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Advances in the neurobiological bases for food 'liking' versus 'wanting'

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HIGHLIGHTS

- We describe the anatomical localization of three "hedonic hotspots".
- A description of how the hotspots functionally interact
- A proposed hedonic circuit that unites the hotspots

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ABSTRACT

The neural basis of food sensory pleasure has become an increasingly studied topic in neuroscience and psychology. Progress has been aided by the discovery of localized brain subregions called hedonic hotspots in the early 2000s, which are able to causally amplify positive affective reactions to palatable tastes ('liking') in response to particular neurochemical or neurobiological stimulations. Those hedonic mechanisms are at least partly distinct from larger mesocorticolimbic circuitry that generates the incentive motivation to eat ('wanting'). In this review, we aim to describe findings on these brain hedonic hotspots, especially in the nucleus accumbens and ventral pallidum, and discuss their role in generating food pleasure and appetite.

1. Introduction

Over the last 15 years, research has yielded several unexpected findings on how hedonic circuitry in the brain interacts with food to produce reward and appetite. Evidence now suggests that discrete, anatomically localized "hedonic hotspots" exist in limbic-related brain structures, and are able to magnify the hedonic impact of natural sensory rewards, such as sweet tastes. So far, these hotspots have been found in the forebrain nucleus accumbens (particularly in medial shell), ventral pallidum, and in the brainstem parabrachial nucleus. In this review, we will discuss where these hotspots were found, what neurochemical systems enhance hedonic impact in them, and how the hotspots may interact within hedonic circuitry and with a larger mesocorticolimbic circuitry that produces appetite or the motivation to eat.

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1.1. Nucleus accumbens hotspot

1.1.1. The striatum

The nucleus accumbens (NAc), as well as the striatum as a whole, is well known to be involved in reward and motivation. However, it has also become increasingly clear that subregions within the nucleus accumbens and striatum can differently influence distinct aspects of behavior and motivation [6,39,84,134]. One potential contributing factor may be related to the anatomical make up of different zones within the striatum. For example, though there are general striatal neurobiological features shared by NAc and neostriatum (D1/Dynorphin and D2/Enkephalin descending projections, inputs from prefrontal cortex, amygdala, and hippocampal nuclei, etc.), there are also clear anatomical differences between ventral and dorsal striatum, between core and shell components within nucleus accumbens, and even between different subregions within the medial shell of the nucleus accumbens [52,61,73,117,133].

1.1.2. *Affective taste reactivity as a tool to measure hedonic function*

The taste reactivity test can be used as an objective measure of hedonic impact or 'liking' reactions to taste palatability, based on quantifying discrete orofacial affective reactions to different tastes [112]. Originally applied to rats in behavioral neuroscience studies by Grill and Norgren for use in decerebrate and thalamic rats [48,49], this affective reactivity test was even earlier pioneered in human infants [111]. Converging evidence from animal and human comparisons showed that the orofacial reactions elicited by rats and humans (as well as several species of apes, monkeys, horses and mice), in response to palatable or unpalatable tastes, are strikingly homologous, with positive hedonic 'liking' reactions including tongue protrusions, lateral tongue protrusions and paw licks, and negative 'disgust' reactions including gapes, head shakes, and chin rubs [62,112]. 'Liking' and 'disgust' are placed in quotation marks to acknowledge that these are objective positive or negative hedonic reactions that are not necessarily accompanied by subjective feelings of pleasure or disgust (even if they often are) [94,125], and to distinguish them from the everyday use of the English term, liking. Similarly, 'wanting' in quotes refers specifically to the motivation process of incentive salience, which also can occur in brain and behavioral responses either with or without accompanying subjective feelings of ordinary wanting [94,94,125].

While at first it seemed possible that these taste-elicited reactions were merely sensory-specific reactions (e.g. sweet versus bitter), or merely brainstem reflexes rather than affective responses (taste reactions are emitted by decerebrates with only a brainstem to control behavior [47,49]), accumulating studies suggested that the orofacial reactions truly reflected hedonic impact for intact-brain individuals by the 1980s. For example, initially 'liked' tastes, such as sugars or saccharin, after being paired with injections of lithium chloride to produce a conditioned taste aversion (CTA), subsequently produced aversive gapes, which requires forebrain control [12,49,82,109,123]. Reciprocally, intraoral infusions of a normally disgusting hypertonic NaCl solution (e.g., 1.5 M) can produce hedonic reactions in a salt depleted state [19,33,93,118]. Further, affective orofacial reaction patterns are not tied to particular sensory stimuli in any one-to-one fashion that would reflect sensory-specific coding; palatable sucrose, palatable NaCl at isotonic or hypotonic concentrations, and palatable fat emulsions can all evoke similar hedonic reactions [33,102,104]. Further, the affective taste reactivity pattern elicited by a particular taste can be altered by factors that also alter human palatability ratings, ranging from relevant appetite/satiety physiological states, to pharmacological opioid, endocannabinoid, etc. brain states of particular neuroanatomical structures, and types of neurobiological lesions [14,26,35,69,75,84,131]. Finally, specific brain microinjections, lesions, or optogenetic stimulations in forebrain structures can profoundly control taste-elicited 'liking' reactions as described below, which indicates a top-down or hierarchical control over brainstem circuitry that involves the entire brain. Altogether, these considerations indicate that the taste reactivity test reflects the affective (sensitive to homeostatic and learned cues), rather than merely a reflex or the sensory quality of a food reward.

1.1.3. The nucleus accumbens hedonic hotspot

In an effort to uncover the neural mechanisms of hedonic processing, taste reactivity has been used in conjunction with brain manipulations, such as pharmacological microinjections in particular structures. Using this coupled paradigm, Susana Peciña in the Berridge lab was able to demonstrate that a unique hedonic function was localized to a subregion of NAc medial shell; a 1^3 mm "hedonic hotspot" in the rostrodorsal quadrant of NAc medial shell [84]. Within the confines of the cubic-millimeter hotspot in shell, mu opioid receptor activation via microinjection of the mu agonist DAMGO [71] enhanced hedonic 'liking' reactions to a sweet sucrose solution, in addition to suppressing negative 'disgust' reactions to quinine [84,106]. Within the NAc hotspot, mu opioid stimulation was found to double to triple the number of positive orofacial 'liking' reactions elicited by sweetness, in addition to dramatically stimulating intake of palatable food.

Outside the hotspot, the same opioid stimulation completely failed to increase 'liking' reactions, even though it increased intake just as much. In fact, at posterior locations in medial shell, opioid stimulation tended to oppositely suppress 'liking' reactions in a hedonic coldspot. However, at all sites in accumbens core and shell, DAMGO microinjections are equally effective at stimulating increases in food intake and in 'wanting' to obtain food, despite not enhancing 'liking' at most of those sites [7,84,85,134]. Indeed, food intake can be stimulated at a number of related sites outside NAc, without enhancing 'liking' reactions, including the central nucleus of the amygdala [46,68] and even regions of the ventral and dorsal neostriatum [39,134]. Thus, opioid circuitry for 'wanting' to eat is more widely distributed throughout NAc and related structures than opioid circuitry for 'liking'.

More recently, we have replicated the original mu opioid hotspot localization in the rostrodorsal quadrant of NAc shell for enhancements of sucrose 'liking' by DAMGO microinjections [30] (Fig. 1). Further, we have found evidence that the same anatomical site for the rostrodorsal mu hotspot can mediate opioid hedonic enhancements for delta stimulation (DPDPE) by three-fold and even kappa stimulation (U50488H) by two-fold, whereas no hedonic enhancements are produced at other locations in medial shell of NAc by either mu, delta or kappa stimulations [30] (Fig. 1). Oppositely instead, in a hedonic coldspot in the posterior half of medial shell, all three forms of opioid stimulation suppress hedonic reactions to sucrose, apparently reducing 'liking'. However, each specific agonist had different anatomical patterns of effects on 'wanting' to eat in the sense of changing food intake despite their similar (rostral) enhancement hotspot versus (caudal) suppressive coldspot pattern of 'liking' effects [30] (Fig. 1). Mu stimulation increased eating at all sites throughout medial shell, as previously reported, both in the caudal coldspot and the rostral hotspot. However, delta stimulation only increased eating in the rostral hotspot but not at other sites, and kappa stimulation never consistently increased food intake at any site in medial shell. These differences speak again to the fundamental differences in mechanisms mediating 'liking' versus 'wanting', even within opioid systems contained in the medial shell of NAc. Related evidence has demonstrated endocannabinoid stimulation in the NAc hotspot and even GABAergic hyperpolarizations in the same hotspot can also enhance 'liking' reactions to sweet tastes [43,69,84,91,92].

All three types of opioid receptors couple to Gi subunits, subsequently leading to ERK activation and typically decreasing neuronal activity, which conceivably could be related to shared enhancement effects in the rostral hedonic hotspot and shared hedonic suppression effects in the caudal coldspot. However, though mu, delta and kappa pathways converge to activate ERK, they do so via different intracellular channels, which might possibly be relevant to how the three receptors have such different effects on motivated 'wanting' to eat reflected in food intake. However, the precise relation between intra-cellular mechanisms and 'liking'/'wanting' effects still remains to be clarified.

1.1.4. Dopamine fails to alter taste reactions

By contrast to hedonic neurochemical manipulations, NAc dopamine stimulation by amphetamine microinjections within or outside the shell hotspot [106,129], by genetic elevation of dopamine in the synapse (via knockdown of dopamine transporter in presynaptic dopamine neurons) [87], or by systemic amphetamine administration [119,121], all consistently fail to enhance positive hedonic reactions to sweet tastes. Conversely, reduction of NAc dopamine by 6-OHDA lesions [17,18], or by systemic dopamine blockade [86] all fail to reduce positive hedonic reactions. However, those same dopamine manipulations do potently alter motivated 'wanting' for the food rewards. Thus, unlike opioid or endocannabinoid neurotransmitters, dopamine in NAc does not appear to be a mechanism for hedonic 'liking', but rather is restricted to motivation 'wanting' roles regarding food rewards.

1.1.5. Anatomical basis for functional uniqueness of NAc hotspot

What anatomical basis might help explain the functional existence of an anatomically unique hotspot for opioid/endocannabinoid

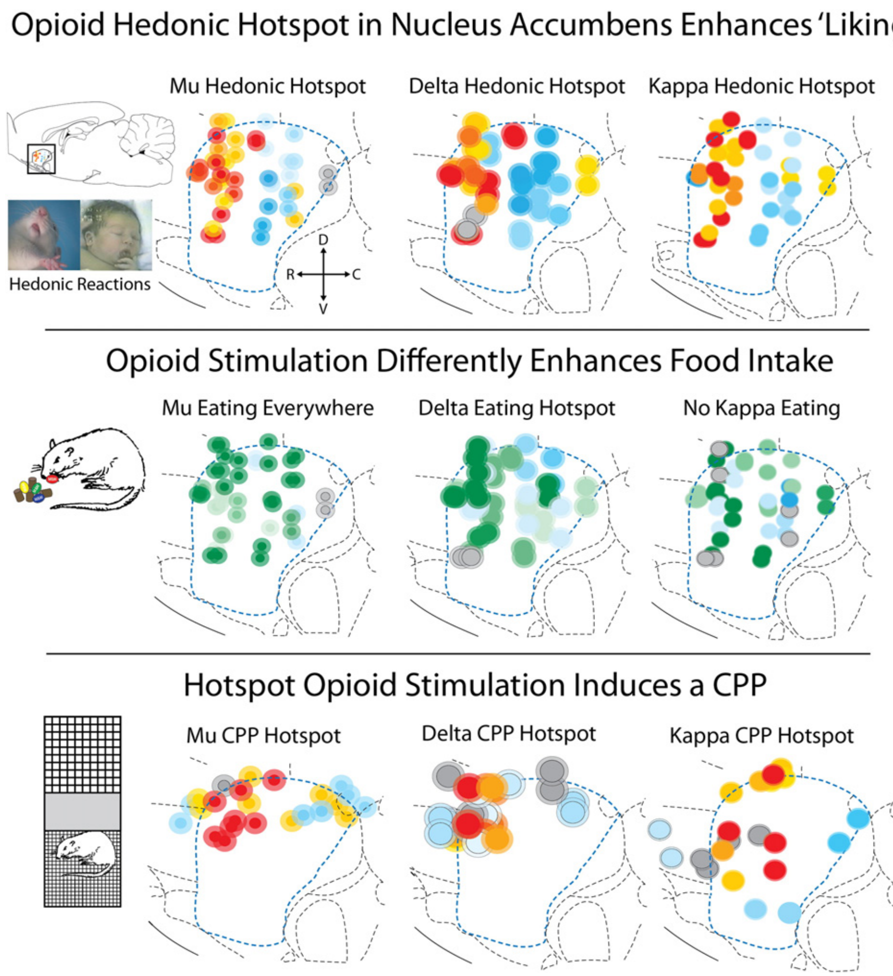

Fig. 1. *Mu, delta or kappa opioid hotspots for 'liking' enhancements in the nucleus accumbens.* Top row: 'liking' reactions to sweetness. All three types of opioid signaling mechanisms share essentially the same hedonic hotspot in NAc medial shell. Activation of any of the three types of receptor (mu, delta or kappa) enhances hedonic 'liking' reactions to sucrose taste within the same rostral cubic millimeter hotspot. Conversely, all three opioid stimulations suppress hedonic reactions in a caudal coldspot in medial shell. Each circle represents a single microinjection site. Yellow to red colors indicate increases in positive 'liking' reactions caused by opioid stimulation, and gray to blue indicatea suppression .of 'liking' to below normal control levels in the same individual rat. Middle row: different effects on 'wanting' to eat food. Stimulation of the three receptor subtypes have very different effects on food intake, highlighting that there are differences in the opioid neural mechanisms mediating 'liking' and 'wanting'. Gray to green symbols indicate increases in food intake, and gray to blue indicate a suppression of food intake. Mu stimulation enhanced food intake at all sites throughout the entire NAc. Delta stimulation enhanced eating only within the hotspot (similarly to 'liking' enhancement). Kappa stimulation never consistently enhanced eating at any anatomical site. Bottom row: confirmation of hotspot identity via place preference conditioning. Conditioned place preferences are an independent way of measuring reward, which turns out to confirm that the rostrodorsal quadrant of medial shell is unique for opioid reward effects. Stimulation of either mu or kappa receptors within the hotspot also generated a conditioned place preference (and delta showed a similar trend), whereas no preference was induced at other sites in medial shell. Yellow to red symbols indicate a positive place preferences, and gray to blue symbols indicate induction of negative place avoidances. Modified by permission from [30].

amplification of sensory pleasure, and why is it uniquely able to enhance hedonic impact to tastes, compared to other regions of NAc shell?

Recently, two independent groups of neuroanatomists have evaluated the anatomical connectivity patterns of the NAc rostrodorsal quadrant of medial shell, and found that this hotspot region differs from other subregions of medial shell (e.g., caudal shell). Thompson and Swanson [117] revealed, using a double injection of anterograde and retrograde tracers, that the rostrodorsal quadrant appears to belong to a different striato–pallido–hypothalamo–thalamo-cortical closed circuit loop from other subregions of medial shell. In other words, if one follows the projections from the rostrodorsal quadrant of medial shell along a point to point axis, one will end up back in the hotspot. This loop travels from the NAc hotspot to particular subregions of pallidum or hypothalamus, up to paraventricular nucleus of the thalamus, next passing through the infralimbic region of prefrontal cortex, and finally projecting back again to rostrodorsal medial shell. The subregions of each of these structures are distinct from the subregions visited by other parallel loops that pass through more posterior regions of medial shell. Exactly how many parallel loops pass through medial shell of NAc remains to be elucidated, but it seems clear now that there are at least two (visiting rostral vs caudal shell) and possibly additional loops that more finely dissect NAc shell into further subregions, each belonging to its own loop [117].

Similarly, Zahm and colleagues [133] recently found a related pattern of distinct connectivity that distinguishes the rostral hotspot from more caudal subregions of NAc medial shell. Those authors suggest that the rostral hotspot projects to particular regions of lateral preoptic area and lateral hypothalamus, and receives inputs from infralimbic (analogous to Brodmann's area 25) and other nearby regions of prefrontal cortex such as prelimbic and orbitofrontal cortex. They also suggest that the projection patterns of NAc rostral shell are similar to those of lateral septum, compared to the caudal shell, and that the rostral zone of medial shell is a unique transition region between NAc and lateral septum. In contrast, they suggest the caudal zone is a different transition region blending features of NAc and extended amygdala. While the Zahm et al. and the Thompson and Swanson studies differ on some points, the overall anatomical scheme presented by the two studies seems to agree that the circuitry belonging to the rostrodorsal hotspot quadrant of NAc medial shell is fundamentally different compared to the connectivity patterns of the rest of the medial shell, and that these anatomical differences may in part contribute to the hotspot's unique abilities to amplify the hedonic impact of taste sensations.

In addition to differences in projection patterns, there may also be other local neurobiological features of neurons in NAc medial shell that are relevant to hedonic contributions compared to other NAc components such as core. Meredith et al. [73] suggest that the local characteristics of neurons in NAc medial shell are different from other regions of NAc and striatum. For example, the projecting medium spiny neurons (MSNs) within medial shell are less spiny and smaller compared to NAc core or dorsal striatum. Furthermore, the distinction between different MSNs belonging to D1/dynorphin/direct pathway versus D2/enkephalin/indirect pathway, which is known from dorsal striatum, is somewhat diluted in NAc medial shell, where at least 17% of MSNs harbor both D1 and D2 receptors [22,61]. Intriguingly, volume ratios of patch/matrix compartments in dorsal striatum (as delineated by mu opioid or calbindin binding) may also be flipped, or at the very least are not as cleanly split in nucleus accumbens [63,72]. Although the roles of these neurobiological features is still unclear, some of these unique anatomical or cellular features of NAc medial shell might be relevant to its ability to generate hedonic functions that are fundamentally different from other regions of striatum.

1.2. Ventral pallidum hotspot

1.2.1. Evidence for a ventral pallidum hotspot

The ventral pallidum (VP) receives the densest projections from NAc, compared to other target structures [77,78]. Similar to NAc, VP also has been shown to be important for rewards [35,70,74,104,110,114,115,130]. Also similar to NAc, the VP has been shown to contain a hedonic hotspot of its own [104].

In an initial microinjection mapping study of the VP hedonic hotspot, Kyle Smith in the Berridge lab made microinjections of DAMGO throughout the ventral pallidum and measured taste reactivity responses to sucrose and quinine, as well as changes in food intake [104]. Results showed that DAMGO microinjections in a roughly cubic-millimeter site of caudal VP enhanced hedonic reactions to sucrose, revealing a hedonic hotspot in the posterior half, as well as stimulating the motivation to eat more food. In behavioral and anatomical contrast to the posterior VP hotspot, microinjections into more rostral subregions of VP suppressed 'liking' reactions to sucrose and reduced food intake, indicating a VP opioid coldspot [104]. The caudal VP zone which enhanced hedonic reactions was slightly smaller (~0.8^3 mm) than the 1^3 mm NAc hotspot, although it is proportionally similar to the NAc hotspot when the relative size of the structures are taken into account. Thus, like NAc, the VP also appears to house a hedonic hotspot (but positioned caudally in VP, rather than rostrally as in NAc).

1.2.2. An orexin hotspot in VP

In addition to opioid signals, orexin signals in the posterior VP also can enhance the hedonic impact of sucrose [60]. This was found by performing microinjections of orexin-A directly into the VP hotspot or into the surrounding regions of lateral hypothalamus (lateral preoptic area) or into the extended amygdala. Chao-Yi Ho in the Berridge lab found that orexin microinjections enhanced 'liking' reactions when infused into the VP hotspot, but did not do so when infused into rostral ventral pallidum or into nearby structures such as lateral hypothalamus or extended amygdala [60]. Whether or not orexin also acts in the NAc hotspot to enhance hedonic impact is still unknown, but preliminary observations in our lab suggest that orexin may also perform a similar role in this NAc region as well (Castro and Berridge, unpublished observations).

1.2.3. Necessity of the VP hotspot

During the 1960s and 70s, it was reported that lesions to LH would produce intense aphagia [23,80,99,116]. In particular, Teitelbaum and Epstein [116] reported that LH lesions, in addition to disrupting eating and drinking behavior, also disrupted hedonic/appetitive reactions to sweet solutions and replaced them with aversive or 'disgust' reactions, which suggests a role for LH in affective processing and behavior. However, with the benefit of hindsight, it can be noted that those hypothalamic lesions were very large by modern standards, and the damage actually extended well outside the lateral hypothalamus. Additional structures were damaged, ranging from caudal ventral pallidum in a direction anterior to LH, and as far back as premammillary nucleus in a caudal direction. Subsequently Schallert and Whishaw [98] identified the anterior direction as most important, showing that electrolytic lesions only in anterior LH produced intense 'disgust' reactions to sucrose in addition to producing aphagia, whereas posterior LH lesions produced merely aphagia without any aversion. To more thoroughly localize the site of 'disgust' release, Cromwell and Berridge [35] made discrete excitotoxic lesions in VP (anterolateral to LH) or in nearby regions such as lateral hypothalamus and the preoptic area. They confirmed that lesions to all LH and VP sites produced aphagia, but found that only lesions that damaged VP produced the flip in affective responses to sucrose from 'liking' to 'disgust'. Even anterior LH lesions did not release 'disgust' if VP was spared. Temporary inhibitions by muscimol microinjections into VP also have been reported to increase aversive reactions to sucrose [101]. More recently, a PhD dissertation study by Chao-Yi Ho, which mapped the increase of aversive reactions to sucrose, demonstrated that it was the VP hotspot in caudal VP that appears responsible for both lesion-induced 'disgust' and muscimol-induced 'disgust': sites for either in the posterior VP hotspot produced intense 'disgust' reactions to sucrose, whereas other sites in anterior VP as well as in anterior LH did not (as long as the posterior VP hotspot remained untouched) [59]. Such findings suggest that the VP hotspot in particular is especially important for generating normal hedonic impact, as well as for amplifying intense hedonic impact, since it is the only region in the brain known so far in which lesions not only suppress hedonic reactions, but also replaces them with aversive reactions to sweetness.

1.2.4. Anatomical basis for the VP hotspot

The larger anatomical zone in which VP is located was traditionally called the substantia innominata (SI), or unnamed substance. This was due to its lack of distinguishing features (as far as was then known), and the confusing nature of what constituted its borders, however the term substantia innominata was later criticized as too vague [57]. The VP boundaries reveal themselves when tissue is stained for enkephalin or substance P; VP produces more enkephalin and substance P than other nearby SI regions, and has distinct afferent and efferent patterns from that of the dorsally positioned globus pallidus [50,54], marking it as a relatively distinct structure within SI.

Like the NAc hotspot, the VP hotspot in its posterior region has several unique characteristics that differ from other VP subregions that may contribute to its hedonic function. For example, Kupchik and Kalivas [66] showed that the electrophysiological signature of the neurons in VP change, depending on where they recorded along a rostrocaudal axis. Neurons in anterior VP included a mix of "Type I" and "Type II" neurons, whereas posterior VP was characterized solely by Type I neurons. Type I neurons are tonically active and easily excited, while Type II neurons have low basal firing rates, and require more stimulation to elicit an action potential. In addition to this, Type II neurons morphologically resemble the accumbens medium spiny neurons, whereas Type I neurons that predominate in posterior VP are relatively aspiny and are somewhat larger than Type II. Although it is still unclear how Type I and II neurons differ functionally, it is interesting to note that the change in neuron type follows the rostrocaudal functional difference between caudal VP hotspot and rostral VP coldspot sites.

1.3. Parabrachial nucleus hotspot

1.3.1. Brainstem mechanisms of reward

In addition to the two forebrain hotspots of NAc and VP, there is also some evidence for a brainstem hedonic hotspot within the parabrachial nucleus (PBN) of the pons [108]. Although best known as a visceral/taste sensory relay [38,79], the PBN has additional functions, including food intake [28,40,124,127], establishing a conditioned taste aversion [28,36,130], and REM sleep [90,120].

As noted above, Grill and Norgren [47,49] pioneered the taste reactivity paradigm in order to compare normal and decerebrate (and thalamic or detelencephalic) rats. Mesencephalic decerebrate rats receive transections above the superior colliculus at the level of the midbrain, removing inputs from hypothalamus, thalamus and all telencephalic forebrain structures, and display no voluntary eating. However, despite the complete lack of spontaneous eating behavior, decerebrates show normal taste reactivity patterns to palatable sucrose or aversive quinine [47,49]. Although decerebrate taste reactions are reflexive in nature, another potential implication of that finding is that even at the level of the brainstem, the beginnings of some elementary hedonic processing may be occurring [15].

To more directly assess brainstem hedonic function, Berridge [13] made systemic injections of chlordiazepoxide, a benzodiazepine drug that enhances hedonic reactions in normal rats as well as enhancing food intake [34,121], into decerebrate rats and found that this benzodiazepine stimulation of the functional midbrain and hindbrain was still sufficient to enhance sucrose 'liking' reactions. Pecina and Berridge [83] then went on to show that fourth ventricular microinjections of diazepam into the brainstem fourth ventricle of intact rats also enhanced hedonic 'liking' reactions even at low doses that were ineffective in the forebrain lateral ventricles, again indicating that indeed there was a brainstem site capable of amplifying hedonic impact for normal animals.

Providing further localization of brainstem benzodiazepine mechanisms of food motivation, Higgs and Cooper [58] demonstrated that microinjections of a related benzodiazepine, midazolam, into the pontine parabrachial nucleus (PBN), but not nearby regions of brainstem, could significantly enhance food intake in non-deprived rats. Building on these findings, Soderpalm and Berridge [107] found that similar microinjections of midazolam into the lateral parabrachial nucleus of normal rats enhanced positive 'liking' taste reactivity patterns to sucrose taste, in addition to its hyperphagic effects, whereas microinjections into the hindbrain nucleus of the solitary tract or into midbrain ventral tegmental area did not.

Taken together, these studies implicate PBN benzodiazepine mechanisms in hedonic processing, extending the hedonic hotspot circuit to include brainstem, as well as forebrain, sites of action.

Recent work on the parabrachial nucleus has supported its role in food intake. For example, work by Simansky and colleagues showed that opioid and endocannabinoid stimulation within parabrachial nucleus also robustly increases consumption of palatable food [40,124]. Further, endogenous opioid function within PBN appears to be required for food motivation, as infusions of naloxonazine completely prevented DAMGO induced hyperphagia [32].

More recently, Palmiter and colleagues have shown that the PBN interacts with hypothalamic mechanisms to control appetite [28,126–128]. Wu et al. [127] showed that PBN neurons are normally inhibited by GABAergic projections from agouti-related protein (AgRP) neurons in the hypothalamic arcuate nucleus, and that destruction of AGRP neurons abolished eating. They then went on to show that the starvation effects they observed through AgRP neuron ablation were not due to increased melanocortin signaling [126], but rather to over-excitation of PBN from glutamate projections originating in the hindbrain nucleus of the solitary tract or serotonin neurons [128]. Similarly, Carter et al (2013b) showed that direct optogenetic stimulation of lateral PBN neurons that express calcitonin gene-related peptide also decreased food intake. Such mechanisms are potential candidates for future studies of PBN roles in hedonic impact.

1.4. A functional circuit for hedonic processing

The existence of multiple hedonic hotspots allows for the possibility that the hotspots interact and work together within a coordinated hedonic circuit. A functional circuit would not necessarily imply that the hotspots are all directly connected anatomically, since intermediary stops could be equally effective in creating a functional circuit. To determine whether at least a functional interaction existed, Smith and Berridge unbalanced the circuit by infusing DAMGO into one hotspot (e.g. NAc), while simultaneously infusing naloxone, an opioid antagonist, into another hotspot (e.g. VP) [105]. The guiding hypothesis was that if the simultaneous opioid neurotransmission is required in both hotspots, essentially creating unanimous opioid votes for enhancement in both sites, to increase 'liking' reactions to a palatable sweet solution, then blocking endogenous opioid signals in one hotspot should prevent exogenous opioid stimulation by DAMGO microinjection in the other from causing any hedonic enhancement. The results supported this hypothesis: opioid blockade in either the VP or NAc hotspot prevented DAMGO enhancement of positive 'liking' reactions in the other hotspot. Further supporting the functional relationship between the NAc and VP hotspots, it was also found that DAMGO activation in one hotspot enhanced Fos activity both locally and in the other hotspot, and in both directions, demonstrating that their functional interactions could be detected via neural markers of genomic transcription. It should be noted that although naloxone in VP prevented DAMGO-enhanced 'liking' in the NAc hotspot, enhancements of eating by NAc DAMGO were still robustly generated, suggesting again independent controls for hedonic 'liking' versus motivated 'wanting' of the same food reward.

In a further electrophysiological demonstration of NAc–VP hotspot interactions, Smith et al. [106] recorded taste reactivity responses and extracellular neuronal firing patterns in the VP hotspot during an intraoral infusion of sucrose. They found that neurons in the VP hotspot appeared to encode the impact of sucrose in neuronal firing, correlating with behavioral 'liking' reactions. This hedonic pattern manifested itself by steadily increasing the neural firing rate in a slow-onset but sustained the burst of action potentials, becoming evident during the first 1.5 s after the sweet taste was introduced, and sustaining this elevation in firing for the duration of the 10-s sucrose infusion. DAMGO microinjection into the NAc hotspot enhanced both behavioral hedonic taste reactivity to sucrose and the hedonic pattern of neural firing in VP elicited by the sweet taste. In behavioral contrast, amphetamine microinjections that potentiated dopamine transmission in the NAc hotspot only increased food intake and a more transient VP neural signal burst that encoded cue-triggered 'wanting', and correlated with amount of food eaten, but had no effect on behavioral taste reactivity 'liking' patterns or on the hedonic-encoding VP neural response to sucrose. Altogether, these results show that the VP and NAc hotspots interact to form a larger functional circuit that mediates the hedonic reaction to a palatable taste.

1.4.1. Anatomically unconnected hotspots?

Although the evidence presented so far clearly indicates a functional relationship between the hotspots, it may be surprising to note that the NAc, VP and PBN hotspots do not have any known direct reciprocal anatomical connections between them. For example, although the NAc hotspot sends robust projections to the ventral pallidum, they are primarily directed toward rostromedial VP, and not to the posterior hotspot [50,117,122,133]. Instead, the caudolateral core sends projections to the caudolateral VP region that contains the hotspot [50]. Beyond the NAc–VP projection, a NAc–PBN projection also exists. However, these NAc projections originate from the ventral half of medial shell, and not the dorsal half that primarily houses the rostral hotspot, leaving it unclear if NAc hotspot and PBN hotspot are directly connected [122] (Fig. 2).

An analysis of VP connections shows that it sends topographic efferents to NAc, so that anterior NAc connects with anterior VP, whereas posterior NAc connects with posterior VP [51]. This suggests that these two hotspots do not anatomically connect directly to each other (despite their clear functional relationship). Unlike NAc, VP does not project to PBN at all, although VP does reach other brainstem areas such as locus coeruleus and the raphe nuclei [51]. Similarly, PBN efferents do not appear to innervate NAc as far as is known [3], though they still might possibly interact, such as via lateral PBN efferents to the VP hotspot [96]. However, no study to our knowledge has systematically mapped PBN projections to caudal VP, leaving this connection somewhat unresolved [53,76].

Altogether, an anatomical analysis of what is known of the current hotspot boundaries suggests that although the hotspots must work together, it cannot be via direct connections. If this is true, then hotspot activity is likely monitored and mediated by an as yet unidentified brain region that shares reciprocal connections with the hotspots.

1.4.2. A role for orexin in hedonic processing

Hunger modulates the hedonic impact of food through the phenomenon known as alliesthesia [24,25]. One candidate mechanism to help mediate interactions between regulatory-hedonic circuitry is the hypothalamic orexin/hypocretin neurons, which both project to and receive direct inputs from all of the hotspots [4,8,50,51,56,89,132].

Orexin neurons relevant to reward appear to be localized within a small portion of perifornical and lateral hypothalamus [4,9,29,55,56,88]. In other hypothalamic regions, such as in dorsomedial hypothalamus orexin/hypocretin neurons are mostly implicated in attention, arousal and sleep/wake cycles [1,11,27,42,45].

Reward-related orexin neurons in lateral hypothalamus are located just medial to the internal capsule and lateral to the perifornical area, heavily concentrated in the dorsal and magnocellular portions of LH.

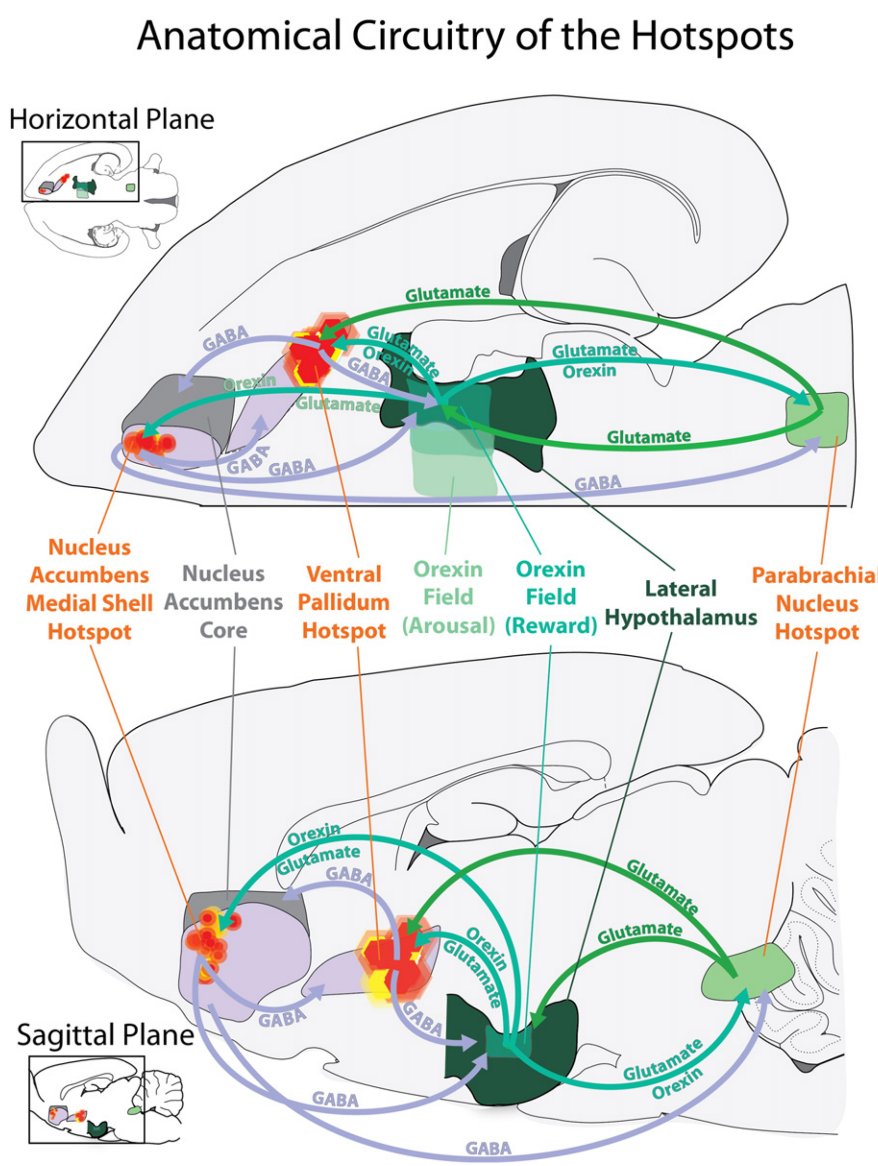

Fig. 2. *Anatomical connections of the hotspots*. Horizontal and sagittal maps show anatomical connections of nucleus accumbens and ventral pallidum (purple), and locations of hotspots within each (red/yellow), and interactions with brainstem parabrachial nucleus (light green) and lateral hypothalamus (dark green). As indicated, the three hotspots do not share any known reciprocal connections. Potentially relevant to the homeostatic regulation of the hedonic circuit, lateral hypothalamic orexin/glutamate neurons (shown in blue/green) have reciprocal connections with all the hotspots. Based on anatomical studies cited in text.

While a few orexin neurons can be found as far dorsal as zona incerta, most are located more ventrally (although many MCH-containing neurons are located in zona incerta), though still more dorsal than medial tuberal nucleus. The anterior–posterior extent of orexin neurons more or less coincides with the medial tuberal nucleus, which appears just after and ends just before the orexin field boundaries [8,113].

Orexin is implicated in hunger alliesthesia [5,20,21,41,44,67,81,97]. As mentioned above, recent work by Chao-Yi Ho in our lab found that direct orexin microinjections into the VP hotspot can selectively enhance sucrose 'liking' reactions [60], supporting the idea that activation of hypothalamic orexin projections to VP might enhance the hedonic impact of food.

We have recently conducted pilot studies of the role of LH-to-VP projections using optogenetic techniques to activate neurons [31]. Optogenetics has the special advantage of allowing stimulation of specific point-to-point projections [2,10]. This potentially includes LH to VP projections (by putting virus in one location such as LH to infect neuron cell bodies but putting the stimulating optic fiber in a different location such as VP that receives axon terminals).

We recently infused an excitatory channelrhodopsin-2 virus into the reward-related orexin field of lateral hypothalamus, and implanted an optic fiber in the VP hotspot, which contains orexin/glutamate terminals from that field. We found that VP illumination of the orexin terminals from LH enhanced the hedonic 'liking' reactions to sucrose and also enhanced the motivation to consume food (measured by intake of palatable M&M candies) [31]. In contrast, direct illumination of LH neurons, by placing both optic fiber and virus in LH, increased only food intake, but did not increase sucrose 'liking', consistent with similar effects previously found from electrical stimulation of the LH [16,35]. Finally, direct stimulation of VP neurons, by placing both illuminating optic fiber and virus microinjection in posterior VP, specifically enhanced hedonic reactions to sucrose, without increasing food intake, supporting VP hotspot involvement in amplifying hedonic impact [60,104]. Taken together, these results indicate that neurons in the VP hotspot, and LH projections to the VP hotspot, are capable of amplifying sweetness hedonic impact.

2. Conclusion

Since the identification of localized hedonic hotspots in NAc, VP and brainstem, it has become increasingly clear that these hotspots are specialized generators of hedonic impact in food reward, and that they work together to form a larger functional hedonic circuit. Future work will extend this understanding, as well as the search for additional hotspots in the brain. Some potential targets for future searches include regions of the limbic prefrontal cortex, such as the orbitofrontal cortex and insula, which are known to encode food hedonic impact in human neuroimaging studies [37,64,65,95,100,103].

In conclusion, exciting advances have been made since the initial discovery of the hotspots, and future studies can be expected to further elucidate how the brain takes a simple sensory stimulus, such as the taste of sweet food, and applies a hedonic gloss to make that sensation become positively 'liked'.

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References

[1] Adamantidis AR, Zhang F, Aravanis AM, Deisseroth K, de Lecea L. Neural substrates of awakening probed with optogenetic control of hypocretin neurons. Nature 2007;450:420–4.
[2] Ahmari SE, Spellman T, Douglass NL, Kheirbek MA, Simpson HB, Deisseroth K, et al. Repeated cortico-striatal stimulation generates persistent OCD-like behavior. Science 2013;340:1234–9.
[3] Alden M, Besson JM, Bernard JF. Organization of the efferent projections from the pontine parabrachial area to the bed nucleus of the stria terminalis and neighboring regions: a PHA-L study in the rat. J Comp Neurol 1994;341:289–314.
[4] Aston-Jones G, Smith RJ, Sartor GC, Moorman DE, Massi L, Tahsili-Fahadan P, et al. Lateral hypothalamic orexin/hypocretin neurons: a role in reward-seeking and addiction. Brain Res 2010;1314:74–90.
[5] Atasoy D, Betley JN, Su HH, Sternson SM. Deconstruction of a neural circuit for hunger. Nature 2012;488:172–7.
[6] Badrinarayan A, Wescott SA, Vander Weele CM, Saunders BT, Couturier BE, Maren S, et al. Aversive stimuli differentially modulate real-time dopamine transmission dynamics within the nucleus accumbens core and shell. J Neurosci 2012;32:15779–90.
[7] Bakshi VP, Kelley AE. Feeding induced by opioid stimulation of the ventral striatum: role of opiate receptor subtypes. J Pharmacol Exp Ther 1993;265:1253–60.
[8] Baldo BA, Daniel RA, Berridge CW, Kelley AE. Overlapping distributions of orexin/hypocretin- and dopamine-beta-hydroxylase immunoreactive fibers in rat brain regions mediating arousal, motivation, and stress. J Comp Neurol 2003;464:220–37.
[9] Baldo BA, Gual-Bonilla L, Sijapati K, Daniel RA, Landry CF, Kelley AE. Activation of a subpopulation of orexin/hypocretin-containing hypothalamic neurons by GABAA receptor-mediated inhibition of the nucleus accumbens shell, but not by exposure to a novel environment. Eur J Neurosci 2004;19:376–86.
[10] Bernstein JG, Boyden ES. Optogenetic tools for analyzing the neural circuits of behavior. Trends Cogn Sci 2011;15:592–600.
[11] Berridge CW, Espana RA, Vittoz NM. Hypocretin/orexin in arousal and stress. Brain Res 2010;1314:91–102.
[12] Berridge K, Grill HJ, Norgren R. Relation of consummatory responses and preabsorptive insulin release to palatability and learned taste aversions. J Comp Physiol Psychol 1981;95:363–82.
[13] Berridge KC. Brainstem systems mediate the enhancement of palatability by chlordiazepoxide. Brain Res 1988;447:262–8.
[14] Berridge KC. Modulation of taste affect by hunger, caloric satiety, and sensory-specific satiety in the rat. Appetite 1991;16:103–20.
[15] Berridge KC. Wanting and liking: observations from the neuroscience and psychology laboratory. Inquiry (Oslo) 2009;52:378.
[16] Berridge KC, Valenstein ES. What psychological process mediates feeding evoked by electrical stimulation of the lateral hypothalamus? Behav Neurosci 1991;105:3–14.
[17] Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev 1998;28:309–69.
[18] Berridge KC, Venier IL, Robinson TE. Taste reactivity analysis of 6-hydroxydopamine-induced aphagia: implications for arousal and anhedonia hypotheses of dopamine function. Behav Neurosci 1989;103:36–45.
[19] Berridge KC, Flynn FW, Schulkin J, Grill HJ. Sodium depletion enhances salt palatability in rats. Behav Neurosci 1984;98:652–60.
[20] Berthoud HR. Mind versus metabolism in the control of food intake and energy balance. Physiol Behav 2004;81:781–93.
[21] Berthoud HR, Munzberg H. The lateral hypothalamus as integrator of metabolic and environmental needs: from electrical self-stimulation to opto-genetics. Physiol Behav 2011;104:29–39.
[22] Bertran-Gonzalez J, Bosch C, Maroteaux M, Matamales M, Herve D, Valjent E, et al. Opposing patterns of signaling activation in dopamine D1 and D2 receptor-expressing striatal neurons in response to cocaine and haloperidol. J Neurosci 2008;28:5671–85.
[23] Boyle PC, Keesey RE. Chronically reduced body weight in rats sustaining lesions of the lateral hypothalamus and maintained on palatable diets and drinking solutions. J Comp Physiol Psychol 1975;88:218–23.
[24] Cabanac M. Physiological role of pleasure. Science 1971;173:1103–7.
[25] Cabanac M. Sensory pleasure. Q Rev Biol 1979;54:1–29.
[26] Cameron JD, Goldfield GS, Doucet E. Fasting for 24 h improves nasal chemosensory performance and food palatability in a related manner. Appetite 2012;58:978–81.
[27] Carter ME, de Lecea L, Adamantidis A. Functional wiring of hypocretin and LC-NE neurons: implications for arousal. Front Behav Neurosci 2013;7:43.
[28] Carter ME, Soden ME, Zweifel LS, Palmiter RD. Genetic identification of a neural circuit that suppresses appetite. Nature 2013;503:111–4.
[29] Cason AM, Smith RJ, Tahsili-Fahadan P, Moorman DE, Sartor GC, Aston-Jones G. Role of orexin/hypocretin in reward-seeking and addiction: implications for obesity. Physiol Behav 2010;100:419–28.
[30] Castro DC, Berridge KC. Opioid hedonic hotspot in nucleus accumbens shell: mu, delta, and kappa maps for enhancement of sweetness "liking" and "wanting". J Neurosci 2014;34:4239–50.
[31] Castro DC, Berridge KC. Optogenetic enhancement of food 'liking' versus 'wanting' in the ventral pallidum hotspot and lateral hypothalamus. Soc Neurosci Abstr 2013.
[32] Chaijale NN, Aloyo VJ, Simansky KJ. A naloxonazine sensitive (mu1 receptor) mechanism in the parabrachial nucleus modulates eating. Brain Res 2008;1240:111–8.
[33] Clark JJ, Bernstein IL. Sensitization of salt appetite is associated with increased "wanting" but not "liking" of a salt reward in the sodium-deplete rat. Behav Neurosci 2006;120:206–10.
[34] Cooper SJ. Effects of chlordiazepoxide and diazepam on feeding performance in a food-preference test. Psychopharmacology (Berl) 1980;69:73–8.

[35] Cromwell HC, Berridge KC. Where does damage lead to enhanced food aversion: the ventral pallidum/substantia innominata or lateral hypothalamus? Brain Res 1993;624:1–10.
[36] Dayawansa S, Ruch S, Norgren R. Parabrachial–hypothalamic interactions are required for normal conditioned taste aversion. Am J Physiol Regul Integr Comp Physiol 2013;306:190–200.
[37] de Araujo IE, Rolls ET, Kringelbach ML, McGlone F, Phillips N. Taste–olfactory convergence, and the representation of the pleasantness of flavour, in the human brain. Eur J Neurosci 2003;18:2059–68.
[38] Di Lorenzo PM, Monroe S. Transfer of information about taste from the nucleus of the solitary tract to the parabrachial nucleus of the pons. Brain Res 1997;763:167–81.
[39] Difeliceantonio AG, Mabrouk OS, Kennedy RT, Berridge KC. Enkephalin surges in dorsal neostriatum as a signal to eat. Curr Biol 2012;22:1918–20.
[40] DiPatrizio NV, Simansky KJ. Activating parabrachial cannabinoid CB1 receptors selectively stimulates feeding of palatable foods in rats. J Neurosci 2008;28:9702–9.
[41] Elias CF, Saper CB, Maratos-Flier E, Tritos NA, Lee C, Kelly J, et al. Chemically defined projections linking the mediobasal hypothalamus and the lateral hypothalamic area. J Comp Neurol 1998;402:442–59.
[42] Espana RA, Baldo BA, Kelley AE, Berridge CW. Wake-promoting and sleep-suppressing actions of hypocretin (orexin): basal forebrain sites of action. Neuroscience 2001;106:699–715.
[43] Faure A, Richard JM, Berridge KC. Desire and dread from the nucleus accumbens: cortical glutamate and subcortical GABA differentially generate motivation and hedonic impact in the rat. PLoS ONE 2010;5:e11223.
[44] Funahashi H, Yamada S, Kageyama H, Takenoya F, Guan JL, Shioda S. Co-existence of leptin- and orexin-receptors in feeding-regulating neurons in the hypothalamic arcuate nucleus—a triple labeling study. Peptides 2003;24:687–94.
[45] Gompf HS, Aston-Jones G. Role of orexin input in the diurnal rhythm of locus coeruleus impulse activity. Brain Res 2008;1224:43–52.
[46] Gosnell BA. Involvement of mu opioid receptors in the amygdala in the control of feeding. Neuropharmacology 1988;27:319–26.
[47] Grill HJ, Norgren R. Neurological tests and behavioral deficits in chronic thalamic and chronic decerebrate rats. Brain Res 1978;143:299–312.
[48] Grill HJ, Norgren R. The taste reactivity test. II. Mimetic responses to gustatory stimuli in chronic thalamic and chronic decerebrate rats. Brain Res 1978;143:281–97.
[49] Grill HJ, Norgren R. The taste reactivity test. I. Mimetic responses to gustatory stimuli in neurologically normal rats. Brain Res 1978;143:263–79.
[50] Groenewegen HJ, Russchen FT. Organization of the efferent projections of the nucleus accumbens to pallidal, hypothalamic, and mesencephalic structures: a tracing and immunohistochemical study in the cat. J Comp Neurol 1984;223:347–67.
[51] Groenewegen HJ, Berendse HW, Haber SN. Organization of the output of the ventral striatopallidal system in the rat: ventral pallidal efferents. Neuroscience 1993;57:113–42.
[52] Groenewegen HJ, Wright CI, Beijer AV, Voorn P. Convergence and segregation of ventral striatal inputs and outputs. Ann N Y Acad Sci 1999;877:49–63.
[53] Grove EA. Neural associations of the substantia innominata in the rat: afferent connections. J Comp Neurol 1988;277:315–46.
[54] Haber SN, Nauta WJ. Ramifications of the globus pallidus in the rat as indicated by patterns of immunohistochemistry. Neuroscience 1983;9:245–60.
[55] Harris GC, Aston-Jones G. Arousal and reward: a dichotomy in orexin function. Trends Neurosci 2006;29:571–7.
[56] Harris GC, Wimmer M, Aston-Jones G. A role for lateral hypothalamic orexin neurons in reward seeking. Nature 2005;437:556–9.
[57] Heimer L, Harlan RE, Alheid GF, Garcia MM, de Olmos J. Substantia innominata: a notion which impedes clinical–anatomical correlations in neuropsychiatric disorders. Neuroscience 1997;76:957–1006.
[58] Higgs S, Cooper SJ. Hyperphagia induced by direct administration of midazolam into the parabrachial nucleus of the rat. Eur J Pharmacol 1996;313:1–9.
[59] Ho C. The ventral pallidum as a limbic pleasure generator. [PhD Dissertation] Ann Arbor, MI: University of Michigan; 2010.
[60] Ho CY, Berridge KC. An orexin hotspot in ventral pallidum amplifies hedonic 'liking' for sweetness. Neuropsychopharmacology 2013;38:1655–64.
[61] Humphries MD, Prescott TJ. The ventral basal ganglia, a selection mechanism at the crossroads of space, strategy, and reward. Prog Neurobiol 2010;90:385–417.
[62] Jankunis ES, Whishaw IQ. Sucrose Bobs and Quinine Gapes: horse (*Equus caballus*) responses to taste support phylogenetic similarity in taste reactivity. Behav Brain Res 2013;256:284–90.
[63] Jongen-Relo AL, Groenewegen HJ, Voorn P. Evidence for a multi-compartmental histochemical organization of the nucleus accumbens in the rat. J Comp Neurol 1993;337:267–76.
[64] Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog Neurobiol 2004;72:341–72.
[65] Kringelbach ML, O'Doherty J, Rolls ET, Andrews C. Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. Cereb Cortex 2003;13:1064–71.
[66] Kupchik YM, Kalivas PW. The rostral subcommissural ventral pallidum is a mix of ventral pallidal neurons and neurons from adjacent areas: an electrophysiological study. Brain Struct Funct 2012;218:1487–500.
[67] Li Y, van den Pol AN. Differential target-dependent actions of coexpressed inhibitory dynorphin and excitatory hypocretin/orexin neuropeptides. J Neurosci 2006;26:13037–47.
[68] Mahler SV, Berridge KC. What and when to "want"? Amygdala-based focusing of incentive salience upon sugar and sex. Psychopharmacology (Berl) 2012;221:407–26.
[69] Mahler SV, Smith KS, Berridge KC. Endocannabinoid hedonic hotspot for sensory pleasure: anandamide in nucleus accumbens shell enhances 'liking' of a sweet reward. Neuropsychopharmacology 2007;32:2267–78.
[70] Mahler SV, Vazey EM, Beckley JT, Keistler CR, McGlinchey EM, Kaufling J, et al. Designer receptors show role for ventral pallidum input to ventral tegmental area in cocaine seeking. Nat Neurosci 2014;17:577–85.
[71] Mansour A, Lewis ME, Khachaturian H, Akil H, Watson SJ. Pharmacological and anatomical evidence of selective mu, delta, and kappa opioid receptor binding in rat brain. Brain Res 1986;399:69–79.
[72] Meredith GE, Pattiselanno A, Groenewegen HJ, Haber SN. Shell and core in monkey and human nucleus accumbens identified with antibodies to calbindin-D28k. J Comp Neurol 1996;365:628–39.
[73] Meredith GE, Baldo BA, Andrezjewski ME, Kelley AE. The structural basis for mapping behavior onto the ventral striatum and its subdivisions. Brain Struct Funct 2008;213:17–27.
[74] Mickiewicz AL, Dallimore JE, Napier TC. The ventral pallidum is critically involved in the development and expression of morphine-induced sensitization. Neuropsychopharmacology 2009;34:874–86.
[75] Miller JM, Vorel SR, Tranguch AJ, Kenny ET, Mazzoni P, van Gorp WG, et al. Anhedonia after a selective bilateral lesion of the globus pallidus. Am J Psychiatry 2006;163:786–8.
[76] Moga MM, Herbert H, Hurley KM, Yasui Y, Gray TS, Saper CB. Organization of cortical, basal forebrain, and hypothalamic afferents to the parabrachial nucleus in the rat. J Comp Neurol 1990;295:624–61.
[77] Mogenson GJ, Swanson LW, Wu M. Neural projections from nucleus accumbens to globus pallidus, substantia innominata, and lateral preoptic-lateral hypothalamic area: an anatomical and electrophysiological investigation in the rat. J Neurosci 1983;3:189–202.
[78] Nauta WJ, Smith GP, Faull RL, Domesick VB. Efferent connections and nigral afferents of the nucleus accumbens septi in the rat. Neuroscience 1978;3:385–401.
[79] Norgren R, Leonard CM. Taste pathways in rat brainstem. Science 1971;173:1136–9.
[80] Oltmans GA, Harvey JA. Lateral hypothalamic syndrome in rats: a comparison of the behavioral and neurochemical effects of lesions placed in the lateral hypothalamus and nigrostriatal bundle. J Comp Physiol Psychol 1976;90:1051–62.
[81] Park ES, Yi SJ, Kim JS, Lee HS, Lee IS, Seong JK, et al. Changes in orexin-A and neuropeptide Y expression in the hypothalamus of the fasted and high-fat diet fed rats. J Vet Sci 2004;5:295–302.
[82] Parker LA. Taste avoidance and taste aversion: evidence for two different processes. Learn Behav 2003;31:165–72.
[83] Pecina S, Berridge KC. Brainstem mediates diazepam enhancement of palatability and feeding: microinjections into fourth ventricle versus lateral ventricle. Brain Res 1996;727:22–30.
[84] Pecina S, Berridge KC. Hedonic hot spot in nucleus accumbens shell: where do mu-opioids cause increased hedonic impact of sweetness? J Neurosci 2005;25:11777–86.
[85] Pecina S, Berridge KC. Dopamine or opioid stimulation of nucleus accumbens similarly amplify cue-triggered 'wanting' for reward: entire core and medial shell mapped as substrates for PIT enhancement. Eur J Neurosci 2013;37:1529–40.
[86] Pecina S, Berridge KC, Parker LA. Pimozide does not shift palatability: separation of anhedonia from sensorimotor suppression by taste reactivity. Pharmacol Biochem Behav 1997;58:801–11.
[87] Pecina S, Cagniard B, Berridge KC, Aldridge JW, Zhuang X. Hyperdopaminergic mutant mice have higher "wanting" but not "liking" for sweet rewards. J Neurosci 2003;23:9395–402.
[88] Petrovich GD, Hobin MP, Reppucci CJ. Selective Fos induction in hypothalamic orexin/hypocretin, but not melanin-concentrating hormone neurons, by a learned food-cue that stimulates feeding in sated rats. Neuroscience 2012;224:70–80.
[89] Peyron C, Tighe DK, van den Pol AN, de Lecea L, Heller HC, Sutcliffe JG, et al. Neurons containing hypocretin (orexin) project to multiple neuronal systems. J Neurosci 1998;18:9996–10015.
[90] Quattrochi J, Datta S, Hobson JA. Cholinergic and non-cholinergic afferents of the caudolateral parabrachial nucleus: a role in the long-term enhancement of rapid eye movement sleep. Neuroscience 1998;83:1123–36.
[91] Reynolds SM, Berridge KC. Positive and negative motivation in nucleus accumbens shell: bivalent rostrocaudal gradients for GABA-elicited eating, taste "liking"/"disliking" reactions, place preference/avoidance, and fear. J Neurosci 2002;22:7308–20.
[92] Richard JM, Castro DC, Difeliceantonio AG, Robinson MJ, Berridge KC. Mapping brain circuits of reward and motivation: in the footsteps of Ann Kelley. Neurosci Biobehav Rev 2013;37:1919–31.
[93] Robinson MJ, Berridge KC. Instant transformation of learned repulsion into motivational "wanting". Curr Biol 2013;23:282–9.
[94] Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev 1993;18:247–91.
[95] Rolls ET, Kringelbach ML, de Araujo IE. Different representations of pleasant and unpleasant odours in the human brain. Eur J Neurosci 2003;18:695–703.
[96] Saper CB, Loewy AD. Efferent connections of the parabrachial nucleus in the rat. Brain Res 1980;197:291–317.
[97] Schaeffer M, Langlet F, Lafont C, Molino F, Hodson DJ, Roux T, et al. Rapid sensing of circulating ghrelin by hypothalamic appetite-modifying neurons. Proc Natl Acad Sci U S A 2013;110:1512–7.
[98] Schallert T, Whishaw IQ. Two types of aphagia and two types of sensorimotor impairment after lateral hypothalamic lesions: observations in normal weight, dieted, and fattened rats. J Comp Physiol Psychol 1978;92:720–41.
[99] Schallert T, Whishaw IQ, Flannigan KP. Gastric pathology and feeding deficits induced by hypothalamic damage in rats: effects of lesion type, size, and placement. J Comp Physiol Psychol 1977;91:598–610.

[100] Sescousse G, Redoute J, Dreher JC. The architecture of reward value coding in the human orbitofrontal cortex. J Neurosci 2010;30:13095–104.
[101] Shimura T, Imaoka H, Yamamoto T. Neurochemical modulation of ingestive behavior in the ventral pallidum. Eur J Neurosci 2006;23:1596–604.
[102] Shin AC, Townsend RL, Patterson LM, Berthoud HR. "Liking" and "wanting" of sweet and oily food stimuli as affected by high-fat diet-induced obesity, weight loss, leptin, and genetic predisposition. Am J Physiol Regul Integr Comp Physiol 2011;301:R1267-280.
[103] Small DM. Taste representation in the human insula. Brain Struct Funct 2010;214:551–61.
[104] Smith KS, Berridge KC. The ventral pallidum and hedonic reward: neurochemical maps of sucrose "liking" and food intake. J Neurosci 2005;25:8637–49.
[105] Smith KS, Berridge KC. Opioid limbic circuit for reward: interaction between hedonic hotspots of nucleus accumbens and ventral pallidum. J Neurosci 2007;27:1594–605.
[106] Smith KS, Berridge KC, Aldridge JW. Disentangling pleasure from incentive salience and learning signals in brain reward circuitry. Proc Natl Acad Sci U S A 2011;108: E255–64.
[107] Soderpalm AH, Berridge KC. Food intake after diazepam, morphine or muscimol: microinjections In the nucleus accumbens shell. Pharmacol Biochem Behav 2000;66:429–34.
[108] Soderpalm AH, Berridge KC. The hedonic impact and intake of food are increased by midazolam microinjection in the parabrachial nucleus. Brain Res 2000;877:288–97.
[109] Spector AC, Norgren R, Grill HJ. Parabrachial gustatory lesions impair taste aversion learning in rats. Behav Neurosci 1992;106:147–61.
[110] Stefanik MT, Kupchik YM, Brown RM, Kalivas PW. Optogenetic evidence that pallidal projections, not nigral projections, from the nucleus accumbens core are necessary for reinstating cocaine seeking. J Neurosci 2013;33:13654–62.
[111] Steiner JE. The gustofacial response: observation on normal and anencephalic newborn infants. Symp Oral Sens Percept 1973:254–78.
[112] Steiner JE, Glaser D, Hawilo ME, Berridge KC. Comparative expression of hedonic impact: affective reactions to taste by human infants and other primates. Neurosci Biobehav Rev 2001;25:53–74.
[113] Swanson LW, Sanchez-Watts G, Watts AG. Comparison of melanin-concentrating hormone and hypocretin/orexin mRNA expression patterns in a new parceling scheme of the lateral hypothalamic zone. Neurosci Lett 2005;387:80–4.
[114] Taha SA, Katsuura Y, Noorvash D, Seroussi A, Fields HL. Convergent, not serial, striatal and pallidal circuits regulate opioid-induced food intake. Neuroscience 2009;161:718–33.
[115] Tang XC, McFarland K, Cagle S, Kalivas PW. Cocaine-induced reinstatement requires endogenous stimulation of mu-opioid receptors in the ventral pallidum. J Neurosci 2005;25:4512–20.
[116] Teitelbaum P, Epstein AN. The lateral hypothalamic syndrome: recovery of feeding and drinking after lateral hypothalamic lesions. Psychol Rev 1962;69:74–90.
[117] Thompson RH, Swanson LW. Hypothesis-driven structural connectivity analysis supports network over hierarchical model of brain architecture. Proc Natl Acad Sci U S A 2010;107:15235–9.
[118] Tindell AJ, Smith KS, Berridge KC, Aldridge JW. Dynamic computation of incentive salience: "wanting" what was never "liked". J Neurosci 2009;29:12220–8.
[119] Tindell AJ, Berridge KC, Zhang J, Pecina S, Aldridge JW. Ventral pallidal neurons code incentive motivation: amplification by mesolimbic sensitization and amphetamine. Eur J Neurosci 2005;22:2617–34.
[120] Torterolo P, Sampogna S, Chase MH. A restricted parabrachial pontine region is active during non-rapid eye movement sleep. Neuroscience 2011;190:184–93.
[121] Treit D, Berridge KC. A comparison of benzodiazepine, serotonin, and dopamine agents in the taste-reactivity paradigm. Pharmacol Biochem Behav 1990;37:451–6.
[122] Usuda I, Tanaka K, Chiba T. Efferent projections of the nucleus accumbens in the rat with special reference to subdivision of the nucleus: biotinylated dextran amine study. Brain Res 1998;797:73–93.
[123] Wilkins EE, Bernstein IL. Conditioning method determines patterns of c-fos expression following novel taste-illness pairing. Behav Brain Res 2006;169:93–7.
[124] Wilson JD, Nicklous DM, Aloyo VJ, Simansky KJ. An orexigenic role for mu-opioid receptors in the lateral parabrachial nucleus. Am J Physiol Regul Integr Comp Physiol 2003;285:R1055–65.
[125] Winkielman P, Berridge KC, Wilbarger JL. Unconscious affective reactions to masked happy versus angry faces influence consumption behavior and judgments of value. Pers Soc Psychol Bull 2005;31:121–35.
[126] Wu Q, Palmiter RD. GABAergic signaling by AgRP neurons prevents anorexia via a melanocortin-independent mechanism. Eur J Pharmacol 2011;660:21–7.
[127] Wu Q, Boyle MP, Palmiter RD. Loss of GABAergic signaling by AgRP neurons to the parabrachial nucleus leads to starvation. Cell 2009;137:1225–34.
[128] Wu Q, Clark MS, Palmiter RD. Deciphering a neuronal circuit that mediates appetite. Nature 2012;483:594–7.
[129] Wyvell CL, Berridge KC. Intra-accumbens amphetamine increases the conditioned incentive salience of sucrose reward: enhancement of reward "wanting" without enhanced "liking" or response reinforcement. J Neurosci 2000;20:8122–30.
[130] Yamamoto T. Brain regions responsible for the expression of conditioned taste aversion in rats. Chem Senses 2007;32:105–9.
[131] Yeomans MR, Gray RW. Effects of naltrexone on food intake and changes in subjective appetite during eating: evidence for opioid involvement in the appetizer effect. Physiol Behav 1997;62:15–21.
[132] Yoshida K, McCormack S, Espana RA, Crocker A, Scammell TE. Afferents to the orexin neurons of the rat brain. J Comp Neurol 2006;494:845–61.
[133] Zahm DS, Parsley KP, Schwartz ZM, Cheng AY. On lateral septum-like characteristics of outputs from the accumbal hedonic 'hotspot' of Pecina and Berridge with commentary on the transitional nature of basal forebrain 'boundaries'. J Comp Neurol 2012;521:50–68.
[134] Zhang M, Kelley AE. Enhanced intake of high-fat food following striatal mu-opioid stimulation: microinjection mapping and fos expression. Neuroscience 2000;99:267–77.