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Affective Neuroscience: Food 'Wanting' Hotspot in Dorsal Striatum

New research has uncovered a micro-domain within dorsal neostriatum where enkephalin surges are triggered by the opportunity to consume tasty foods and where μ-opioid microinjections generate intense motivational 'wanting' to eat without enhancing food 'liking'.

Andrew D. Lawrence

The increased prevalence of obesity poses a global challenge to health. Over-consumption of aggressively marketed, abundant, cheap, tasty, energy-dense foods is one contributor to intake in excess of metabolic demand [1], resulting in increased attention to neural mediators of food reward. A new study [2], reported in this issue of *Current Biology*, has uncovered a novel brain substrate in dorsal neostriatum that mediates excessive consumption of energy-dense foods, where μ-opioid signalling generates intense motivational 'wanting' to eat without elevating the hedonic impact ('liking') of feeding.

It is well established that signalling via brain μ-opioid receptors has potent effects on feeding and that the ventral striatum (nucleus accumbens) is a critical substrate where opioids exert their rewarding effects [3]. A striking aspect of μ-opioid-induced eating is its specificity for foods rich in sugar, fat, or both [3]. Kelley *et al.* [3] proposed that, whilst normal feeding can occur without release of enkephalin (an endogenous μ-opioid receptor ligand), enkephalin release, by enhancing the pleasure of eating, serves to stimulate intake of energy-dense foods beyond that required to maintain energy balance. In an evolutionary context, a μ-opioid-driven urge to overeat when presented with a calorific food source would serve to increase fat stores, aiding survival in the event of future famine [3]. But in the current food-rich environment, such a mechanism seems more of a hindrance than a help.

A detailed account of the role of accumbens opioid transmission in food reward is emerging, based on the work of Peciña *et al.* [4,5]. The hedonic impact of tastes can be measured objectively by orofacial taste reactivity patterns ('liking' reactions), which are homologous across rodent and primate species [4] and which fluctuate in similar ways to human subjective pleasure during hunger/fullness states. For example, sweet tastes elicit a positive hedonic pattern of reactions including tongue protrusions (licking of the lips) [4].

By selectively stimulating μ-opioid receptors in discrete rat brain regions via local microinjection of μ-opioid agonists and studying the extent to which such manipulations enhance 'liking' reactions, Berridge *et al.* [4,5] have previously identified discrete hedonic 'hotspots': micro-domains where μ-opioid receptor stimulation powerfully increases 'liking' reactions to sweet tastes. One such hotspot (1 mm^3 volume) resides in the medial-dorsal accumbens shell [4,5]. Another (0.8 mm^3 volume) resides in a caudal zone of the ventral pallidum, chief accumbens output target [4,5]. These hedonic hotspots act in concert to increase 'liking' reactions to sweet sensations [4,5]. The hedonic hotspots are also 'wanting' hotspots, in that the same microinjections of μ-opioid agonist simultaneously increase both 'liking' and motivational 'wanting' for food, as reflected in vigorous eating [4,5]. The tight localization of opioid hedonic hotspots contrasts strikingly with a looser distribution of substrates, encompassing almost the entire medial accumbens shell (plus amygdaloid regions), where μ-opioid stimulation generates only 'wanting' to eat (large increases in food intake) without enhancing 'liking' reactions (pure 'wanting' hotspots) [4,5]. Treatment with μ-opioid agonists/antagonists also elevates/suppresses consumption of sweet and fatty foods in the wider ventral striatum [3–5].

The new study [2] reveals that μ-opioids stimulate food 'wanting' without enhancing food 'liking' not only in ventral, but also in the dorsal striatum, a region seldom associated with reward. The dorsal striatum has a mosaic organization comprising island-like striosomes/patches embedded in a more extensive matrix [6]. Striosomes are distinguished from matrix by a dense concentration of μ-opioid receptors [6]. Orbitofrontal, cingulate and insular cortices preferentially innervate striosomes, which form part of a 'limbic' circuit embedded in sensorimotor and associative striatum [6]. DiFeliceantonio *et al.* [2] focused on the medial dorsal striatum, which, like the accumbens, contains neurons responding to food [7], is enriched in μ-opioid receptors [8], receives amygdaloid projections [9], and receives body-state signals from lateral hypothalamus via midline thalamic projections [3].

In vivo measurements are critical for revealing normal functioning of opioid transmission within striatal networks. Microdialysis is one approach for *in vivo* studies; however, until recently, measurement of opioid-peptide release in behaving animals has been stymied by problems with recovery and detection sensitivity [10]. DiFeliceantonio *et al.* [2] adopted a novel analysis method — capillary liquid chromatography coupled off-line to multistage mass spectrometry, to determine endogenous opioids in microdialysis samples collected *in vivo*. This technique has been validated for measurement of opioid peptides, showing high sensitivity and specificity [10]. Using this

technique on samples obtained from probes implanted in rat anteromedial dorsal striatum, DiFeliceantonio *et al.* [2] measured extracellular levels of endogenous opiates — enkephalin and dynorphin, an endogenous κ-opioid receptor ligand — during feeding. These peptides were measured initially during a quiet baseline 'pre-meal' period in mildly food-deprived rats, and then following the abrupt appearance of a large quantity of chocolate M&Ms®.

The tasty treats were readily consumed, evoking an immediate surge in endogenous enkephalin, peaking at >150% of pre-meal baseline levels. Enkephalin levels remained elevated throughout the ~20–40 minute 'meal', tapering off as rats ceased eating. By contrast, dynorphin levels were unaltered. Opioid levels were also measured during periods when rats performed vigorous non-ingestive movements, such as grooming. Enkephalin levels never rose during such behaviours, and enkephalin levels were greater during eating than during any other activity. The demonstration [2] of feeding-linked enkephalin release represents a long-awaited result for the field. The use of microdialysis coupled with analytical chemistry techniques is an innovation in peptide neurobiology that allows previously intractable questions to be asked regarding the timing of opioid peptide release during reward processes, allowing stronger inferences to be made about the functional role of opioids in food intake.

Notably, the faster a rat began to eat, the higher its relative increase in anteromedial dorsal striatum enkephalin. This links enkephalin surges with a 'command' signal to eat energy-dense foods: "Stop what you are doing and eat now!" [2,3]. To test this causal hypothesis, microinjections of a μ-opioid receptor agonist, [D-Ala^2, N-Me-Phe^4,Gly^5-ol]-enkephalin (DAMGO), or a δ-opioid agonist, [D-Pen^{2,5}]-enkephalin (DPDPE), were made via cannulae targeting one of four dorsal striatum quadrants — anterior and posterior dorsomedial striatum, and anterior and posterior dorsolateral striatum — whilst 'wanting' (eating) and (separately) 'liking' reactions were measured and compared to an inactive-injection control.

The extent of drug-induced neural activation was assessed by mapping the intensity of local 'Fos plumes' [4,5] caused by DAMGO microinjection in separate animals. DiFeliceantonio *et al.* [2] found that exogenous μ-, but not δ-, opioid stimulation within a circumscribed anteromedial dorsal striatum zone (0.02 mm^3 volume) stimulated intense eating of M&Ms® (>250% increase relative to control) in non-deprived rats. Eating was not significantly elevated following injection into other dorsal striatum sites. Feeding was voracious — roughly equivalent to an average-weight human eating two 'huge' (1.4 kg) bags of M&Ms® in a single hour, indicating suppression of satiety-related signalling. DAMGO microinjection in anteromedial dorsal striatum not only made rats eat more, it also made them faster to begin eating. DAMGO microinjections in all injection sites, however, failed to produce increases in non-feeding behaviours.

By contrast, DAMGO microinjections into anteromedial dorsal striatum completely failed to increase 'liking' reactions for a sweet taste (sucrose). Crucially, since a food's fat content is an important, though not obligatory, feature predicting sensitivity to μ-opioid-mediated changes in intake [11], DAMGO microinjections into anteromedial dorsal striatum also failed to enhance 'liking' of M&Ms® themselves, despite markedly increasing intake. Thus, the anteromedial dorsal striatum feeding hotspot is another striatal pure 'wanting' hotspot, not a 'pleasure patch', where μ-opioids stimulate food intake by a mechanism separable from hedonic impact.

The observation of increased eating without enhanced pleasure resembles dissociations of food 'wanting' from 'liking' produced by brain dopamine manipulations [12]. Striosomes are innervated by dopamine neurons of the substantia nigra, pars compacta (SNc) [6], and are the only striatal neurons projecting directly to SNc dopamine neurons [13], paralleling a ventral striatal SNc input [6]. Striosomes and ventral striatum are thus pivotally placed to influence dopamine signalling in dorsal striatum [6], critical for feeding [14]. Interactions between μ-opioid and dopamine in anteromedial dorsal striatum are now an important topic for future studies.

Superficially, DiFeliceantonio *et al.*'s findings [2] appear inconsistent with prior reports of null effects of dorsal striatum-injected DAMGO on feeding [3]. However, the earlier studies did not specifically target the micro-domain revealed by DiFeliceantonio *et al.* [2], and consistent with the latter study, following blockade of (striosomal) acetylcholine muscarinic receptors in anterior dorsal striatum, rats reduced their subsequent daily intake of food by 50% — an effect likely mediated by reduced enkephalin availability [3].

The identification of a dorsal striatum 'wanting' hotspot has ramifications for recent human clinical studies. A case report linked dorsal striatum damage following stroke to a complete cessation of alcohol and nicotine addiction [15]. Dorsal striatum activity in response to images of energy-dense foods is elevated in obese individuals [16], and individuals with loss-of-control over eating show enhanced dorsal striatum activity when anticipating tasty food [17]. Such activations may encompass a homologous anteromedial dorsal striatum 'wanting' hotspot [8] and the extent to which local μ-opioid transmission (measured using positron emission tomography) is linked to such neural activations will be important to uncover. Activation of dorsal striatum μ-opioid receptors is required for affiliative reward [18], and the role of the dorsal striatum 'wanting' hotspot in other forms of reward can now be studied.

Like all the best treats, this feast of a paper from DiFeliceantonio *et al.* [2] only leaves the reader 'wanting' more. What are the precise anatomical and functional relationships between dorsal striatum and accumbens/pallidal 'wanting' and 'hedonic' hotspots and how do they fit within broad corticostriatal-hypothalamic circuits [3–5] and even broader gut-brain circuits [19] influencing food intake? Given that enhanced pleasure is not required to drive enhanced intake of energy-dense foods, and that hedonic hotspots appear far more rare than pure 'wanting' hotspots, what functional role does (enhanced) pleasure play in (over)eating? Most urgently, perhaps, what precise motivational mechanism underpins enhanced 'wanting' without enhancement of 'liking'? A likely mechanism is incentive salience, a type of dopamine-dependent implicit cue-triggered motivation distinguishable from cognitive desires mediated by explicit expectations of pleasure [12]. One consequence

of heightened incentive salience to food-related stimuli is elevated intake, though consumption by itself is a downstream measure of incentive salience [5]. Future studies on the back of this pioneering report [2] will no doubt accompany 'wanting' measures of food intake with measures that better isolate incentive salience [5,12,20].

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Closed Mitosis: A Timely Move before Separation

Faithful chromosome segregation entails long-range chromosome movement into newly dividing cells. A recent study implicates CDK1 function in releasing mitotic telomeres from the nuclear envelope, thereby liberating chromosomes for mitotic segregation.

Hani Ebrahimi and Julia Promisel Cooper

In a sea of relatively free-floating nucleoplasm, the nuclear envelope (NE) provides a solid platform to which chromosomes can anchor and limit their movement [1,2]. Settling of a chromosome within its territory [3] allows the creation of distinct subnuclear microenvironments that can influence gene expression and recombination [4–6]. During mitosis, however, replicated chromosomes must be able to move freely into newly dividing cells. In many eukaryotes, the nuclear envelope (NE) is broken down prior to mitosis, allowing unhindered chromosome movement directed by the mitotic spindle. What happens in organisms that do not break down the NE prior to mitosis? A new paper by Fujita and colleagues [7] published in this issue of *Current Biology* highlights the importance of cell cycle regulated telomere detachment from the NE during the closed mitosis of the fission yeast *Schizosaccharomyces pombe*, and raises fascinating questions about the control of chromosome location in all organisms.

Telomeres are associated with the NE during interphase of the fission yeast cell cycle (Figure 1) [8,9]. By measuring the telomere-to-NE distance throughout the cell cycle, Fujita and colleagues show that fission yeast telomeres detach from the NE during early stages of mitosis and remain detached until mitotic completion. This cell cycle regulated positioning is reminiscent of the dynamics of budding yeast telomeres, which tend to attach to the NE but dislodge as cells prepare for mitosis [10,11]. The dislodgment of budding yeast telomeres occurs in late S phase and is triggered by telomeric DNA replication [12]. In contrast, fission yeast telomeres attach to the NE through G2, detaching only at early mitosis, an observation which is in keeping with experiments showing that fission yeast utilize G2/M regulation more prominently than budding yeast. This mitosis-specific telomere dislodgment points to a cell cycle regulated modification in the telomere–NE anchoring pathway.

Telomere–NE attachment is mediated by the highly conserved telomere-associated protein Rap1, which interacts with both the telomeric DNA binding protein Taz1 (ortholog of human TRF1 and TRF2) and the inner NE protein Bqt4 (Figure 1, top inset) [8]. Rap1 also functions collectively with Taz1 during other cell cycle phases, preventing chromosome end-fusions in G1 and regulating