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

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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 2000's, 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.

Keywords

Nucleus Accumbens; Ventral Pallidum; Hedonic Hotspot; Pleasure; Parabrachial Nucleus; Optogenetics; Reward; Motivation

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, 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.

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 (Zhang and Kelley, 2000; Pecina and Berridge, 2005; Badrinarayan et al., 2012; Difeliceantonio et al., 2012). One potential

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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 (Groenewegen et al., 1999; Meredith et al., 2008; Humphries and Prescott, 2010; Thompson and Swanson, 2010; Zahm et al., 2012).

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 (Steiner et al., 2001). Originally applied to rats in behavioral neuroscience studies by Grill and Norgren for use in decerebrate and thalamic rats (Grill and Norgren, 1978b, c), this affective reactivity test was even earlier pioneered in human infants (Steiner, 1973). 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 (Steiner et al., 2001; Jankunis and Whishaw, 2013). '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) (Robinson and Berridge, 1993; Winkielman et al., 2005), 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 (Robinson and Berridge, 1993; Winkielman et al., 2005).

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 (Grill and Norgren, 1978a, c)), 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 (Grill and Norgren, 1978c; Berridge et al., 1981; Spector et al., 1992; Parker, 2003; Wilkins and Bernstein, 2006). Reciprocally, intraoral infusions of a normally disgusting hypertonic NaCl solution (e.g., 1.5 M) can produce hedonic reactions in a salt depleted state (Berridge et al., 1984; Clark and Bernstein, 2006; Tindell et al., 2009; Robinson and Berridge, 2013). 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 (Smith and Berridge, 2005; Clark and Bernstein, 2006; Shin et al., 2011). 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 (Berridge, 1991; Cromwell and Berridge, 1993; Yeomans and Gray, 1997; Pecina and Berridge, 2005; Miller et al., 2006; Mahler et al., 2007; Cameron et al., 2012). 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 1^3mm "hedonic hotspot" in the rostrodorsal quadrant of NAc medial shell (Pecina and Berridge, 2005). Within the confines of the cubic-millimeter hotspot in shell, mu opioid receptor activation via microinjection of the mu agonist DAMGO (Mansour et al., 1986) enhanced hedonic 'liking' reactions to a sweet sucrose solution, in addition to suppressing negative 'disgust' reactions to quinine (Pecina and Berridge, 2005; Smith et al., 2011). 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 (Bakshi and Kelley, 1993; Zhang and Kelley, 2000; Pecina and Berridge, 2005, 2013). 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 (Gosnell, 1988; Mahler and Berridge, 2012) and even regions of the ventral and dorsal neostriatum (Zhang and Kelley, 2000; Difeliceantonio et al., 2012). 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 (Castro and Berridge, 2014) (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(Castro and Berridge, 2014) (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 (Castro and Berridge, 2014) (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 (Reynolds and Berridge, 2002; Pecina and Berridge, 2005; Mahler et al., 2007; Faure et al., 2010; Richard et al., 2013).

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 (Wyvell and Berridge, 2000; Smith et al., 2011), by genetic elevation of dopamine in the synapse (via knockdown of dopamine transporter in presynaptic dopamine neurons) (Pecina et al., 2003), or by systemic amphetamine administration (Treit and Berridge, 1990; Tindell et al., 2005), all consistently fail to enhance positive hedonic reactions to sweet tastes. Conversely, reduction of NAc dopamine by 6-OHDA lesions (Berridge et al., 1989; Berridge and Robinson, 1998), or by systemic dopamine blockade (Pecina et al., 1997) 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 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 (2010) 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 (Thompson & Swanson, 2010).

Similarly, Zahm and colleagues (2012) 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 these anatomical differences may in part contribute to the hotspot's unique abilities to amplify 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. (2008) 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 (Bertran-Gonzalez et al., 2008; Humphries and Prescott, 2010). 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 (Jongen-Relo et al., 1993; Meredith et al., 1996). 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.

2.1 Ventral pallidum hotspot

2.1.1 Evidence for a ventral pallidum hotspot

The ventral pallidum (VP) receives the densest projections from NAc, compared to other target structures (Nauta et al., 1978; Mogenson et al., 1983). Similar to NAc, VP also has been shown to be important for rewards (Cromwell and Berridge, 1993; Smith and Berridge, 2005; Tang et al., 2005; Yamamoto, 2007; Mickiewicz et al., 2009; Taha et al., 2009; Stefanik et al., 2013; Mahler et al., 2014). Also similar to NAc, the VP has been shown to contain a hedonic hotspot of its own (Smith and Berridge, 2005).

In an initial microinjection mapping study of the VP hedonic hotspot, Smith and Berridge (2005) made microinjections of DAMGO throughout the ventral pallidum and measured taste reactivity responses to sucrose and quinine, as well as changes in food intake. 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 (Smith and Berridge, 2005). The caudal VP zone which enhanced hedonic reactions was slightly smaller (~0.8^3mm) than the 1^3mm 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).

2.1.2 An orexin hotspot in VP

In addition to opioid signals, orexin signals in the posterior VP also can enhance the hedonic impact of sucrose (Ho and Berridge, 2013). 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 (Ho and Berridge, 2013). 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).

2.2.1 Necessity of the VP hotspot

During the 1960's and 70's, it was reported that lesions to LH would produce intense aphagia (Teitelbaum and Epstein, 1962; Boyle and Keesey, 1975; Oltmans and Harvey, 1976; Schallert et al., 1977). In particular, Teitelbaum and Epstein (1962) 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 (1978) 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 (1993) 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 (Shimura et al., 2006). 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) (Ho, 2010). 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 replace them with aversive reactions to sweetness.

2.2.2 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 (Heimer et al., 1997). 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 (Haber and Nauta, 1983; Groenewegen and Russchen, 1984), 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 (2012) 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.

3.1 Parabrachial nucleus hotspot

3.1.1 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 (Soderpalm and Berridge, 2000a). Although best known as a visceral/taste sensory relay (Norgren and Leonard, 1971; Di Lorenzo and Monroe, 1997), the PBN has additional functions, including food intake (Wilson et al., 2003; DiPatrizio and Simansky, 2008; Wu et al., 2009; Carter et al., 2013b), establishing a conditioned taste aversion (Yamamoto, 2007; Carter et al., 2013b; Dayawansa et al., 2013), and REM sleep (Quattrochi et al., 1998; Torterolo et al., 2011).

As noted above, Grill and Norgren (1978a, c) 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 (Grill and Norgren, 1978a, c). 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 (Berridge, 2009).

To more directly assess brainstem hedonic function, Berridge (1988) made systemic injections of chlordiazepoxide, a benzodiazepine drug that enhances hedonic reactions in normal rats as well as enhancing food intake (Cooper, 1980; Treit and Berridge, 1990), into decerebrate rats and found that this benzodiazepine stimulation of the functional midbrain and hindbrain was still sufficient to enhance sucrose ‘liking’ reactions. Peciña and Berridge (1996) 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 (1996) 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 (2000b) 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 (Wilson et al., 2003; DiPatrizio and Simansky, 2008). Further, endogenous opioid function within PBN appears to be required for food motivation, as infusions of naloxonazine completely prevented DAMGO induced hyperphagia (Chaijale et al., 2008).

More recently, Palmiter and colleagues have shown that the PBN interacts with hypothalamic mechanisms to control appetite (Wu et al., 2009; Wu and Palmiter, 2011; Wu et al., 2012; Carter et al., 2013b). Wu et al. (2009) 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 (Wu and Palmiter, 2011), but rather to over-excitation of PBN from glutamate projections originating in the hindbrain nucleus of the solitary tract or serotonin neurons (Wu et al., 2012). Similarly, Carter et al (2013b) showed that optogenetic stimulation of lateral PBN neurons that express calcitonin gene-related peptide also decreased food intake.

4.1 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) (Smith and Berridge, 2007). 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 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. (2011) 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 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 burst of action potentials, becoming evident during the first 1.5s after the sweet taste was introduced, and sustaining this elevation in firing for the duration of the 10-sec 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.

4.1.2 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 (Groenewegen and Russchen, 1984; Usuda et al., 1998; Thompson and Swanson, 2010; Zahm et al., 2012). Instead, the caudolateral core sends projections to the caudolateral VP region that contains the hotspot (Groenewegen and Russchen, 1984). 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 (Usuda et al., 1998).

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(Groenewegen et al., 1993). 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 (Groenewegen et al., 1993). Similarly, PBN efferents do not appear to innervate NAc as far as is known (Alden et al., 1994), though they still might possibly interact, such as via lateral PBN efferents to the VP hotspot (Saper and Loewy, 1980). However, no study to our knowledge has systematically mapped PBN projections to caudal VP, leaving this connection somewhat unresolved (Grove, 1988; Moga et al., 1990).

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.

4.2.1 A role for orexin in hedonic processing

Hunger modulates the hedonic impact of food through the phenomenon known as alliesthesia (Cabanac, 1971, 1979). 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 (Groenewegen and Russchen, 1984; Groenewegen et al., 1993; Peyron et al., 1998; Baldo et al., 2003; Harris et al., 2005; Yoshida et al., 2006; Aston-Jones et al., 2010).

Orexin neurons relevant to reward are appear localized within a small portion of perifornical and lateral hypothalamus (Baldo et al., 2004; Harris et al., 2005; Harris and Aston-Jones, 2006; Aston-Jones et al., 2010; Cason et al., 2010; Petrovich et al., 2012). In other hypothalamic regions, such as in dorsomedial hypothalamus orexin/hypocretin neurons are mostly implicated in attention, arousal and sleep/wake cycles (Espana et al., 2001; Adamantidis et al., 2007; Gompf and Aston-Jones, 2008; Berridge et al., 2010; Carter et al., 2013a).

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. 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 (Baldo et al., 2003; Swanson et al., 2005).

Orexin is implicated in hunger alliesthesia (Elias et al., 1998; Funahashi et al., 2003; Berthoud, 2004; Park et al., 2004; Li and van den Pol, 2006; Berthoud and Munzberg, 2011; Atasoy et al., 2012; Schaeffer et al., 2013). 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 (Ho and Berridge, 2013), 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 (Castro and Berridge, 2013). Optogenetics has the special advantage of allowing stimulation of specific point-to-point projections (Bernstein and Boyden, 2011; Ahmari et al., 2013). 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) (Castro and Berridge, 2013). 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 (Berridge and Valenstein, 1991; Cromwell and Berridge, 1993). 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 (Smith and Berridge, 2005; Ho and Berridge, 2013). 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.

5.1 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 (de Araujo et al., 2003; Kringelbach et al., 2003; Rolls et al., 2003; Kringelbach and Rolls, 2004; Sescousse et al., 2010; Small, 2010).

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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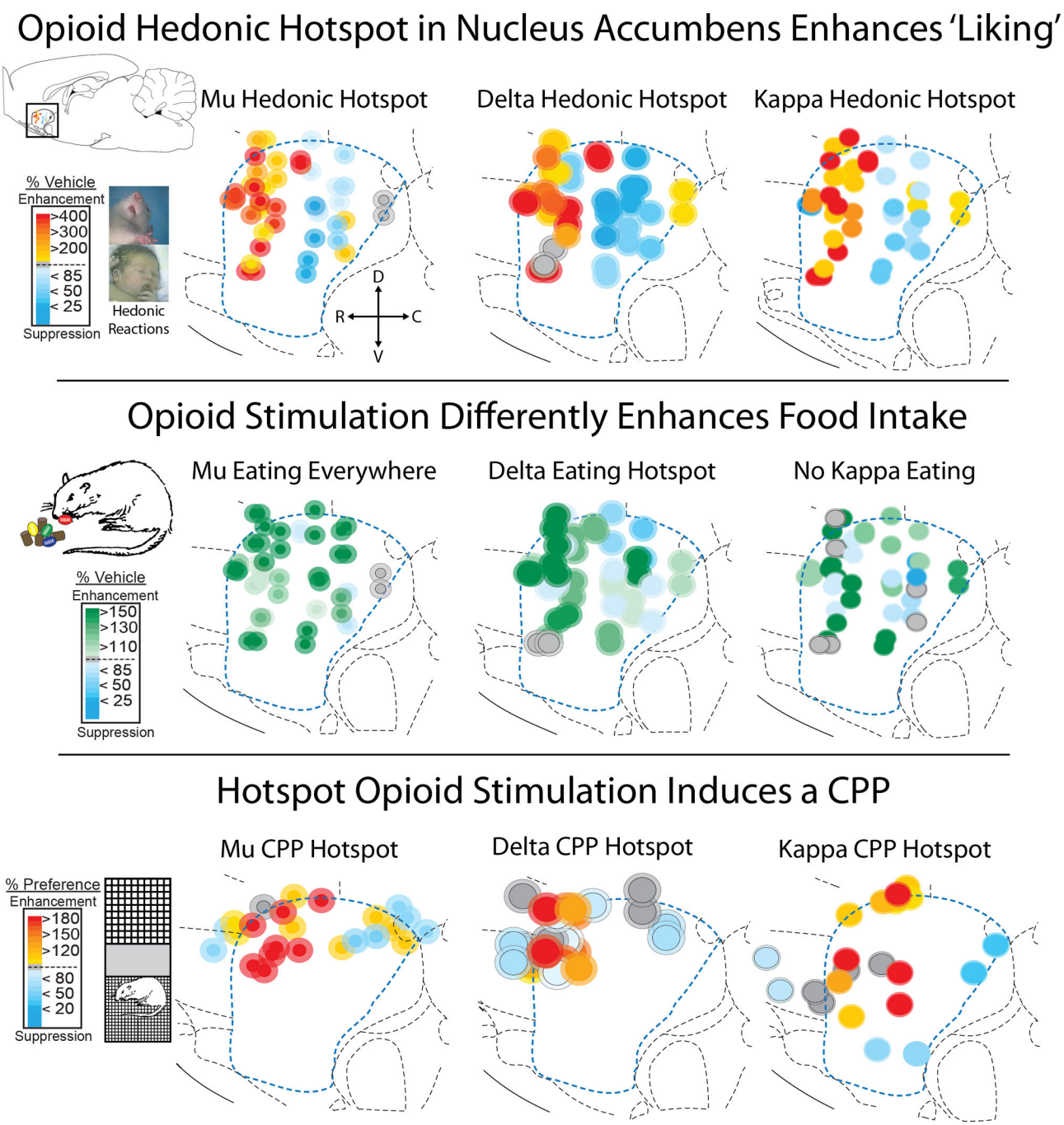

Figure 1. Mu, delta or kappa opioid hotspots for 'liking' enhancements in the nucleus accumbens

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 indicates suppression

'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 indicates 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 (Castro and Berridge, 2014).

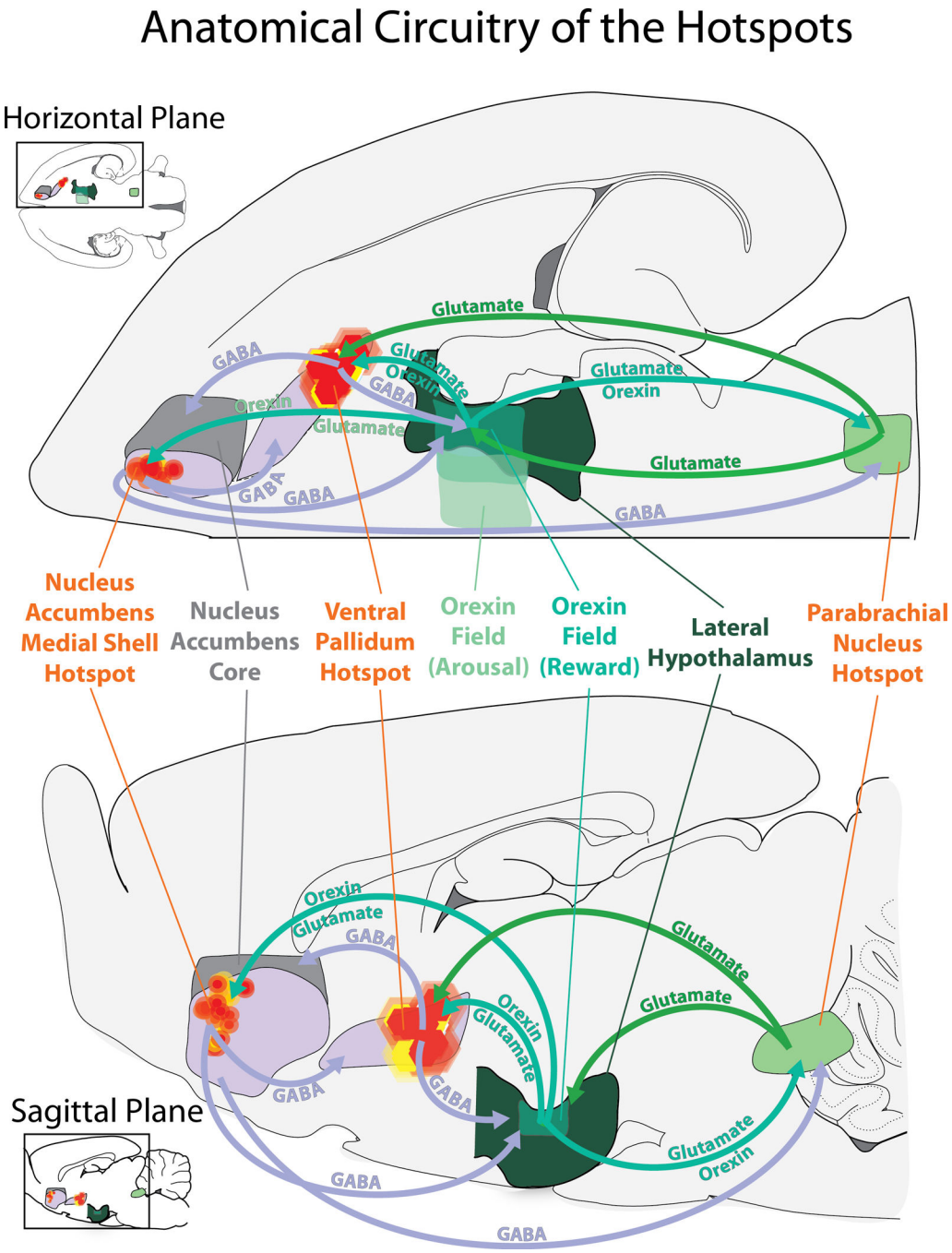

Figure 2. Anatomical connections of the hotspots

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.