

Hedonic Hot Spots in the Brain

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Hedonic “liking” for sensory pleasures is an important aspect of reward, and excessive ‘liking’ of particular rewards might contribute to excessive consumption and to disorders such as obesity. The present review aims to summarize recent advances in the identification of brain substrates for food ‘liking’ with a focus on opioid hot spots in the nucleus accumbens and ventral pallidum. Drug microinjection studies have shown that opioids in both areas amplify the ‘liking’ of sweet taste rewards. Modern neuroscience tools such as Fos plume mapping have further identified hedonic hot spots within the accumbens and pallidum, where opioids are especially tuned to magnify ‘liking’ of food rewards. Hedonic hot spots in different brain structures may interact with each other within the larger functional circuitry that interconnects them. Better understanding of how brain hedonic hot spots increase the positive affective impact of natural sensory pleasures will help characterize the neural mechanisms potentially involved in ‘liking’ for many rewards. *NEUROSCIENTIST* 12(6):500–511, 2006. DOI: 10.1177/1073858406293154

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Hedonic impact, or ‘liking,’ is a critical aspect of reward. Food and sex, for example, are potent sensory pleasures with liked hedonic impact, and it is widely acknowledged that the ‘liking’ of food and sex carries important survival and reproductive benefits for humans and animals. However, sensory pleasure may not always be beneficial. Rewards with large hedonic impact (e.g., junk food) may often be consumed more than those with low hedonic impact (e.g., vegetables), and in this way, hedonics may contribute to overeating and obesity and also to abuse of drugs. Although the ‘wanting’ and ‘liking’ of rewards are separable, pleasure ‘liking’ may be a major contributor to normal and excessive reward consumption. Thus, it is important that behavioral neuroscience gains an understanding of how the brain causes reward hedonic impact.

So how does it? How does the brain transform a mere sensory stimulus into a pleasurable and liked stimulus? For example, taste sweetness by itself is merely a sensation, so its pleasure must arise within the brain, where neural systems actively paint pleasure onto the gustatory sensation to generate a ‘liking’ reaction, as a sort of “pleasure gloss” (Berridge 2004). The question of how sensations are painted with pleasure to become liked can be answered in part by identifying which particular neural systems are able to amplify objective indicators of the hedonic impact of natural rewards.

Parts of the brain opioid system may be especially important in painting a pleasure gloss onto sensation in both humans and animals (Cooper 1983; Morley and

Levine 1983; Doyle and others 1993; Peciña and Berridge 1995; Rideout and Parker 1996; Peciña and Berridge 2000; Kelley and others 2002). Injections of drugs that boost μ -opioid neurotransmission can dramatically increase consumption of palatable food, and opioid drugs also increase taste hedonic reactions to palatable sucrose in humans and rodents (Parker and others 1992; Doyle and others 1993; Cooper and Higgs 1994; Peciña and Berridge 1995; Rideout and Parker 1996; Peciña and Berridge 2000). Conversely, manipulations that block or attenuate μ -opioid activity reduce the consumption and incentive qualities of sweet tastes and other rewards (Parker and others 1992; Cooper and Higgs 1994).

Affective neuroscientists have begun to pinpoint particular brain systems responsible for opioid effects on hedonic ‘liking’ using behavioral techniques that reflect the affective value of tastes and novel mapping procedures. Two brain structures have emerged as likely candidates to contain opioid hot spots that mediate hedonic impact, based in part on work conducted in our laboratory: the nucleus accumbens and the ventral pallidum. These structures are located within the ventral forebrain, share reciprocal projections with one another, and are embedded within larger mesocorticolimbic reward systems (Heimer and Wilson 1975; Mogenson and others 1983; Churchill and Kalivas 1994; Zahm 2000). Not only does opioid neurotransmission in these structures contribute generally to reward motivation (Majeed and others 1986; Mucha and Iversen 1986; Bakshi and Kelley 1993; Peciña and Berridge 2000; Peciña and Berridge 2005; Smith and Berridge 2005b), but also each structure contains an anatomical subregion in which opioids are particularly able to amplify the hedonic impact of sensory pleasure (Peciña and Berridge 2005; Smith and Berridge 2005b). This is what we refer to as a hedonic hot spot.

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In the following sections, we describe advances in functional mapping of hedonic hot spots. We begin by describing a behavioral measure to assess ‘liking’ of natural sensory pleasure in animals and techniques for mapping hedonic hot spots, proceed to review hedonic hot spots within the nucleus accumbens and ventral pallidum, and then speculate about circuitry dynamics and additional hedonic transmitters and structures.

How Can We Measure Hedonic ‘Liking’ in Rats?

Traditional studies of pleasure ‘liking’ have focused on human adult subjects who can describe their feelings (Cabanac 1971). But how can we measure ‘liking’ in nonverbal animals such as rats for detailed neurobiological research? The premise that underlies our research is that hedonic impact or ‘liking’ is a basic evaluative reaction of the brain, with objective neural and behavioral indicators that can be quantified by appropriate methods. One method involves measuring affective reactions to rewards as an objective measure of hedonic stimulus impact (Fig. 1; Movie 1*). Given a sweet taste of sugar, rats emit distinctive facial and body affective expressions that mirror human affective reactions to tastes (Grill and Norgren 1978; Grill and Berridge 1985). Sweet tastes elicit a positive hedonic pattern of reactions such as tongue protrusions (licking of lips), paw licking, and related movements. Bitter tastes elicit an aversive pattern of different expressions such as gapes, head shakes, and frantic wiping of the mouth. These affective reactions are homologous across rodents, primates, and human infants (Steiner and others 2001), share some basic movement patterns with equivalent human expressions of hedonics, and fluctuate in similar ways as human subjective pleasure when circumstances change (e.g., in hunger or satiety states; Berridge 1996). Readers are referred to Grill and Berridge (1985) and Berridge (2000) for a more detailed review of taste reactivity and ‘liking’ analysis.

Neuroscience Tools for Identifying Hedonic Hot Spots: Microinjections and Fos Plumes

Finding brain systems responsible for painting a pleasure gloss onto sensation requires brain manipulation experiments that can ethically be done only in animals. Pharmacological microinjections and analysis of behavioral consequences have been the principal means to identify hedonic hot spots in brain structures. In these studies, microinjections of neurotransmitter receptor agonists or antagonists are made into a brain structure of interest and are staggered in placement to fill the entire

* A video showing affective taste reactivity is available online at <http://nro.sagepub.com/supplemental/>. Video examples of affective ‘liking’ and ‘disliking’ reactions to tastes are shown. The babies receive a taste solution from a dropper. The rats are viewed from underneath a transparent floor as tastant solutions are painlessly infused into its mouth through a previously-implanted oral cannula. Sucrose taste elicits positive hedonic or ‘liking’ reactions from rats (e.g., rhythmic tongue protrusions). Quinine taste elicits negative aversive or ‘disliking’ reactions (e.g., gapes).

Hedonic Reactions (sweet)



Aversive Reactions (bitter)



Fig. 1. Taste ‘liking’ reactions across species. The top row shows an example of positive ‘liking’ reactions to a pleasant sweet taste in a rat, primate, and human infant (homologous rhythmic tongue protrusions). The bottom row shows an example of aversive ‘disliking’ reactions to an unpleasant bitter taste (homologous gapes). Orofacial expressions such as these provide an objective index of ‘liking’ and ‘disliking’ reactions to the hedonic impact of tastes.

structure and allow comparison of subregions. To measure the impact of drug/site manipulations on hedonic ‘liking’, taste solutions are orally infused and ‘liking’ or ‘disliking’ reaction patterns are quantified and compared to normal vehicle levels.

For precision mapping of hedonic hot spots, however, it is not enough to know where a drug has been injected. Drugs can diffuse from the site of injection, which makes pinpointing functional ‘liking’ effects rather tenuous and imprecise unless one knows exactly how far the impact spreads. Recently, we have developed a microinjection Fos plume tool based on local Fos protein expression measurement for mapping of drug effects (Peciña and Berridge 2000; Peciña and Berridge 2005; Smith and Berridge 2005b; Peciña and others 2006). Fos plumes are elevations of Fos protein expression 2 times to >10 times around the microinjection tip (Fig. 2). Many drugs microinjected into the brain activate particular immediate early genes in surrounding neurons that begin producing proteins, such as Fos, the spread of which can be seen later as a dark plume of stained neurons on a slice of brain tissue. Measurement of Fos activation around the site of microinjection has proven to be a useful technique for identifying zones of local neuronal activation (Peciña and Berridge 2000; Peciña and Berridge 2005; Smith and Berridge 2005b; Peciña and others 2006). Quantifying intense and moderate zones of Fos activation within these plumes compared to control tissue from vehicle-microinjected or uninjected rats reveals the zones in which drugs are acting to elevate ‘liking’ in behavioral experiments. By assigning the

Nucleus Accumbens Hedonic Hot Spot

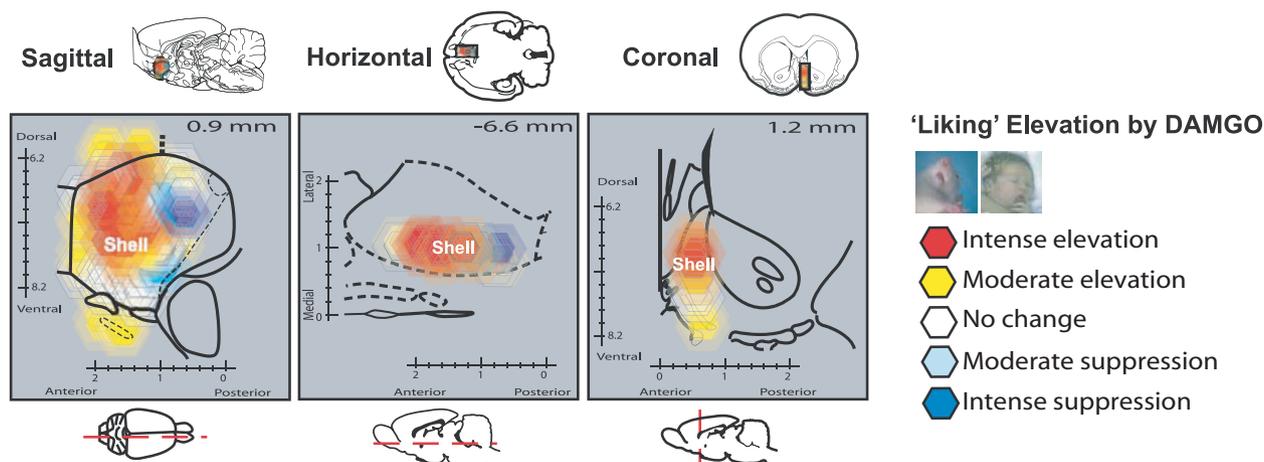


Fig. 2. Opioid hedonic hot spot in nucleus accumbens. The nucleus accumbens hedonic hot spot is localized to the rostrocaudal quarter of medial shell, represented in orange and red in sagittal, horizontal, and coronal views. The colors denote the intensity of μ -opioid amplification of ‘liking’ reactions elicited by sucrose taste, compared to control vehicle levels in the same rats, and the symbol size shows the diameter of Fos plumes surrounding DAMGO microinjections. A nucleus accumbens affective cold spot is represented in blue and purple in the caudal half of the nucleus accumbens, where DAMGO suppressed ‘liking’ reactions to sweetness. Modified from Peciña and Berridge (2005). Reprinted with permission.

behavioral ‘liking’ enhancements caused by microinjections at particular sites to Fos plume-sized spreads of activation around those sites, mapping of the ‘liking’ consequences of Fos plumes in particular locations allows for objective and precise plots of hedonic hot spots in the brain.

Hedonic Hot Spot in Nucleus Accumbens Shell

Evidence for an Accumbens Opioid Hedonic Hot Spot

Using the experimental techniques described above, we have identified a hedonic hot spot of an approximate 1-mm³ size within the nucleus accumbens and in particular within its medial shell subregion. Although the nucleus accumbens has long been linked to reward processes, the location within it of specialized opioid circuits for amplifying hedonic impact was not previously known. Within this 1-mm³ rostral and dorsal hedonic hot spot in the nucleus accumbens shell, the opioid agonist DAMGO robustly elevates hedonic ‘liking’ reactions to a sucrose taste. Specifically, a DAMGO microinjection in the hot spot causes sucrose taste infusions into the rat’s mouth to elicit up to quadruple the usual number of positive ‘liking’ reactions (Peciña and Berridge 2005). This hedonic subregion or ‘liking’ hot spot appears to be located in the rostral half of the medial shell and slightly dorsal within it, just anterior to the caudal edge of the islands of Calleja but posterior to the caudal edge of the dorsal tenia tecta and the lateral septum and at or rostral to the level of the anterior commissure (Fig. 2).

Interestingly, DAMGO does not increase hedonic reactions at other sites of the nucleus accumbens tested so far, such as the caudal or ventral subregions of medial shell, even though DAMGO in these sites still stimulates a ‘wanting’ for food as reflected in increased intake. In fact, DAMGO microinjections in a small cold spot in the caudal half of the medial shell appear to suppress ‘liking’ reactions below vehicle control levels (while still stimulating intake). DAMGO microinjections also simultaneously decreased aversive ‘disliking’ reactions to quinine to less than 25% of control levels, sometimes nearly abolishing aversive reactions entirely, both in the hedonic hot spot and in surrounding regions in which DAMGO selectively stimulated intake (Fig. 3).

One way in which opioids might modulate taste hedonics in the nucleus accumbens shell is by modulating neuronal firing patterns there. Neurons in the dorsomedial hot spot of the medial shell respond electrophysiologically to intraoral sucrose taste infusion, which is correlated at least with mouth movements (Roitman and others 2005). Accumbens shell firing is also sensitive to the concentration of sucrose, which influences its palatability, and to other rewards, such as cocaine or heroin (Chang and others 1994; Peoples and West 1996; Carelli and Deadwyler 1997; Cromwell and others 2005; Taha and Fields 2005). In humans, neuroimaging studies report accumbens activation during consumption of foods and juices that are rated as highly pleasant (Berns and others 2001). Although it is unknown whether reward stimuli particularly activate opioid neurons in the shell hedonic hot spot for ‘liking’ reactions to sweetness, it may be relevant that accumbens opioid activity has

Hedonic vs Aversive vs Intake Contrast

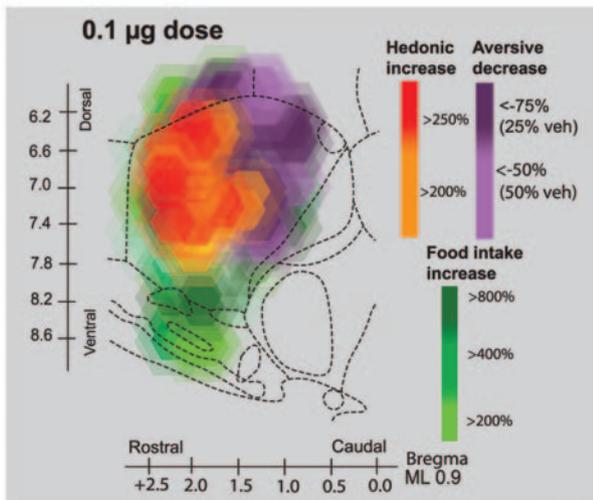


Fig. 3. Contrast map for opioid ‘liking’ amplification, ‘disliking’ suppression, and eating stimulation functions in nucleus accumbens. Summary map shows hedonic enhancement effects of DAMGO microinjections on positive hedonic ‘liking’ reactions to sucrose (shown in red/orange), reduction of negative aversive ‘disliking’ reactions to quinine (shown in purple), and stimulation of food intake (shown in green; green eating sites also extend beneath red/orange and purple sites; purple aversion suppression sites also extend beneath the red/orange hedonic hot spot). The localized hedonic hot spot contrasts sharply with the moderately larger and overlapping aversive suppression spot, and both contrast with the massively large and overlapping stimulation zone for voluntary food intake. Modified from Peciña and Berridge (2005). Reprinted with permission.

been linked to both positive heroin reward (Greenwald and others 2003) and affective relief from negative pain (Zubieta and others 2005) and that systemic opioids modulate the pleasantness of foods in humans (Yeomans and Gray 2002).

Neurobiological Support of the Nucleus Accumbens Shell Hedonic Hot Spot

Neurobiological and neuroanatomical studies have revealed details about the accumbens opioid hedonic hot spot that might be relevant to its special ability to enhance positive hedonic impact, although the exact mechanisms responsible are still unclear. For example, μ -opioid receptors appear particularly dense in the rostromedial region of the medial shell that contains our hedonic hot spot, compared with other regions (Tempel and Zukin 1987). Regarding inputs to the accumbens hedonic hot spot, the rostromedial shell receives denser excitatory projections than does the caudal shell from brain structures such as the dorsal intermediate subiculum, septohippocampal area, basal amygdaloid complex, and caudal prelimbic area. By comparison, the caudal shell receives greater inputs from ventral subiculum, septohippocampal area,

basal amygdaloid complex, caudal prelimbic area, and brain stem norepinephrine projections (Phillipson and Griffiths 1985; Groenewegen and others 1987). Regarding dorsoventral differences, the dorsal half of the medial shell that contains the hot spot receives more fibers than the ventral shell from the parvocellular basal nucleus, medial amygdale nucleus, caudal periamygdaloid cortex, and basal parvocellular amygdaloid nucleus and receives special convergence of inputs from the medial and central amygdala, at least in primates (Fudge and others 2002). In efferent projections, the dorsal shell sends more outputs to the medioventral tegmental area (Voorn and others 1986; Berendse and others 1992), whereas the ventral shell sends more to the lateroventral tegmental area (Berendse and others 1992). However, which (if any) of these features are actually important in generating the hot spot’s capacity to amplify hedonic impact remains unclear and will need to be resolved by future research.

Food-Wanting Roles of Accumbens Opioids

The localization of the opioid hedonic hot spot for enhancing sensory ‘liking’ reactions contrasts dramatically with the widespread distribution of substrates able to stimulate eating (a reflection of food ‘wanting’) in the nucleus accumbens. Microinjections of DAMGO throughout the entire medial shell (roughly 2.87 mm³) dramatically increase chow intake, including in the hedonic cold spots, whereas the hedonic hot spot is only 1 mm³ in size (Peciña and Berridge 2005). μ -Opioid agonists/antagonists also elevate/suppress consumption of sucrose solution or palatable food in the wider 2.87-mm³ accumbens region (Peciña and Berridge 2000; Kelley and others 2002; Ward and others 2006). Thus, μ -opioid ‘liking’ functions are much more anatomically restricted than intake or ‘wanting’ functions in the nucleus accumbens. In other words, food intake can be stimulated throughout all parts of the medial shell of the nucleus accumbens, but the opioid driving force behind eating behavior may vary depending on the subregion (Fig. 3). This suggests that individuals with excessive μ -opioid activity in the hedonic hot spot may eat, at least partly, because food tastes nicer, whereas individuals with opioid activation in surrounding areas of the accumbens shell (but not the hot spot) may eat because of nonhedonic incentive motivational reasons (‘wanting’ food more, even if not ‘liking’ it any more than usual). This opioid subregional difference highlights the distinction between ‘wanting’ and ‘liking’ the same reward, which previously has been an important theme for understanding brain systems such as mesolimbic dopamine (Robinson and Berridge 2003).

The large opioid eating zone may not stop at the medial shell borders, either. Indeed, μ -opioid agonists have been reported to stimulate intake in the nucleus accumbens core and even in regions of the dorsal striatum and other structures, too, suggesting that the area for opioid-regulated eating within the brain might be quite large (Peciña and Berridge 2000; Zhang and Kelley 2000; Kim and others 2004). However, so far as we know, there is no direct evidence yet for specific hedonic impact amplification by opioid circuits in these other brain regions.

Ventral Pallidum Hedonic Hot Spot

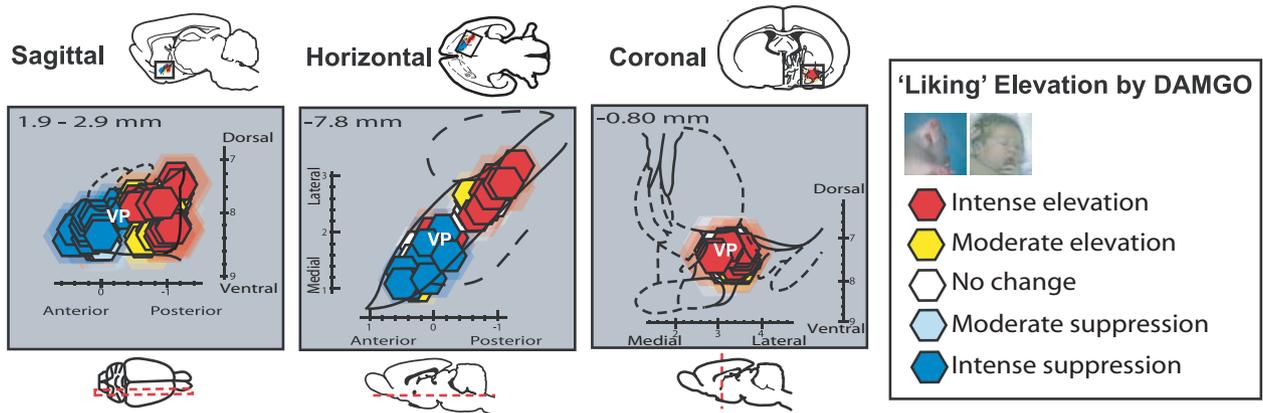


Fig. 4. Ventral pallidum hedonic hot spot. The ventral pallidum hedonic hot spot is localized to the caudal portion, represented in red in sagittal, horizontal, and coronal views. The colors denote the intensity of μ -opioid amplification of 'liking' reactions elicited by sucrose taste caused by DAMGO microinjections, similar to Figure 1. A ventral pallidum hedonic cold spot is depicted in blue in the rostral portion, where DAMGO microinjections (0.01 μ g) suppressed 'liking' reactions to sweetness (and also suppressed food intake). From Smith and Berridge (2005b). Reprinted with permission.

Possible Cannabinoid Involvement in Accumbens Hedonics

Recent preliminary evidence in our laboratory suggests that endogenous cannabinoids may additionally participate in amplifying hedonic 'liking' for sweetness, in a region of the nucleus accumbens that overlaps with the opioid hot spot (Mahler and others 2004). Microinjections of the endocannabinoid anandamide in the medial shell of the nucleus accumbens elevate 'liking' reactions to sucrose, just as a μ -opioid agonist microinjection does. Although much precise mapping work remains to be done, early evidence suggests that the endocannabinoid hedonic hot spot includes the opioid hot spot and possibly extends beyond it. Overlap between the endocannabinoid and opioid hot spots raises the possibility that opioids and cannabinoids interact within synaptic circuits of this local region to amplify hedonic reactions to sensory pleasure, a possibility that is consistent with known interactions between those neurochemical signals (Kirkham and Williams 2001; Pickel and others 2004; Solinas and Goldberg 2005; Caille and Parsons 2006).

Hedonic Hot Spot in the Ventral Pallidum

Evidence for a Ventral Pallidum Opioid Hedonic Hot Spot

There is at least one other opioid hedonic hot spot that we have found to be capable of enhancing 'liking' reactions to sweet sensation, namely, in the ventral pallidum. The ventral pallidum is the chief output target of nucleus accumbens projections (Fig. 4) and contains an opioid hedonic hot spot in its caudal portion where μ -opioid stimulation magnifies hedonic 'liking' as well as motivational 'wanting' for food reward. A Fos plume-mapping

study of opioid hedonic function in our laboratory showed the hedonic hot spot in the ventral pallidum to be approximately 0.84 mm³ in cubic volume (Smith and Berridge 2005b). Although this is slightly smaller than the 1-mm³ nucleus accumbens opioid 'liking' hot spot, it is roughly equal in the proportion of the structure that it fills when one accounts for the ventral pallidum's being roughly two thirds the size of the accumbens medial shell. Both hot spots fill approximately 35% to 45% of their containing structure (Fig. 4).

The features of the ventral pallidum hot spot are similar to those of the nucleus accumbens. In the caudal hot spot, microinjections of the μ -opioid agonist DAMGO nearly double the number of hedonic 'liking' reactions to a sucrose taste compared to vehicle microinjections (Smith and Berridge 2005b). Opioid receptor activation in the hedonic hot spot of the ventral pallidum stimulates eating behavior as well (Smith and Berridge 2005b; Shimura and others 2006). By contrast, if the same DAMGO microinjections are made in more rostral portions of the ventral pallidum, 'liking' reactions to both sucrose taste and eating behavior are actually suppressed below normal. Also by contrast, eating was stimulated by local GABA blockade in all regions of the ventral pallidum (bicuculline microinjection) but was never accompanied by enhanced 'liking' reactions (Smith and Berridge 2005a). Instead, bicuculline-stimulated eating always appeared as increased "wanting without liking" (Stratford and others 1999; Smith and Berridge 2005b; Shimura and others 2006). Eating behavior stimulated by opioid circuits in the ventral pallidum may thus be tightly bound to hedonics and hot spot, whereas GABA-related stimulation of eating may be more widespread throughout the ventral pallidum and independent of hedonic impact.

The hot spot in the caudal ventral pallidum is not only a sufficient cause to increase hedonic 'liking' through opioid activation but also might turn out to be a necessary cause for normal hedonic reactions to sweet rewards. It has long been known that aversive 'disliking' reactions (e.g., gapes) to normally palatable tastes can accompany the aphagia (failure to eat) caused by large electrolytic or excitotoxic lesions of the lateral hypothalamus, at least if the lesions extend far enough anteriorly and laterally to penetrate the caudal ventral pallidum (Anand and Brobeck 1951; Teitelbaum and Stellar 1954; Teitelbaum and Epstein 1962; Schallert and Whishaw 1978; Stellar and others 1979; Berridge 1996). In a lesion-mapping study of the site responsible for increased aversion (Cromwell and Berridge 1993), excitotoxin lesions that hit the central-to-caudal ventral pallidum were found to cause aversion to sucrose taste, whereas lesions restricted to the lateral hypothalamus did not (even if both caused aphagia). Hedonic reactions to a normally liked sucrose taste were completely abolished after ventral pallidal lesions that likely included the hedonic hot spot and replaced by aversive reactions that are normally evoked by disliked tastes such as quinine (Cromwell and Berridge 1993).

A recent case study of a human patient with bilateral lesions to the ventral pallidum (overlapping with internal globus pallidus) provides another example of what may happen after dysfunction of ventral pallidal hedonic mechanisms (Miller and others 2006). Following damage involving the ventral pallidal area, the patient "endorsed a depressed mood, anhedonia and a 20-lb weight gain over the ensuing year." The patient was previously a drug addict, and after the lesion, "reported the disappearance of all drug cravings and remained abstinent from all recreational drugs other than an occasional glass of wine with dinner" and "reported that he no longer experienced pleasure from drinking alcohol" (p 786). Although it is not known how the precise location or nature of this patient's damage compares with the hedonic hot spot we have identified in the rat ventral pallidum, it appears striking that both pallidal lesions appear to induce distortions of hedonic impact or cravings and consumption of rewards.

The special capacities of manipulations of ventral pallidum to magnify or abolish 'liking' reactions may reflect in part the capacity of neurons there to code hedonic impact in quite a strong sense (Smith and others 2004; Tindell and others 2004, 2005, 2006). In electrophysiological recording studies conducted in collaboration with the laboratory of J. Wayne Aldridge at the University of Michigan, we have found that neuronal firing rates in the hedonic hot spot of the ventral pallidum dramatically increase during an oral infusion of a hedonic sucrose taste that evokes positive 'liking' reactions (Smith and others 2004; Tindell and others 2004, 2005, 2006). Even more striking, ventral pallidum neurons also code changes in hedonic impact produced by integration of physiological signals with taste quality that can transform 'disliking' into 'liking' for a given sensation (Smith and others 2004; Tindell and others 2006). Such homeostatically induced changes in sensory pleasure have been called alliesthesia (Cabanac 1971). For example, infusion of an intensely

salty taste (triple seawater NaCl concentration) normally evokes 'disliking' reactions from rats and not much firing from their neurons in the ventral pallidum hedonic hot spot (Tindell and others 2004, 2006). But when rats are depleted of bodily sodium by injections of furosemide and deoxycorticosterone acetate, the same salty taste becomes liked in the sense of evoking positive hedonic reactions. Simultaneously, cells in the caudal hot spot begin to fire more to the intense salt taste, without changing to sucrose taste, so that the rates of firing become high and equivalent for both tastes (Smith and others 2004; Tindell and others 2006).

Neurobiological Features of the Ventral Pallidum Hedonic Hot Spot

There are several neurobiological features of the hot spot in the caudal ventral pallidum that might be relevant to its special hedonic function, though much remains to be known. For example, the caudal ventral pallidum may have higher enkephalin immunoreactivity than the rostral ventral pallidum (Maidment and others 1989) and a higher ratio of noncholinergic to cholinergic cells (Bengtson and Osborne 2000). Caudal ventral pallidum may also contain less dense concentrations of presynaptic μ -opioid receptors compared to rostral regions (Olive and others 1997). No studies to our knowledge have explicitly compared caudal versus rostral connectivity of the ventral pallidum, but it is worth noting that the ventral pallidum, including its caudal portion, is interconnected with many reward-related structures including the accumbens, amygdala, parabrachial nucleus, and orbitofrontal, prefrontal, and infralimbic cortex (Grove 1988a, 1988b; Groenewegen and others 1993). Clearly, however, much more work remains to be done before the neurobiological basis of the hedonic hot spot in the ventral pallidum can be understood.

Interaction between Accumbens-Pallidum Opioids: From Hot Spots to a Hot Circuit

How do the accumbens and ventral pallidum hot spots interact? Do they influence each other or are they independent? If they interact, does one dominate over the other for control of hedonic reward signals or are both equally necessary for opioid hedonic enhancement? Very little is known yet about how the accumbens and ventral pallidal hot spots interact functionally, but some information is beginning to emerge.

Preliminary observations in our lab indicate that accumbens and ventral pallidum hot spots may exchange opioid-related information when amplifying the hedonic impact of a sensory reward (Smith and Berridge 2005a). Ordinarily, opioid activation in the accumbens hot spot amplifies 'liking' reactions to sucrose, but that increase can be blocked if naloxone simultaneously is used to block opioid signals in the ventral pallidum and vice versa (Smith and Berridge 2005a). In addition, opioid elevation of hedonics in either hot spot also causes distant Fos protein elevation in the other hot spot, providing neurobiological verification of functional interaction between

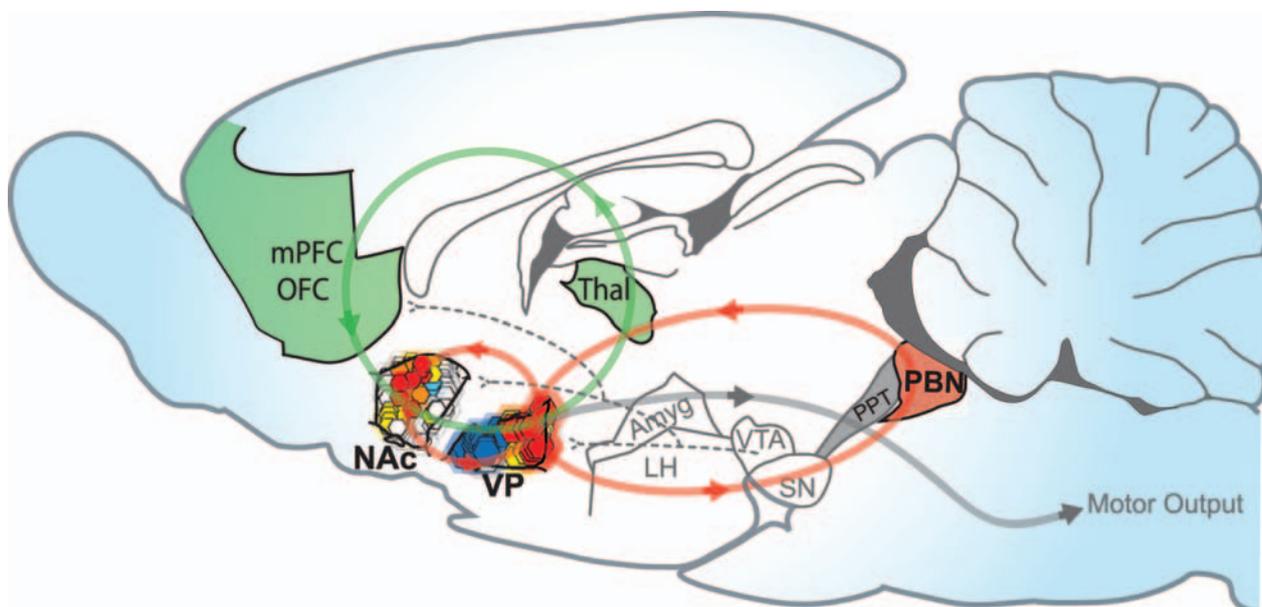


Fig. 5. Brain hedonic hot spots and hedonic circuits. A sagittal brain view of the hedonic hot spots discussed here in the nucleus accumbens, ventral pallidum, and parabrachial nucleus. Each hedonic hot spot can cause amplification of 'liking' reactions to sweetness in response to appropriate drug microinjection within it (e.g., μ -opioid agonist or benzodiazepine). Anatomical projections are indicated by lines that may create a hedonic circuit by connecting hot spots together (red circles) or incorporating hot spots into larger mesocorticolimbic loops (green). NAc = nucleus accumbens shell; VP = ventral pallidum; mPFC = medial prefrontal cortex; OFC = orbitofrontal cortex; Thal = thalamus; LH = lateral hypothalamus; Amyg = amygdala; SN = substantia nigra; VTA = ventral tegmental area; PPT = pedunculopontine tegmentum; PBN = parabrachial nucleus. Modified from Paxinos and Watson (1998).

them. Thus, the accumbens and ventral pallidum hot spots may interact with one another, either directly or indirectly, and opioid neurotransmission to both hot spots may be required for the overall amplification of taste hedonics by either one (Fig. 5).

Supporting the possibility of interaction between hot spots in the nucleus accumbens and ventral pallidum, both structures share reciprocal connections with each other (Heimer and Wilson 1975; Phillipson and Griffiths 1985; Zahm and others 1985; Churchill and Kalivas 1994; Usuda and others 1998; Zahm 2000), and each structure can modulate electrophysiological activity in the other (Hakan and others 1992; Hakan and Eyl 1995; Napier and Mitrovic 1999).

Hedonic Networks Stretch across the Entire Brain

The interaction described above highlights the point that sensory pleasure does not arise from activity in any one hedonic hot spot, of course, but rather by activation of widespread hedonic brain systems that coordinate multiple hot spots. Although opioid hot spots in the accumbens shell and ventral pallidum have received the most attention in our discussion of hedonic reward so far, hedonic hot spots are not limited to the forebrain or to opioids. Rather, sensory hedonic systems are distributed in neural circuits that stretch across the brain, possibly extending caudally to include some brain stem circuits.

The notion that the brain stem might code aspects of sensory pleasure might come as a surprise to anyone used to thinking of the brain stem solely in terms of reflexive functions. Yet several experiments including recent studies in our laboratory have indicated compelling evidence that brain stem substrates participate in the processing of taste hedonic signals. The brain stem may even contain a hedonic hot spot of its own that uses a different and perhaps surprising neurochemical signal, namely, a benzodiazepine/GABA signal. This signal functions around the parabrachial nucleus of the pontine hindbrain to enhance 'liking' reactions to sucrose hedonic impact and to simulate eating behavior (Higgs and Cooper 1996; Peciña and Berridge 1996; Söderpalm and Berridge 2000).

The first evidence that a benzodiazepine/GABA system somewhere in the brain stem might contribute to hedonic processing came from a demonstration that a systemic benzodiazepine drug enhanced positive affective reactions to sweet tastes even in decerebrate animals, in which the brain had been transected and the brain stem surgically separated from connections to the forebrain (Berridge 1988).

Even in intact animals, benzodiazepines more effectively increase positive affective reactions to taste in the brain stem than in the forebrain. Microinjections of low doses of benzodiazepine most effectively increase positive affective reactions to sucrose taste when injected into the brain stem ventricle (i.e., fourth ventricle) of normal rats than when injected into the forebrain ventricle

(i.e., lateral ventricle; Pecina and Berridge 1996). Thus, brain stem circuits participate in hedonic enhancements, perhaps as the lower rung of a brain hedonic hierarchy. Brain stem circuits may even be primary for benzodiazepine-related modulation of affective reactions to tastes.

Recent experiments suggest that the parabrachial nucleus in the pons might be a brain stem hot spot for benzodiazepine circuits relevant to taste's hedonic impact. Microinjection of the benzodiazepine midazolam directly into the parabrachial nucleus is able to increase the number of hedonic reactions to a sucrose taste, in addition to increasing eating behavior, apparently more effectively than into several other brain stem sites (Söderpalm and Berridge 2000). Benzodiazepines have long been suggested to augment food hedonics (Cooper and Estall 1985; Berridge and Treit 1986). Therefore, it is likely that the parabrachial nucleus plays an important role in brain stem modulation of taste hedonics and may be embedded within the brain's distributed circuitry for mediating hedonic pleasure, although the parabrachial hot spot has yet to be mapped by Fos plume techniques (Fig. 5).

Benzodiazepine/GABA Hedonic Hot Spots Interact with Opioid Hedonic Hot Spots

Consistent with the idea that hedonic networks stretch across the entire brain, a recent study suggests that benzodiazepine and opioid circuits interact together to amplify hedonic taste reactivity. That is, benzodiazepine-induced potentiation may in turn involve an opioid link in the larger neural chain that leads to an increase in 'liking' reactions. Richardson and others (2005) showed that benzodiazepine enhancement of taste hedonic impact may at least require permissive activation of endogenous opioid systems somewhere in the brain and is prevented by opioid receptor blockade. They found that prior treatment with an opioid antagonist (naloxone) completely blocked the typical 200% elevation of sucrose 'liking' reactions that was otherwise caused by diazepam administration (Richardson and others 2005).

How might such interactions be mediated by brain hedonic circuits? One possibility is that connections between hot spots connect them into a larger distributed hedonic network that drugs activate as a whole. Such anatomical connections make direct interaction at least possible between parabrachial nucleus and forebrain hot spots. Ascending projections connect the parabrachial nucleus to the ventral pallidum, and descending projections connect both the ventral pallidum and nucleus accumbens to the parabrachial nucleus (Saper and Loewy 1980; Grove 1988b; Groenewegen and others 1993; Usuda and others 1998). The parabrachial nucleus projects also to a number of structures that in turn target the accumbens, such as the lateral hypothalamus, bed nucleus of the stria terminalis, and amygdala (Norgren 1976; Lundy and Norgren 2004). Thus, several circuits allow the potential for interaction between hedonic hot spots. It is not yet known whether the opioid/benzodiazepine interaction described above actually involves such separate hot spot connections or instead is mediated by multiple neurotransmitters interacting in the same site (e.g., brain stem).

However, it is not hard to imagine future experiments that would help resolve the question, for example, combining multiple microinjections of different neurotransmitter agents simultaneously in separate brain hot spots.

Where Other Hedonic Hot Spots May and May Not Be

Thus far, we have discussed hedonic hot spots that have been identified in the nucleus accumbens, ventral pallidum, and brain stem pons, within a hedonic network that stretches across the brain. Are there other hedonic hot spots in the brain, similarly capable of causing increases in the hedonic impact of rewards? There are intriguing candidates and also perhaps some surprising failures to amplify sensory pleasure. One promising additional candidate may be regions of the neocortex that respond specifically to hedonic stimuli, including especially the orbitofrontal cortex (Kringelbach 2004, 2005). In human imaging studies, the orbitofrontal cortex, particularly its caudal region, is preferentially activated by tastes, flavors, and odors that are rated as pleasant (O'Doherty and others 2002; Rolls and others 2003; Small and others 2003). The orbitofrontal cortex is also able to track reductions in hedonic impact caused by eating foods to satiety (O'Doherty and others 2000; Small and others 2001; Kringelbach and others 2003). Primate and rodent electrophysiology studies generally confirm that orbitofrontal cortex neurons fire in response to palatable sweet tastes and that reward-related firing also is diminished after reward satiation (Rolls and others 1989; Schoenbaum and others 1998; Tremblay and Schultz 1999; Gutierrez and others 2006; Padoa-Schioppa and Assad 2006). Some might suggest the ventromedial prefrontal cortex, insula, and cingulate cortex could be involved in hedonics as well because they play a key role in many positive emotional and affective processes, including food preferences (Baylis and Gaffan 1991; Damasio 1994; Francis and others 1999; Bechara and others 2000; De Araujo and others 2003).

An open question is whether orbitofrontal, ventromedial prefrontal, or other regions of the cortex actually cause hedonics and hedonic reactions or instead merely code and represent them as consequences of hedonic reactions. If the latter, then presumably, causation arises from hot spots elsewhere in the brain, such as the ones we described above. Little direct evidence for pleasure causation by the orbitofrontal or ventromedial prefrontal cortex exists as of yet. Ventral medial prefrontal cortex lesions may moderately disrupt food selection in monkeys, but rats with lesions to the orbitofrontal cortex retain a normal decline in food intake after food has been paired with illness, although they are impaired in using conditioned stimulus cues that signal nonreward or devaluation to guide their choices (Gallagher and others 1999; Pickens and others 2003; Rolls 2004). Human patients with damage to the ventral prefrontal cortex show fascinating changes in cognition and emotion, but it is not clear whether they actually lose any capacities for experiencing or reacting to sensory pleasures (Damasio 1994; Bechara and others 2000). Clearly, it

will be of interest to know in the future whether the orbitofrontal or other prefrontal cortical areas contain hot spots capable of either amplifying or abolishing a basic hedonic reaction to sensory pleasure. If so, the hedonic generating network would truly stretch across the entire brain, from brain stem to cortex.

False Pleasure Electrode

Perhaps the most famous and original candidates for pleasure-generating brain systems come from so-called pleasure electrodes, which used brain electrical stimulation to reinforce self-administration behavior such as pressing a lever or pushing a button (Olds and Milner 1954). But critical reinspection of the effects of electrode self-stimulation has indicated that many of the most dramatic electrodes may not have been reliable generators of strong pleasure after all. Instead, mesolimbic electrodes may have generally produced a false pleasure, that is, by generating motivational ‘wanting’ without hedonic ‘liking’ (Berridge and Valenstein 1991; Berridge 2003).

In some early experiments on electrical brain stimulation performed in humans (Heath 1972; Sem-Jacobsen 1976), patients with pleasure electrodes pressed a button that stimulated an electrode in their brain (usually in pathways related to mesolimbic systems) thousands of times in a single session of several hours (Heath 1972; Valenstein 1974; Sem-Jacobsen 1976). Many textbooks cite these cases as examples of intense pleasure electrodes. However, if one reads closely what subjects were reported to have said, it is not at all clear that they experienced intense pleasure per se after stimulation. Pleasure thrills are generally not what was reported, not even in the most extreme brain-stimulation examples. For example, “B-19,” a young man implanted with stimulation electrodes by Heath and colleagues in the 1960s, voraciously self-stimulated his electrode and protested when the stimulation button was taken away. But there is no clear evidence that B-19’s electrodes ever caused intense pleasure. B-19 never was quoted as saying they did. Instead B19’s electrodes evoked desire to stimulate again and strong sexual arousal, although never producing sexual orgasm or clear evidence of actual pleasure sensation from the electrode. The brain stimulation did not serve as a substitute for sexual acts, but it did instead make him want to do sexual acts as well as want to press the electrode again.

What could these electrodes be doing, if not causing pleasure? Among other things, they might be activating incentive salience attribution to surroundings and perceived stimuli, especially the act of stimulating the electrode. For example, electrode stimulation of lateral hypothalamus pathways causes rats to want to eat more without causing them to like food more, similar to the ‘wanting’ without ‘liking’ effects described above (Berridge and Valenstein 1991). If human electrodes caused selective ‘wanting’ in the same way, a person might well describe a sudden feeling that life was suddenly more attractive, desirable, and compelling to pursue. They might well want to activate their electrode that produced no pleasure sensation. That would be mere incentive ‘wanting’ without ‘liking’.

False Pleasure Transmitter

Similarly, the transmitter dopamine has been famous as a so-called pleasure neurotransmitter for more than 30 years, especially within the mesolimbic system that projects to the nucleus accumbens (Wise 1985; Hoebel and others 1999; Shizgal 1999). One reason that claim was made is that dopamine neurons are turned on by many pleasurable stimuli ranging from foods, sex, and drugs to social and cognitive rewards (Fiorino and others 1997; Schultz 1998; Wise 1998; Ahn and Phillips 1999; Becker and others 2001; Robinson and others 2005; Aragona and others 2006). Furthermore, if dopamine was blocked, all rewards appeared to lose certain rewarding properties in instrumental paradigms (Wise and Bozarth 1985; Hoebel and others 1999; Shizgal 1999).

But dopamine is probably not a pleasure neurotransmitter. Recent work has shown dopamine to be involved in incentive salience or motivational aspects of reward (‘wanting’) and to have little if anything to do with generating hedonic ‘liking’ per se. Even massive destruction of ascending dopamine projections does not impair affective ‘liking’ reactions elicited by a sweet taste (Berridge and others 1989; Berridge and Robinson 1998). Nor does dopamine blockade by neuroleptic drugs reduce ‘liking’ for sweetness (Peciña and others 1997).

Conversely, activation of dopamine transmission by genetic manipulation in hyperdopaminergic mice does not enhance hedonic ‘liking’ for sweetness, even though the same mice are more motivated to obtain sweet rewards and more resistant to distractions from the goal they excessively want (Peciña and others 2003; Cagniard and others 2006). Similarly, amphetamine administration that promotes dopamine release, either directly into the nucleus accumbens or systemically, completely fails to increase hedonic reactions to taste (Wyvell and Berridge 2000; Tindell and others 2005). Finally, indirect facilitation of dopamine activation by drug-induced neural sensitization also fails to increase positive ‘liking’ reactions to sweetness (Wyvell and Berridge 2000; Tindell and others 2005). Thus, dopamine is neither necessary for normal hedonic impact of sweet rewards nor sufficient to increase hedonic impact above normal. In short, dopamine appears unable to cause changes in basic ‘liking’ reactions to sucrose. It stands in contrast to the hedonic hot spots described above, which use opioid, cannabinoid, and benzodiazepine signals to powerfully amplify the hedonic impact of natural sensory pleasures.

Conclusion

Contemporary neuroscience research techniques have made it possible to map hedonic hot spots within the brain. The ventral pallidum and the nucleus accumbens each contain hedonic hot spots for taste rewards, within which activation of μ -opioid receptors causes an increase in hedonic valuation of sweet taste stimuli. Accumbens and ventral pallidum hot spots functionally interact with one another in their opioid-mediated amplification of ‘liking’ reactions to sweetness, and those limbic hot spots

have connections to other potential hot spots distributed elsewhere in the brain. Thus, the brain hot spots we have described here likely form a larger hot circuit for hedonic signals that enhance sensory pleasure.

Future work on limbic functional circuitry will be useful to determine what other brain hot spots or transmitters contribute to the hot circuit for hedonic reward. Such knowledge will help illuminate how mere sensory information becomes painted with hedonic qualities and liked. In short, the future of hedonic research promises to be quite hot.

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