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Review

Hedonic and motivational roles of opioids in food reward: Implications for overeating disorders

Susana Peciña [a,*,1], Kyle S. Smith [b,1]

[a] Department of Behavioral Sciences, University of Michigan-Dearborn, United States
[b] McGovern Institute for Brain Research, Massachusetts Institute of Technology, United States

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ABSTRACT

Food reward can be driven by separable mechanisms of hedonic impact (food 'liking') and incentive motivation (food 'wanting'). Brain mu-opioid systems contribute crucially to both forms of food reward. Yet, opioid signals for food 'liking' and 'wanting' diverge in anatomical substrates, in pathways connecting these sites, and in the firing profiles of single neurons. Divergent neural control of hedonic and motivational processes raises the possibility for joint or separable modulation of food intake in human disorders associated with excessive eating and obesity. Early findings confirm an important role for 'liking' and 'wanting' in human appetitive behaviors, and suggest the intriguing possibility that exaggerated signals for 'wanting,' and perhaps 'liking,' may contribute to forms of overeating.

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1. Introduction

Food is one of the intense pleasures in life, and also a hard to resist incentive. We eat the foods that we like and avoid the ones we dislike. We also want the food that we like, sometimes too much, sometimes

* Corresponding author. 4012 CASL, 4901 Evergreen Road, Dearborn, MI 48128, United States. Tel.: +313 583 6443; fax: +1 313 583 6358.
E-mail address: pesu@umich.edu (S. Peciña).
[1] These authors contributed equally to the writing of this manuscript.

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uncontrollably. We like and want food when we are hungry but also at times even when our needs for energy and nutrients are fully met. Contributing crucially to nearly all varieties of eating are brain mechanisms of pleasure and incentive motivation for food and food-associated cues (Berridge, 1996; Toates, 1981). Accordingly, dysfunction within one or both mechanisms may contribute fundamentally to eating disorders including obesity and binge eating behaviors that show characteristics of excessive 'wanting' and/or 'liking' (Berridge, 2009; Berthoud and Morrison, 2008; Finlayson et al., 2007b; Mela, 2006; Nasser, 2001).

As we will review, endogenous opioid receptor activation in limbic brain substrates participates in eating processes via hedonic mechanisms, beyond endocrine and metabolic signals arising from organs involved in energy storage or utilization. Opioid agonists increase the hedonic value of foods making them more pleasurable and palatable ('liking,' in shorthand). In a world full of palatable foods, increases in the pleasure derived from food might contribute to overeating. But opioid agonists also seem to powerfully increase the motivational power of food cues, making foods and food-associated cues more motivationally relevant and possibly hard to resist ('wanting'). The aim of this review is to consider brain opioid mechanisms for 'liking' and 'wanting' food and how these reward circuits might be related to eating regulation and to eating disorders.

2. Mu opioids enhance food hedonics

Mu-opioid signaling plays a fundamental role in attributing pleasure value to sensory experiences like the taste of food. Administration of mu-opioid agonist or antagonist drugs in species ranging from rodents to humans potently modulate palatability ratings of food (Barbano and Cador, 2005; Berridge, 1996; Bodnar, 1998; Cooper, 1980; Kelley et al., 2002; Le Magnen et al., 1980; Levine and Billington, 2004; Panksepp, 1986; Peciña, 2008; Smith et al., 2010; Woolley et al., 2007; Yeomans and Gray, 2002). A major question that arises is where in the brain mu opioids are acting to enhance the hedonic value of sensory experience. Hedonic value can be measured in laboratory animals through the taste-reactivity technique developed by Grill and Norgren (1978). Rats, monkeys, and human infants emit orofacial and body reactions to intraorally infused tastes that closely track their hedonic valence (Berridge, 2000; Steiner et al., 2001) (Fig. 1). For example, a sweet taste of sucrose evokes a series of rhythmic midline tongue protrusions, lateral tongue protrusions, and paw licks. By contrast, a bitter taste evokes aversive reactions including oral gapes, headshakes, and forelimb flails. Importantly, these 'liking' and 'disliking' reactions modulate according to physiogical appetite states, similar to human verbal ratings, to dynamically reflect ongoing hedonic valuation of foods (Berridge, 2000; Havermans et al., 2009).

Systemic exposure to opioid stimulating drugs (e.g., intraperitoneal morphine injection) increases hedonic reactions to a sweet taste like sucrose in a similar fashion to natural increases in appetite (Doyle et al., 1993; Rideout and Parker, 1996). One fruitful approach to pinpointing more precisely where these signals arise in the brain has been to manipulate opioid transmission selectively in specific brain areas via local microinjection of opioid agonists or antagonists, and study the extent to which this manipulation affects hedonic reactions to tastes. This determines substrates that have sufficient and/or necessary roles for adding hedonic value to food. In a series of experiments, we along with Kent Berridge at The University of Michigan used these tools to locate hedonic 'hotspots' in the brain: small zones within limbic structures where mu-opioid receptor stimulation dramatically increases hedonic reactions to sweet tastes (Peciña and Berridge, 2005; Peciña et al., 2006; Smith and Berridge, 2005; Smith et al., 2010).

2.1. Hedonic hotspot in the rostrodorsal nucleus accumbens medial shell

One such hotspot resides in the medial–dorsal shell of the accumbens (Fig. 2). To locate this hotspot, deliberately staggered microinjection placements of DAMGO (a mu-opioid agonist) were made throughout the accumbens shell, and orofacial reactions to intraorally delivered sweet sucrose or bitter quinine were measured and compared to vehicle-injection control conditions. In addition, the accumbens zone of drug action was estimated by analyzing expression of Fos (a protein product of the immediate early gene c-Fos) in neurons around the injection site. Drugs like DAMGO produce

Fig. 1. Hedonic and aversive orofacial reaction homologies across species. Top: hedonic tongue protrusion response to a 'liked' taste (e.g., sweet sucrose) in rat, primate, and human infant. Bottom: aversive gape response to a 'disliked' taste (e.g., bitter quinine).

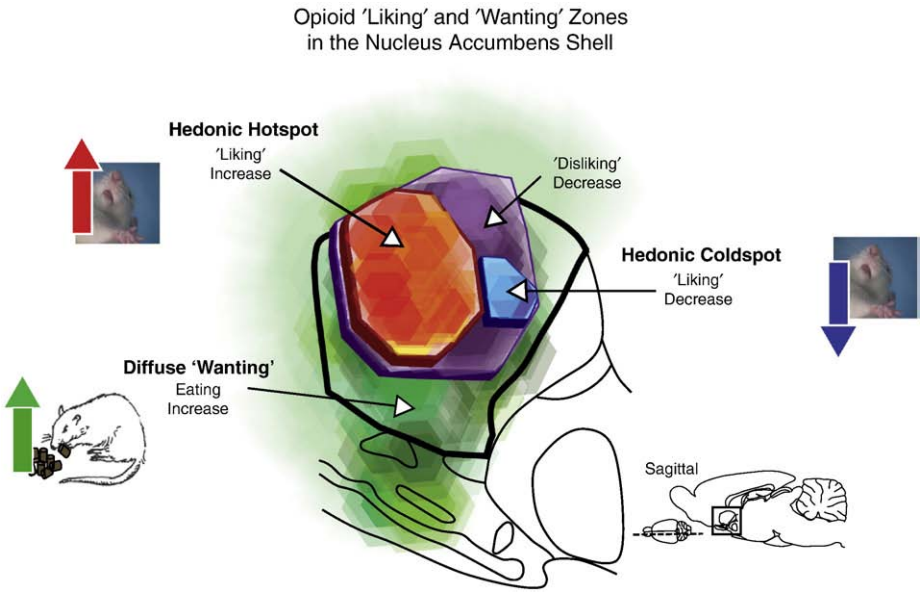

Fig. 2. Mu-opioid hedonic hotspot in the nucleus accumbens shell in sagittal view. Hexagonal symbols represent DAMGO microinjection placements, color-coded to reflect effects on hedonic and aversive taste reactivity, and eating. DAMGO microinjections into the mid-rostral dorsomedial shell dramatically increase hedonic 'liking' reactions to a sweet sucrose taste (red hexagonal placements = hedonic hotspot), and in a larger zone reduced normal aversive reactions to a bitter quinine taste (purple). The same microinjections more caudally actually suppressed normal 'liking' reactions in a small hedonic coldspot (blue). In comparison to these restricted zones, DAMGO increased eating of food chow in nearly every accumbens shell injection site (green), including the hotspot as well as non-hotspot zones. Peciña and Berridge, 2005.

plumes of Fos expression that are intense at the injection tip and grow weaker further away. The intensity of DAMGO-induced Fos plumes can be compared to Fos caused by vehicle microinjection, or endogenous Fos expression in untouched tissue. The fos plumes produced in the end a map where each microinjection was made, how far it spread functionally in Fos activation, and the degree to which it affected normal hedonic reactions to tastes.

This microinjection and Fos plume approach identified a 1 cubic millimeter hedonic hotspot in the nucleus accumbens medial shell where microinjections of the mu-opioid agonists DAMGO enhance the pleasure evoked by sweet sensations (Fig. 2). Within this rostrodorsal quadrant of the nucleus accumbens shell, DAMGO microinjections more than double the usual number of positive 'liking' reactions emitted to sucrose tastes (Peciña, 2008; Peciña and Berridge, 2005; Peciña et al., 2006; Smith and Berridge, 2007). Thus, in this hedonic hotspot of the nucleus accumbens, activation of the mu-opioid receptors increases food reward 'liking.' Aversive 'disliking' reactions to a bitter quinine taste are also suppressed by the same microinjections, as though DAMGO simultaneously decreases the unpleasantness of a bad taste and makes a pleasant taste even better. However, aversive reactions to sucrose and hedonic reactions to quinine (though low) were not typically affected. The dimensionality of positive–negative taste affect that is modulated by accumbens opioids (i.e., a single continuum versus orthogonal dimensions) will require further study.

The nucleus accumbens can be divided into core and shell subregions, but our anatomical studies suggest that the hedonic enhancement is restricted to the shell subregion, in particular to the rostral and medial shell. In fact, this specialized opioid hedonic hotspot constitutes only a third of the medial portion of shell and about a fifth of the whole shell (medial and lateral parts combined), and only a seventh of the entire nucleus accumbens (shell and core). At all other parts of the nucleus accumbens tested so far, microinjections of the same opioid agonist fail to increase hedonic 'liking' reactions to sweet tastes.

Opioid activity in this hotspot may participate in accumbens neural activation patterns across species that represent positive affective responses to tastes or smells of food, as well as a range of other rewarding stimuli like opiate drug reward, affiliative rewards, music/art, sex, humor, and earning money (Carelli, 2002; De Vries and Shippenberg, 2002; Everitt and Robbins, 2005; Gottfried, 2010; Insel and Fernald, 2004; Knutson and Cooper, 2005; Komisaruk and Whipple, 2005; Koob, 2009; Leknes and Tracey, 2010; Menon and Levitin, 2005; Mobbs et al., 2003; Robinson and Berridge, 2003; Skov, 2010; Wang and Aragona, 2004; Wise, 1989). Neuronal firing in the accumbens shell of rodents and primates has been shown to track the palatability of taste rewards across preferences or concentrations (Cromwell et al., 2005; Taha and Fields, 2005), notably responding phasically primarily with inhibition to sweet sucrose tastes that evoke hedonic orofacial reactions versus primarily excitation to aversive tastes that evoke disliking reactions (though with some variability in response profiles) (Roitman et al., 2005). Similarly, in humans increased fMRI BOLD signals in the accumbens correlate with pleasantness ratings of juice (Berns et al., 2001). To what extent local opioid transmission links with such hedonic-like neural representations of food will be an important topic for future research.

2.2. Hedonic hotspot in the caudal ventral pallidum

The nucleus accumbens shares reciprocal connections with the ventral pallidum, a limbic final common pathway for reward signals (Heimer and Wilson, 1975; Kalivas et al., 1999; Mogenson et al., 1980; Napier and Mitrovic, 1999; Smith et al., 2009; Zahm, 2000). The ventral pallidum contains its own mu-opioid hotspot for taste 'liking' in its caudal one-third (Fig. 3). Within this approximately 0.8 mm^3 zone in the rat, microinjections of DAMGO increase by nearly two-times the normal number of positive hedonic orofacial reactions to a sweet taste like sucrose, similar to nucleus accumbens hotspot injections (Smith and Berridge, 2005, 2007). By comparison, the same microinjections in more central zones of the ventral pallidum fail to reliably increase hedonic reactions, and in more rostral zones actually suppress them below normal. Interestingly, compared to the rostral ventral pallidum coldspot, the caudal hotspot supports a lower self-stimulation current threshold (Panagis et al., 1995) reflecting perhaps greater hedonic (and/or incentive) properties of neuronal excitation in this caudal zone.

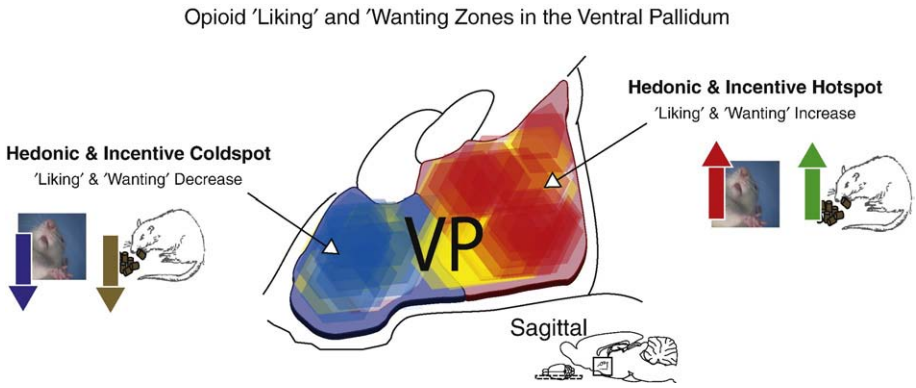

Fig. 3. Mu-opioid hedonic hotspot in the ventral pallidum. DAMGO microinjections enhanced hedonic reactions to sucrose and enhanced eating behavior in a caudal hotspot (red microinjection placement symbols). As DAMGO injections were shifted to more anteriorly in the ventral pallidum, hedonic reactions to sucrose and eating behavior were actually suppressed below normal levels (blue coldspot placements).
Smith and Berridge, 2005.

Beyond sufficient causal roles for mu opioids to stimulate an increase in hedonics, this caudal ventral pallidum hotspot is also necessary for taste 'liking' and encodes taste 'liking' in neural firing representations. Concerning necessary roles, rats with lesions to this site respond with aversive reactions to a normally pleasant taste like sucrose (Cromwell and Berridge, 1993), while in humans one recent case reports a decrease in drug craving and pleasure as well as general anhedonia following overdose-induced lesions to the ventral pallidum (and segments of the internal and external globus pallidus) (Miller et al., 2006). Opioids specifically are needed for hedonic enhancement there, as well as in the nucleus accumbens shell. A very recent study (Wassum et al., 2009) showed that microinjection of the opioid antagonist naloxone in the nucleus accumbens shell or mid-caudal ventral pallidum reduces the increase in licking frequency on a spout for sucrose that normally occurred with food deprivation (though we note that spout licking could reflect motivational processes in parallel to hedonic reactions).

Concerning neural coding roles, ventral pallidum hotspot neurons also dynamically track the hedonic value of taste rewards (Aldridge and Berridge, 2010) (Fig. 4). They fire in response to 'liked' rewards like sucrose, but fire little to a 'disliked' taste of aversively concentrated salt water. When the valence of the aversive salt taste is flipped to hedonically 'liked' via induction of a salt appetite (diuretic injections that induce a physiological state of sodium depletion) (Berridge et al., 1984), the ventral pallidum neurons begin firing to it with similarly high frequency as to the sweet sucrose taste (Tindell et al., 2006). This pattern of ventral pallidum activation to positive stimuli bears a striking resemblance to human neuroimaging findings of Calder et al. (2007), in which the caudal ventral pallidum (the hotspot) became active in people viewing pictures of appetizing foods whereas the rostral ventral pallidum (coldspot) was more active to aversive food pictures. Thus, in all, the caudal ventral pallidum plays a special role in positive hedonic valuation with necessary, sufficient, and neural encoding functions that likely extend similarly across rats and humans. At present it is unclear why this caudal zone in particular holds such hedonic-modulating capacity, though a few known anatomical distinctions along the rostrocaudal axis may prove to be relevant (e.g., high opioid immunoreactivity, less dense pre-synaptic mu-opioid expression, and greater proportion of non-cholinergic neurons in caudal ventral pallidum) (Bengtson and Osborne, 2000; Maidment et al., 1989; Olive et al., 1997).

2.3. Larger hedonic circuits involving nucleus accumbens and ventral pallidum

Having a brain with at least two opioid hedonic hotspots may implicate a functional hedonic circuit stretching across them both. There is recent evidence that this is the case, and that nucleus accumbens and ventral pallidum opioid hedonic hotspots act in concert for adding 'liking' value to food. Smith and Berridge (2007) have found that microinjections of DAMGO alone in the accumbens or ventral pallidum hotspots increased 'liking' reactions to sucrose as before, and increased Fos expression both locally at the site of injection and distally in the other hotspot. This supports a view that reciprocal recruitment of these substrates underlies hedonic enhancements; activating one activates the other, and taste 'liking' results. Bidirectional connections and physiological influence make this accumbens-pallidum functional circuit likely an anatomically direct one (Churchill and Kalivas, 1994; Hakan et al., 1992; Mogenson and Yang, 1991; Napier and Mitrovic, 1999; Zahm, 2000), though indirect interaction through other intermediary structures is possible as well (e.g., via the limbic/associative cortico-basal ganglia loop passing through mediodorsal thalamus). Reciprocal hotspot recruitment also raises the possibility that each site is needed for hedonic enhancement by the other, which is indeed the case. Simultaneously blocking opioid transmission with microinjections of the antagonist naloxone into the ventral pallidum prevents the increase in hedonics normally evoked by DAMGO microinjections into the accumbens (Smith and Berridge, 2007). The reverse is also true; naloxone in the accumbens prevents hedonic increases from ventral pallidal DAMGO.

As a whole, a story begins to emerge that mu-opioid activity in both hotspots are needed for 'liking' enhancement, that one without the other may be insufficient, and more broadly that the nucleus accumbens and ventral pallidum hotspots function as components of a functionally bidirectional circuit for opioid food hedonic signals. But while hugely important, opioids are not the whole story for hedonics, nor for motivational eating discussed below. 'Liking' substrates extend beyond mu opioids in the accumbens and ventral pallidum to include, at least, endocannabinoid and GABAergic transmission, especially in the accumbens (Jarrett et al., 2005, 2007; Kirkham, 2009; Mahler et al., 2007; Reynolds and Berridge, 2002), benzodiazepine activity, especially in the brainstem parabrachial nucleus (Higgs and Cooper, 1996; Soderpalm and Berridge, 2000), orexin neurotransmission in the ventral pallidum (Ho and Berridge, 2009), and likely neural activity in the orbitofrontal cortex (Burke et al., 2010; Kringelbach, 2010; Murray and Izquierdo, 2007; Small and Veldhuizen, 2010). Anatomically the accumbens-pallidum circuit is reciprocally connected with these sites, indicating the intriguing possibility that they together form an even larger-interconnected network for processing sensory pleasures. More focused anatomical tracing studies of the hotspot sites as well as functional interaction experiments are now needed to identify possible circuit models.

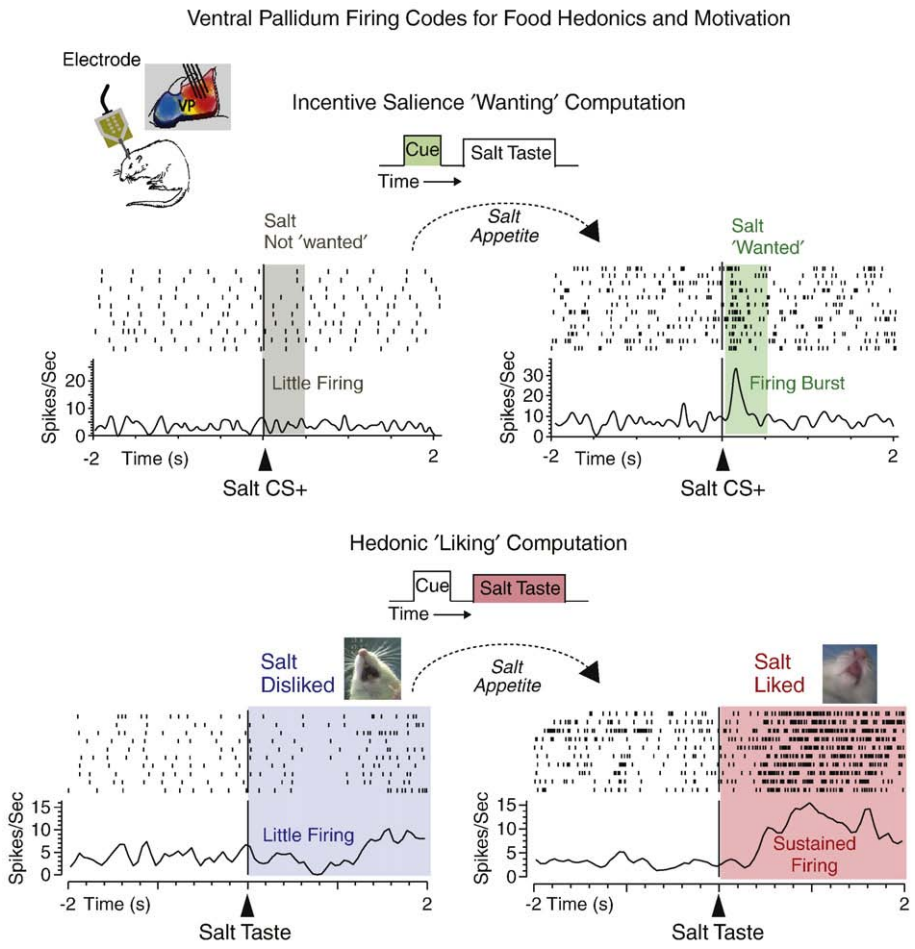

Fig. 4. Neural encoding of food 'liking' and 'wanting' in the ventral pallidum hotspot. Neuronal firing was recorded, via electrodes lowered into the caudal ventral pallidum, in response to intraorally infused tastes of aversively concentrated salt water, as well as an auditory Pavlovian tone predicting it. Raster-histogram plots show example firing responses of ventral pallidum neurons before and after induction of a salt appetite, which induces a shift from 'disliked' and 'unwanted' salt to 'liked' and 'wanted' salt (tick marks show action potentials across time [*x*-axis] and trial [top to bottom], aligned to the stimuli deliveries). Normally, ventral pallidal hotspot neurons fired very little to a cue predicting the aversive salt taste (top left) or to the salt itself (bottom left) that evoked aversive orofacial reactions like gaping. Following induction of a salt appetite, these neurons fired vigorously to the cue predicting salt on the very first trials (top right), and also began to fire in response to the salt taste itself when finally received (bottom right), which now evoked hedonic 'liking' reactions due to the appetite state. Ventral pallidal neural activity therefore dynamically tracks shifts in the hedonic value of food and incentive value of predictive cues. Tindell et al., 2006, 2009.

3. Opioids increase food reward 'wanting,' not just 'liking'

Although we typically crave the food we find pleasurable, a food's motivational 'wanting' and hedonic 'liking' properties are dissociable in the brain and can fluctuate independently. One example substrate is mesolimbic dopamine. Increases or decreases in limbic dopamine transmission always fail to affect hedonic liking reactions in rodents or pleasure ratings in humans for food and other stimuli, yet they potently alter the motivational 'wanting' properties of the same rewards (Berridge, 2007; Berridge and Robinson, 1998; Leyton, 2010; Peciña et al., 2003; Robinson et al., 2005; Wyvell and Berridge, 2000). Similar 'wanting'-without-'liking' roles for food have been found for GABA transmission in the ventral pallidum (Shimura et al., 2006; Smith and Berridge, 2005).

The role of mu-opioid brain systems in food reward are known to be largely dependent on their effects on palatability and hedonic processing. However, our mapping studies in the nucleus accumbens and ventral pallidum suggest that opioids might also play a more specific role in other incentive motivational processes above and beyond their effects on palatability (Figs. 2 and 3). The same hotspot microinjections of DAMGO also stimulate 'wanting' or eating of food (Peciña and Berridge, 2005). But 'wanting' mechanisms can extend far beyond hedonic hotspots. In contrast to the tight localization of the nucleus accumbens hedonic hotspot (rostrodorsal quarter of the nucleus accumbens medial shell), the stimulating effects of opioid microinjections on eating (a reflection of food 'wanting') appear to be widely distributed throughout almost the whole medial shell, and possibly also extend to the core of the nucleus accumbens (Fig. 2). Mu-opioid agonists robustly increase food intake in the rostrodorsal hedonic hotspot, but also in areas caudal and ventral to the hedonic hotspot. Thus, activation of mu-opioid neurotransmission in virtually the entire accumbens shell enhances 'wanting' for food rewards even at sites that fail to enhance 'liking' of food ('wanting' without 'liking') (Peciña and Berridge, 2005).

In the ventral pallidum, eating and hedonic sites overlap more closely (Fig. 3). DAMGO microinjections in the caudal hotspot can quadruple the normal level of food intake at the same sites where 'liking' reactions are similarly enhanced, while injections more rostrally can suppress eating below normal (Shimura et al., 2006; Smith and Berridge, 2005). Similarly, caudal microinjections of an opioid agonist there increase the amount a rat will work for electrical stimulation of the medial forebrain bundle, whereas rostral injections instead decrease it (Johnson et al., 1993). Lesions or GABAergic inhibition through muscimol microinjection to the caudal ventral pallidum also dramatically reduce food consumption (Cromwell and Berridge, 1993; Taha et al., 2009). These overall effects (abolished

intake and 'liking' reactions; predomination of aversive reactions) are presumably the consequence of inhibited neural activity in the caudal ventral pallidum, achieved either temporarily via muscimol microinjection or more permanently via lesions. This indicates that neural firing in this zone is crucial to the process of adding hedonic and incentive value to sensory stimuli. Why food aversion would result from neural silencing here is a curious outcome. It could be because aversion processes are still active in the brain and become a default state, or instead that natural inhibition of ventral pallidal firing contributes to negative affect (which is artificially induced with these manipulations). At present it is too early to distinguish these or other possibilities.

The notion that opioids increase appetitive motivational processes above and beyond their effects on 'liking' processes is consistent with many previous findings that opioids stimulate food intake or 'wanting' measures throughout a range of striatal sites, as well as in many other brain areas (Bodnar, 2004; Higgs and Cooper, 1998; Kelley et al., 2005; Levine and Billington, 2004; Yeomans and Gray, 2002; Zheng et al., 2007). Mice lacking β-endorphin, enkephalin or both show reduced motivation to obtain food when sated but not when food deprived (Hayward et al., 2002), while mice lacking the mu-opioid receptors show reduced responding on demanding operant nose poke schedules (FR3 or progressive ratio) for food rewards (Papaleo et al., 2007) and show diminished food anticipatory activity measured by adjustment of scheduled wheel running (Kas et al., 2004). These opioid induced motivational enhancements can occur even before experience with the reward. Kelley and colleagues have demonstrated that rats injected with mu-opioid agonists in the shell of the nucleus accumbens are willing to work more for a sucrose pellet even before tasting the sweet reward (Zhang et al., 2003).

3.1. Cue-triggered incentive salience motivation as a mechanism for mu-opioid 'wanting'

A biopsychological mechanism by which motivated food 'wanting' occurs is hypothesized to be the attribution of incentive salience to food-associated stimuli, typically through experience with its hedonic attributes (thus, cues associated with particularly hedonic tastes are likely to have stronger incentive salience). This includes its sights and smells, as well as predictive environmental cues, that trigger motivational 'wanting' for itself and its associated reward (Berridge, 2004a; Bindra, 1978; Toates, 1986). Incentive salience is a very basic reward process and not necessarily accessible to conscious awareness (Winkielman and Berridge, 2000). In this sense, incentive salience can differ considerably from the cognitive form of desire in which individuals have in mind a specific food goal, crave it, and deliberately select actions likely to get it.

One consequence of heightened incentive salience to food related stimuli is elevated intake, though intake by itself can be an indirect or downstream measure of incentive salience. Therefore it is important to accompany 'wanting' measures of food intake with measures that better isolate incentive salience mechanisms, such as the Pavlovian-instrumental transfer test (PIT). In this paradigm, rats are first trained to press one of two levers to obtain a reward and then they are separately trained to associate a Pavlovian cue with the same reward. On test days, lever pressing is assessed while the 30 s reward cue comes and goes unpredictably, always in the absence of the unconditioned reward (i.e., under extinction conditions). Using this experimental approach, we have found that mu-opioid microinjections in the nucleus accumbens increase cue-triggered 'wanting' for sucrose associated cues (Peciña and Berridge, 2008). DAMGO microinjections in the core or medial shell of the nucleus accumbens increase cue-triggered lever pressing aimed at a lever previously associated with a sucrose reward. Peaks of cue-triggered 'wanting' are increased, without increasing baseline pressing in the absence of the Pavlovian CS+, either pressing triggered by the control CS− or pressing on an inactive control lever that had not been associated with sucrose. This outcome indicates that enhanced eating caused by accumbens opioid stimulation may be driven by an increase in the incentive properties of food-associated cues.

Another opioid site that similarly mediates incentive salience for food and related stimuli is the central amygdala. This site is important for motivational phenomena including Pavlovian-instrumental transfer (Corbit and Balleine, 2005; Hall et al., 2001; Holland and Gallagher, 2003) and supports enhanced eating after opioid agonist microinjections (Gosnell, 1988; Kim et al., 2004). Mahler and Berridge (2009) also found that DAMGO microinjection into the central nucleus increased motivated behaviors towards Pavlovian food-predicting stimuli depending on baseline preferences for each rat. With training to associate a lever insertion cue with food reward, some rats come to approach the reward-predictive cue itself when presented (and often nibbled and sniffed the lever as though it had food-like qualities), while others run directly to the food dish. Central amygdala opioid stimulation increases these predominant behaviors in each rat (i.e. approach the reward-predictive cue itself or run directly to the food dish), but not the alternate less-dominant behavior, and also increases intake of freely available food (Mahler and Berridge, 2009). It does not, however, similarly enhance hedonic 'liking' reactions to sweet tastes (which may instead be reduced) nor affect aversive reactions to quinine (Mahler and Berridge, 2008). It thus constitutes a site where opioids mediate 'wanting' but not 'liking,' and further underscores the dissociability of these opioid reward components. In a related study, Wassum et al. (2009) used microinjections of naloxone to block opioid transmission in the neighboring basolateral nucleus of the amygdala, a structure important for cued appetitive behavior and motivation (Cardinal et al., 2002; Corbit and Balleine, 2005; Everitt et al., 2003; Holland and Petrovich, 2005). This experiment showed that the amygdala is needed for the integration of enhanced hedonic reward value into subsequent instrumental responses for that reward (i.e., needed for cognitive act–outcome encoding), though is not needed for the increase in reward hedonics itself (measured by spout licking rates), which instead required nucleus accumbens and ventral pallidum opioids. How the amygdala may function overall for opioid reward appears complex, though it is clearly important for attributing incentive salience to specific, learning-gated Pavlovian stimuli (the central nucleus) and integrating reward values into cognitive goal-directed motivation (the basolateral nucleus), in broader terms for motivating behavior towards specific stimuli and rewards.

How is incentive salience for food-associated cues encoded neurally? In the ventral pallidum, a behavioral electrophysiology approach has been taken in the laboratory of J. Wayne Aldridge at The University of Michigan to address this question and to isolate CS+ incentive salience functions of the hotspot (Fig. 4). Ventral pallidum hotspot neurons fire rapidly and phasically to Pavlovian auditory cues that predict a sweet taste, and fire little to cues predicting nothing (Tindell et al., 2004). Although simply firing to a Pavlovian CS+ for reward does not mean the neurons are encoding an incentive signal (e.g., as opposed to a cached associative prediction or expectancy signal), a striking feature of ventral pallidum neuronal activity is that it dynamically tracks changes in incentive salience with fluctuating appetite or limbic states even before rewards are re-experienced and cached associations can be updated. Ventral pallidum firing can even re-compute incentive salience from a zero or negative value to positive, in other words a complete reversal. In a follow-up to the study of salt-appetite hedonic coding described above, rats learned to associate a tone with sucrose, and a second tone with aversive salt delivery (Tindell et al., 2009) (Fig. 4). Initially after learning, ventral pallidum neurons responded with a burst of firing to the tone for hedonic sucrose but with little firing to the tone for aversive salt. A salt appetite was then induced overnight, and tones replayed in extinction. The next day, prior to any experience at all with the salt itself in a newly 'liked' state, ventral pallidum neurons fired equally strongly to the salt cue as they

did to the cue for sucrose. This shows that ventral pallidum firing dynamically recalibrates the incentive salience of Pavlovian cues without the need for relearning of cue-reward associations to update cached predictions. This incentive salience computation can be modeled as a gain-control mechanism for modulation of incentive motivational properties of Pavlovian associative memories (Zhang et al., 2009). This can be expressed in a modified temporal-difference learning algorithm, in which opioids raise a motivational gain-control (κ) leading to a multiplication of 'wanting' (V) when triggered by an incentive food cue, without affecting cached memory (r_t): $\tilde{V}(S_t) = \tilde{r}(r_t, K) + \gamma V(S_{t+1})$.

In humans, similar putative incentive salience representations in ventral pallidum and nucleus accumbens (and amygdala) fMRI BOLD signals have been recently detected in studies on food reward. These sites are part of a large network of sites that are recruited in response to food related stimuli, for example odor cues predicting a tasty drink (Small et al., 2008), the sight of a sweet chocolate desert (Rolls and McCabe, 2007), and pictures of high-calorie foods like deserts or snacks (particularly in obese subjects) (Stoeckel and Weller, 2008, 2009). Although the focus here is on food reward, similar patterns of reward and incentive cue activations in accumbens, ventral pallidum, or amygdala are noted often in studies on drugs, money, sex, music, facial preferences and other incentives in primates and rodents (Aragona et al., 2003; Balleine and Killcross, 2006; Breiter et al., 1997; Brown et al., 2004; Carelli, 2002; Childress et al., 2008; Cooper and Knutson, 2008; Insel and Young, 2001; Kalivas and Volkow, 2005; Kim et al., 2007; Leyton, 2010; McClure et al., 2004; Menon and Levitin, 2005; Monk et al., 2008; Pessiglione et al., 2007), indicating a role in motivation and hedonics that is not limited to food. To what extent these activation patterns are driven by local opioid transmission is mostly unknown. Possibly relevant are PET findings that accumbens opioid transmission is correlated with heroin reward (Greenwald et al., 2003), alcohol craving (Heinz et al., 2005), reward-sensitive personalities (Schreckenberger et al., 2008), and placebo-induced affective relief from pain (Zubieta et al., 2005), while ventral pallidum opioid activity is inversely associated with affective sadness (Zubieta et al., 2003). Also, intravenous morphine injections that produce reported euphoric effects increase fMRI detected activation in the nucleus accumbens and extended amygdala area, as well as orbitofrontal cortex and other sites (Becerra et al., 2006).

3.2. Disentangling mu-opioid 'liking' and 'wanting' signals when both rise together

At a glance, it would appear as though nucleus accumbens and ventral pallidum hotspots represent an entangling of opioid 'liking' and 'wanting' functions such that stimulation of one typically accompanies stimulation of the other. This makes some intuitive sense, as often our motivation is highest for the most sweet, fatty, and otherwise palatable foods. In these commonly occurring moments it may be safe to conclude that accumbens and ventral pallidum hotspots, as well as other sites, are engaged for combined hedonic and motivational processing. Yet it raises the conundrum of how these reward components are told apart locally and in downstream circuits when stimulated in tandem via these hotspots. It turns out that they are indeed independently controlled, and that even when opioids increase both 'liking' and 'wanting' for food in precisely the same hotspot sites, they do so via dissociable pathways and neural firing signatures.

Some evidence for this notion came from the study on hotspot interactions showing bidirectional requirement of both hotspots for 'liking' enhancement, such that opioid blockade in one site prevented opioids in the other from enhancing hedonic taste reactions (Smith et al., 2007). However, the same was not true of food 'wanting' interaction. In striking contrast to hedonics, food intake measured on the same days was found to be asymmetrically dominated by the accumbens. The enhancement of food intake by DAMGO in the ventral pallidum was blocked by simultaneous naloxone microinjection in the accumbens (just as 'liking' increases had been blocked). But the reverse was not true: naloxone microinjection in the ventral pallidum failed to block eating increases evoked by DAMGO microinjection in the accumbens (despite blocking 'liking' increases). One hypothesis is that accumbens opioids enhance food 'wanting' via multiple opioid-dependant neural pathways, some of which bypass ventral pallidum. A related conclusion has been reached by Taha et al. (2009), who showed that unilateral lesions to the ventral pallidum fail to block the enhancement of fatty food consumption caused by ipsilateral accumbens DAMGO microinjection. Candidate pathways include accumbens connections with the ventral tegmental area and central nucleus of the amygdala, both of which contain opioid signals that are needed for accumbens opioids to increase eating (Bodnar et al., 2005; Kim et al., 2004; MacDonald et al., 2003). Other possible efferent routes for accumbens-mediated eating are the nucleus of the solitary tract, lateral and dorsomedial hypothalamus, and basolateral (and central) amygdala, where inactivation via GABAergic inhibition similarly blocks enhanced eating after accumbens opioid stimulation (Will et al., 2003, 2004). An implication of these data is that the hedonic impact of food is much more sensitive to disruption by opioid dysfunction in one site, whereas the motivation to eat may be comparatively resilient due to a much larger distribution in brain circuitry.

In a more recent study we addressed this issue of how opioid 'liking' and 'wanting' are separated as distinct signals in these hotspots at the level of neural firing with Kent Berridge and J. Wayne Aldridge at The University of Michigan (Smith et al., 2007). We designed a serial cue task in which signals for incentive salience, hedonic impact, and cognitive-associative prediction of food reward would be dissociated (Tindell et al., 2005; Zhang et al., 2009). In this task, a CS + 1 is followed by a CS + 2 and then a sucrose UCS. When the sequence is fully learned, the first cue (CS + 1) comes to predict with 100% certainty stimuli to follow (CS + 2, UCS), and therefore contributes maximally to new reward predictions, by definition carrying maximal predictive strength (Schultz et al., 1997; Zhang et al., 2009). The UCS itself contains maximal hedonic value being the moment when the palatable sweet taste is experienced. The CS + 2 is then 'left over' with relatively less predictive or hedonic value. It is fully predicted by the CS + 1, is no longer 'surprising' or generates a prediction error to guide new predictions, and is redundant in information about UCS. However, it still contains substantial, possibly even maximal, incentive value being the closest cue to actual reward when motivational signals can be highest (Corbit and Balleine, 2003; Tindell et al., 2005; Zhang et al., 2009). Thus, incentive salience signals may be detectable in firing representations to the CS + 2, particularly if they modulate immediately (i.e., in extinction) after a physiological or limbic state change prior to any opportunity for CS-UCS relearning, as well as if they parallel behavioral 'wanting' changes.

After training on this paradigm, we recorded neural activity in the ventral pallidum hotspot, where each signal is represented in firing to CS + 1, CS + 2 and UCS stimuli, and then pharmacologically increased 'wanting' and 'liking' together (via DAMGO microinjections in the accumbens hotspot), and compared this to increasing 'wanting' signals alone (via amphetamine microinjections in the accumbens to stimulate dopamine, shown previously to engage purely 'wanting' mechanisms in behavior and ventral pallidum firing) (Tindell et al., 2009; Wyvell and Berridge, 2000). In this task, ventral pallidum neurons normally fired to each stimulus roughly equal, with a CS + 1 prediction-signal bias (Tindell et al., 2005). Intra-accumbens amphetamine enhanced ventral pallidum firing selectively to the incentive CS + 2 on its first exposures in an extinction test (and increased food intake in a later free feeding test), confirming incentive salience magnification. By comparison, accumbens DAMGO microinjection

increased ventral pallidum firing to both the CS + 2 in extinction and UCS once tasted (accordingly, both food intake and UCS hedonic reactions were increased too). Yet, these jointly accentuated CS + 2 'wanting' and UCS 'liking' signals in ventral pallidum firing were still distinguished by non-overlapping populations of neurons that encoded one or the other, and also by distinct patterns of firing to the CS + 2 (short latency and phasic firing response) versus UCS (longer duration and more variable firing response). The relevant conclusion is that 'liking' and 'wanting' enhancements are kept separate via distinct circuit channels. Moreover, even when 'liking' and 'wanting' are enhanced together — which occurs after opioid stimulation of hedonic hotspots, and which may be common in daily eating — they can still be separately tracked and communicated via dissociable opioid-dependant reward networks and firing codes in the ventral pallidum hotspot.

A related point based on these cumulative findings is that 'liking' and 'wanting' are dissociable as distinct reward components even to the level of neural firing. Taste 'liking' reactions and food 'wanting' can increase hand-in-hand after opioid stimulation of the limbic hotspots, or 'wanting' alone can increase after opioid stimulation of wider areas. Pure 'wanting' increases in enhanced eating or instrumental behavior also are achieved via amygdalar opioid stimulation, as well as by mesolimbic dopamine stimulation or ventral pallidal GABA blockade. The co-mingling of 'liking' and 'wanting' in some substrates and their divergence in others, and the separate neural firing profiles for these signals in the ventral pallidum, indicates that they are separable reward components (e.g., rather than a single processes detected at differing sensitivities by different behavioral expression measures).

It is important to acknowledge at this point the remarkably wide distribution of sites in the brain where opioids can modulate feeding (e.g., also in dorsal and lateral striatum, hypothalamic nuclei, ventral tegmentum, parabrachial nucleus, paraventricular nucleus, nucleus of the solitary tract) (Bodnar et al., 2005; Denbleyker et al., 2009; Glass et al., 1999; Glass et al., 2002; Le Merrer et al., 2009; Naleid et al., 2007; Will et al., 2003; Wilson et al., 2003). For most of these, it remains unclear if 'wanting,' 'liking,' associative learning processes, homeostasis/metabolic processes, or some other food reward-related process is engaged by enhanced opioid transmission. Similarly for sites where opioids can function to increase putative food 'wanting' signals in eating behavior or instrumental work for food, it is mostly unclear if 'liking' reactions are also increased in parallel, and if so, how these signals may be anatomically or physiologically disentangled. In short, much work remains to be done in elucidating the neural circuitry for opioid-mediation of food hedonics and motivation.

4. Potential role of opioid reward systems in human overeating disorders

Eating is regulated by an extraordinary complexity of mechanisms that regulate energy metabolism and behaviors that lead to the procurement of food. Eating behavior and its associated overeating disorders (e.g., obesity and binge eating disorders) are at the same time a prototypical model of a complex genetic disease and a product of life-style choice, social–economic influences, and reward and decision making processes. Thus, it is unlikely that we will find a one size-fits-all solution to the problem of overeating and its consequences on weight gain. Recognizing this variability, efforts are being made to distinguish different forms of overeating that may apply best to distinct eating styles and subpopulations of overeaters. As one relevant example, distinctions are now made between eating that is tied closely to homeostatic needs versus eating that extends beyond those needs. The latter may be especially driven by reward processes and has been termed "hedonic hunger" and can involve steady but excessive eating and/or bursts of binge eating (Finlayson et al., 2007a; Lowe and Butryn, 2007; Lowe and Levine, 2005). It is in this category—eating above-and-beyond metabolic needs—that 'liking' and 'wanting' may be hypothesized to play a special role. And if true, the findings that opioids can mediate food 'liking' and 'wanting' via dissociable brain mechanisms raise the intriguing possibility of independent modulation in overeating. Pure 'wanting' mechanisms like mesolimbic dopamine could likewise contribute to overeating driven by motivation versus hedonics (Berridge, 2009). Thus, overeating in some individuals could be due especially to excessively active or strong signals for food 'wanting,' food 'liking,' or perhaps both.

With this in mind important theoretical distinctions can be made between 'rational' and 'irrational' potential contributions of basic reward signals to overeating beyond energy requirements (Berridge, 2009; Berridge, 2004b). 'Rational' motivation to eat would be proportional to the hedonic value of foods. For example, individuals 'want' food the more it is 'liked.' This balance of 'wanting' and 'liking' is modulated almost as a unit by physiological appetite states (e.g., 'wanting' and 'liking' food more when hungry) or changes in the associative contingency of cue-food pairings (e.g., 'wanting' and 'liking' food less after being paired with illness). In other words 'wanting' and 'liking' levels are mostly balanced. Obesity could speculatively result from this form of purely proportional and rational 'wanting' of hedonic foods (e.g., sugars, fats, etc) at the expense of less palatable and healthier foods. But beyond this, a second possibility is 'irrational' motivation to eat in which 'wanting' would surpass the hedonic value of the food to which it is directed. Theoretically in overeaters this would comprise a level of motivation to eat that is disproportionately stronger than how much the target food is pleasurable, in other words, being motivationally pulled to a food strongly despite not finding it tastier or even cognitively deciding it is a good idea to eat. While unbalanced 'wanting' of this sort may sound counterintuitive, it is possible due to the divergence of brain mechanisms for 'liking' versus 'wanting,' and as noted above can occur in laboratory animals after manipulations of the 'wanting' opioid substrates separate from the hedonic hotspots. Irrational motivation can also be observed by stimulation of the dopaminergic 'wanting' system that causes exaggerated motivation and incentive salience neural signals for food cues (Tindell et al., 2005; Wyvell and Berridge, 2001), and sensitization of 'wanting' but not 'liking' is hypothesized to contribute to addictive behaviors (Robinson and Berridge, 1993).

4.1. 'Liking' and 'wanting' roles in human eating behavior

Much experimental and case-study evidence now exists to support the notion that humans draw influence from both incentive motivational 'wanting' and hedonic 'liking' in eating (Berridge, 2009; Finlayson et al., 2007b; Mela, 2006; Nasser, 2001; Sclafani, 1995; van den Bos and de Ridder, 2006). In researching these roles in overeating that extends beyond metabolic deficits, a number of studies have implicated the 'wanting' system in exaggerated motivation to eat and hyper-reactivity to food-associated cues. Hyperactivity of the 'liking' system has been implicated as well, but less consistently, and occasionally exaggerated 'wanting' but not 'liking' has been found in subjects that are obese or at risk for obesity.

Enhanced cue-triggered 'wanting' for food is often implicated in overeating. For example, compared to lean control subjects, when cued by salient stimuli, like food sights and smells, overweight subjects will put forth more effort to obtain foods and eat/drink more as well (Johnson, 1974; Kozlowski and Schachter, 1975; Tetley and Brunstrom, 2009). A greater propensity to salivate in response to food-associated cues has been observed in overweight compared to lean individuals (Epstein et al., 1996; Nirenberg and Miller, 1982) and in subjects gaining weight versus maintaining a steady weight (Guy-Grand and Goga, 1981). This salivation hyper-reaction to a food cue can fail to correlate with greater self-reported hunger or food craving, indicating perhaps it reflects a non-conscious incentive evaluative

reaction that was higher in these overweight subjects. Consistent with the notion of hyper-incentive reactivity to food cues, brain imaging studies of overeaters or those with higher basal levels of reward-sensitivity (using a behavioral activation scale) have detected heightened neural responses to stimuli associated with palatable foods (e.g., pictures of chocolate cake) in the nucleus accumbens, amygdala, and ventral pallidum (and other areas) (Beaver et al., 2006; Stoeckel and Weller, 2008). Motivation to eat can even rise without apparent concomitant rise in liking. For instance, compared to lean control subjects, obese or overweight subjects will choose to spend points earned from a computer task in procuring tasty food versus playing videogames, correlating with greater food consumption but no greater subjective rating of its hedonic value (Saelens and Epstein, 1996).

Binge eating may provide a special case of excessive 'wanting' that results in compulsive and uncontrollable bursts of eating until uncomfortably full (which may or may not be compensated for in fasting or regurgitation afterwards) (Mathes et al., 2009). The propensity to binge eat correlates with an abnormal post-meal lingering desire or motivation to eat (Nasser et al., 2004). The possibility of opioid involvement in overeating finds support in recent results of Davis et al. (2009), which suggest that obese binge eaters have enhanced responsiveness to the rewarding properties of foods greater likelihood of having a functional A118G polymorphism of the mu-opioid receptor gene as well as the three functional polymorphisms related to the D2 receptor (DRD2) gene. They find that 80% of obese binge eaters carry A1−/G+ alleles for genes that code mu opioid and dopamine D2 receptors. Specifically, the authors report that obese binge eaters have a greater than expected frequency of the "gain of function" G allele of the mu-opioid receptor and greater appetitive motivation scores on a 'power of eating' questionnaire scale (e.g., "Just before I taste a favorite food, I feel intense anticipation"). Interestingly, this allele was under-represented in obese individuals without binge eating disorder, suggesting that the over expression of the mu-opioid receptor might influence the tendency to binge eat particularly palatable foods.

A few studies have also examined 'liking' roles in overeating. For example, overweight subjects that tend to consume highly fatty foods report heightened positive enjoyment reactions to these foods compared to their lean counterparts that also tend to prefer consuming fatty food (Blundell et al., 2005). Studies among obese women have reported that body mass index is positively correlated to the hedonic ratings for fat (Drewnowski, 1985; Drewnowski and Schwartz, 1990). Similarly, heightened hedonic responses for sweet and creamy solutions among Pima Indians (highly prone to obesity) is associated with weight gain in these populations (Salbe et al., 2004). However, in other studies, 'liking'-related measures were not inflated in overweight subjects (Mela, 2006; Saelens and Epstein, 1996), perhaps tempering this conclusion and suggesting that heightened hedonic reactions to food may apply to certain overweight subpopulations, food items like fats, or task conditions.

Of course many well-acknowledged caveats exist for these conclusions, including the degree to which 'liking' versus 'wanting' can be reliably separated in response to laboratory stimuli that may trigger both, be available for conscious introspection and reliable self-report, and be disentangled from a potentially complex web of other covarying factors (e.g., cognitive-decision making variables, individual perceptions of metabolic deficits, basal emotional states, concern about weight, etc.). It can also often be unclear to what extent reward dysfunctions in behavior or neuroimaging responses are a cause of overeating, or a consequence of a history of eating beyond energy needs, or dieting, etc. (though the ability of brain manipulations like opioid microinjections to increase 'wanting' and/or 'liking' measures indicates a causal role). However, so far the evidence seems strong that heightened 'wanting' especially, and perhaps 'liking' in some instances, contribute powerfully to excessive eating beyond metabolic needs in humans (Berridge, 2009; Finlayson et al., 2007b; Mela, 2006; Nasser, 2001). Moreover, there appear to be task conditions or subpopulations of individuals in which food 'wanting' may be heightened without concomitant increases in the palatability 'liking' of the food itself. These situations bear a strong resemblance to the 'wanting' without 'liking' consequences of certain brain opioid or dopamine manipulations, and may plausibly constitute genuine cases where irrational food 'wanting' dominates eating behaviors over-and-above 'liking.' Mela (2006) in reviewing the topic concludes just this: "obesity may be associated with greater motivation for food consumption…but without deriving any greater pleasure from the orosensory experience of eating" (p. 12). Neurally, this could occur via exaggerated activity of opioid incentive motivational signals discussed here, but there are numerous other sites and neurochemical substrates that contribute to 'wanting' separately from 'liking,' and when stimulated can potently enhance the pursuit and consumption of food (e.g., mesolimbic dopamine, ventral-striatopallidal GABA, and others) (Berridge, 2009). One potentially relevant idea here, though at present equivocal, is the possibility that neural sensitization of 'wanting' systems occurs in some overeaters and leads to a lasting hyper-reactivity to food and associated cues akin to psychomotor sensitization observed after repeated exposure to narcotic drugs (Bakshi and Kelley, 1994; Berridge, 2009; Robinson and Berridge, 1993).

4.2. A role for opioid antagonists in treating excessive wanting or liking?

As presented here, opioid antagonists would perhaps appear to be effective pharmacological treatments for overeating caused by over-responsive food reward mechanisms of 'liking' and/or 'wanting.' This pharmacological approach has on occasion proven to be an effective intervention measure for harmful compulsive behaviors, such as to reduce the drive and excessive motivation to gamble in some pathological gamblers. In one compelling example, Kim (1998) reports a case study of a severe pathological gambler and compulsive shopper whose symptoms improved dramatically after treatment with the opioid antagonist naltrexone. It is particularly relevant to note the hyper-reactivity of the patient to the gambling related cues: "My most serious problem was gambling. I was addicted to the lights and chatter and other noises of the casino. It helped me get out of myself." Naltrexone effectively controlled the hyper-reactivity to the cues and the urge and motivation to gamble: "I was not calculating and strategizing and breathing shallow. As I walked to the casino my excitement wasn't there. I entered the casino and I felt like I was in a grocery store. I walked past many machines and didn't put in one coin. I didn't have the urge to put in the coins. I did not feel like I was tempted and warding off temptation. It's a miracle." Naltrexone and related drugs have been also used as a tool to treat addiction symptoms of excessive pursuit and consumption of alcohol and other drugs like heroin (O'Malley et al., 1996; Volpicelli et al., 1995).

Opioid antagonists have been used as a treatment strategy for excessive eating behaviors as well. The intimate role of opioids in 'liking' and 'wanting' would perhaps suggest that this would be a fairly successful treatment approach. Yet unfortunately the story is not so simple, and the results appear to be equivocal. While antagonists may be effective at reducing short-term appetitive behaviors (Yeomans and Gray, 2002), long-term compulsions may be harder to curb with antagonist treatment once ingrained in the individual (Atkinson, 1987; Fruzzetti et al., 2002). Opioid receptor antagonists may be somewhat more effective in reducing the frequency and severity of binge eating in some suffers. Early studies in bulimic patients showed reduced binge size and frequency following naltrexone administration (Jonas and Gold, 1988). A subsequent double-blind placebo with naltrexone in bulimic

patients showed improvements in most patients in binge-related indices, including number of binges and purges and a ratio of binge to normal eating (Marrazzi et al., 1995). Further, naltrexone was also found to reduce binge duration in bulimic patients and obese binge eaters (Alger et al., 1991).

In any case, the clinical usefulness of pharmacologically decreasing opioid transmission will likely depend on the type of overeating that is occurring in the individual, and may for many cases benefit from greater specificity in targeting the mu receptor. Yet, we note that while mu antagonists may well dampen excessive 'liking' or 'wanting' signals, they may simultaneously also dampen non-food rewards and general affective states that depend on mu opioids as well. Also, as is known, systemic opioid drugs will likely influence brain functions beyond reward to which mu opioids contribute importantly, leading to unwanted side-effects. Even further complicating matters is the diversity of neurochemical signals for food motivation and pleasure that extend beyond mu opioids, and that would conceivably persist to some degree. One to emphasize is brain endocannabinoids, which can modulate palatability and eating dramatically in humans and animals, particularly within an accumbens shell hotspot, and are targeted in some pharmacological treatments for overeating and obesity (e.g., the cannabinoid signaling reducing drug Rimonabant) (Di Marzo et al., 2005; Jarrett et al., 2005; Kirkham, 2004; Mahler et al., 2007).

Speculatively, in the future—maybe distant future—targeting specifically the signature patterns of neural activity that encode excessive hedonic or motivational signals for food, through which separate neurochemical systems may funnel, would be a promising clinical intervention for individuals presenting with forms of eating disorders that involve hyperactivity in one or the other reward process. Of course, to reach this point will require a great deal more basic science research to uncover what, and where, these signature patterns of neural activity are, and how they might be noninvasively targeted by treatment measures.

5. Conclusion

A substantial body of evidence has now accumulated to show that limbic opioid transmission, particularly involving the mu receptor, participates intimately in assigning pleasure and incentive motivational value to foods and cues that predict them. Hedonic 'liking' of tastes is generated at least in part by a functional circuit linking hedonic hotspots of the dorso-rostral medial nucleus accumbens shell and caudal ventral pallidum. The motivation to pursue hedonic foods and incentive salience of food-associated cues is also stimulated by mu-opioid activity in this hedonic circuit, but extends beyond to include a much larger distributed network of sites where enhanced opioid transmission similarly elevates eating and other appetitive behaviors. Mu-opioid signals for food 'liking' and 'wanting' are dissociable in circuit pathways, as well as in neural firing representations of hedonic and incentive signals within the ventral pallidum. More work must be done to flesh out possible opioid involvement in overeating disorders, as well as the contributions of food pleasure and motivation to forms of overeating. Early evidence in human clinical populations appears to implicate exaggerated processing of both 'liking' and 'wanting' in some forms of obesity or binge eating disorders.

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