NTS) provides glucagon-like peptide 1 (GLP-1). Signals also arise from the parabrachial nucleus (PBN), the raphe nuclei, and the rostromedial (RMTg) and laterodorsal tegmentum (LDTg), the latter also releases acetylcholine (ACh). Main output from the VTA (green) includes projections to the nucleus accumbens (NAc) and prefrontal cortex (PFC), and local release of endocannabinoids (eCBs). For clarity, not all connections between nuclei are shown, only those directly impacting on the VTA and currently considered to be involved in (food) reward processes.

have different underlying mechanisms. The enhanced motivation for sucrose requires both opioid signaling in the VTA, and D1 and D2 receptor dopamine signaling in the NAc [19,20]. By contrast, the increased chow intake requires neither opioids in the VTA nor dopamine in the NAc [19,20]. This difference potentially reflects an important distinction between effort-based intake of (palatable) food and intake of freely available (non-palatable) food [21].

Energy supply signals act on the VTA to regulate palatable feeding

The VTA may be sensitive to alterations in available bodily energy stores. A key mediator in this process is leptin, an adipocytokine that becomes elevated with more stored white adipose tissue (and thus more stored energy), and which suppresses hunger in part by acting on hypothalamic circuitry [22]. However, leptin receptors (LepRs) are also expressed on VTA dopaminergic and GABAergic neurons [23,24]. Leptin directly hyperpolarizes VTA dopamine neurons and decreases their neuronal firing frequency both in slices and *in vivo* [24,25]. Moreover, leptin suppresses glutamatergic input onto VTA dopamine neurons [26]. LepR-containing VTA dopamine neurons have been shown to project to the central amygdala (CeA) [27]. However, LepRs, presumably those in the VTA, also play an important role in regulating dopamine levels in the NAc and have also been suggested to project there [28]. Functionally, leptin suppresses the incentive value of food and other rewards [29,30]. Infusions of leptin into the VTA suppresses food intake [24,31]. Contrarily, LepR knockdown in the VTA results in increased intake of novel palatable foods, such as sucrose and high-fat chow [24]. Interestingly, selective removal of LepRs from dopamine neurons does not affect body weight or intake of either chow or palatable food. Instead, it results in increased anxiety levels due to enhanced dopamine signaling at D1 receptors (D1Rs) in the CeA [32]. Overall, these findings suggest that the effects of leptin on food intake that involve the VTA are potentially mediated by indirect action on the dopamine system. Instead, direct action of leptin on VTA dopamine neurons is likely to reduce anxiety levels.

The VTA also contains insulin receptors [23]. Insulin mildly increases the firing rate of half of the dopamine neurons in the midbrain [33]. Systemic insulin administration enhances dopamine release in the NAc [128]. However, insulin in the VTA reduces local dopamine release within the VTA itself by increasing the activity of the dopamine transporter [34]. Insulin signaling in the VTA reduces the drive for induced intake of palatable food [34,35]. Insulin receptors in the dopamine system may