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Prefrontal Cortical Opioids and Dysregulated Motivation: A Network Hypothesis

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Abstract

Loss of inhibitory control over appetitively motivated behavior occurs in multiple psychiatric disorders, including drug abuse, behavioral addictions, and eating disorders with binge features. In this opinion article, novel actions of μ -opioid peptides in the prefrontal cortex (PFC) that could contribute to inhibitory control deficits will be discussed. Evidence has accrued to suggest that excessive intra-PFC μ -opioid receptor (μ -OR) signaling alters the PFC response to excitatory drive, resulting in supernormal and incoherent recruitment of multiple PFC output pathways. Affected pathways include functionally opposed PFC→hypothalamus ‘appetitive driver’ and PFC→striatum ‘appetitive limiter’ projections. This network perturbation engenders disorganized, impulsive appetitive responses. Evidence supporting this hypothesis from human imaging and animal studies will be discussed, and combinatorial drug treatments targeting μ -ORs and specific PFC subcortical targets will be explored.

Introduction: Is Prefrontal Cortex the ‘Undiscovered Country’ Where Opioid Signaling Provokes Motivational Dysregulation?

Impaired **inhibitory control** (see Glossary) over motivated behavior is a core feature of multiple psychiatric disorders [1–4]. This type of behavioral dysfunction can be manifested in different ways; for example, uncontrolled **binges** of food or drug intake in eating disorders or addiction, craving-induced relapse, and impulsivity in choice behavior. Collectively, drug or behavioral addictions, eating disorders, and other ‘disorders of motivational regulation’ exact a serious toll in public health [5,6]. An effective, early intervention would have the potential to break the cycle of repeated bingeing or relapse episodes before serious health consequences arise, including lifelong addictions, eating disorders, or obesity.

Among the few drugs with at least some efficacy in ameliorating symptomatology in psychiatric disorders characterized by dysregulated **appetitive motivation** are opioid receptor antagonists. Drugs such as naltrexone are approved by the US Food and Drug Administration (FDA) for the prevention of relapse in alcohol dependence [7,8], and there are reports that opioid antagonists ameliorate pathological gambling, binge eating, and

compulsive sexual behavior [9–13]. Aberrant opioid signaling could, therefore, underlie a motivational dysregulation **endophenotype** that crosses nosological boundaries. Nevertheless, some studies have reported only mixed or limited success with these drugs in the treatment of binge eating [14,15], and, in the case of alcoholism, have suggested a modulating effect of genotype on naltrexone efficacy [7,16,17]. Hence, while there is compelling evidence to suggest the involvement of central opioids in addiction and allied disorders, the mixed clinical results with systemically administered opioid blockers indicate that there are mechanistic complexities that are not yet understood. There is room, therefore, to improve a safe and highly promising class of drugs. Understanding the chemical coding of the neural network through which opioids modulate motivation and inhibitory control could suggest poly-drug approaches that would enhance the effectiveness of opioid receptor blockers. This possibility will be explored in the present opinion article.

Extensive work in preclinical animal models has implicated central opioid signaling (particularly through the **μ-opioid receptor, μ-OR**) in dysregulated eating of palatable, energy-dense foods [18–20], excessive alcohol intake [21], and self-administration of opiate and psychostimulant drugs [22,23]. In animal studies, the modulation of motivational processes by central μ-OR signaling has been studied most extensively in subcortical sites, notably the ventral tegmental area (VTA) and **nucleus accumbens (Acb)**. This literature has been reviewed previously [24–26], and it is widely hypothesized that the clinical effects of opioid antagonists are at least partly based upon actions at these subcortical sites. One structure that has been almost completely overlooked, however, is the **prefrontal cortex (PFC)**. The PFC contains appreciable densities of μ-ORs and μ-opioid peptides [21,27–29], and μ-OR signaling modulates PFC neuronal activity [27,30–32]. Furthermore, recent positron emission tomography (PET) human imaging studies employing a μ-OR-selective ligand have detected μ-OR activation in several medial PFC and orbitofrontal sites in association with drug intake [33–35] and in individuals with trait impulsivity [36]. Finally, as will be discussed in detail later, recent animal studies have revealed the PFC to be a crucial site of opioid action in the context of binge-like behavior directed at food or alcohol [19,21,37,38]. These observations suggest the possibility that, in addition to modulating reward processing in subcortical sites, opioid signaling could participate in addiction and other disorders by altering executive control and motivational functions of the PFC. Hence, alongside the more extensively studied subcortical loci of opioid actions, the PFC may be a crucial ‘hot spot’ for opioid-mediated symptom provocation in psychiatric disorders characterized by dysregulated motivated behavior.

Frontal Executive Dysfunction in Psychiatric Disorders Characterized by Motivational Dysregulation: An Opioid Link?

Convergent evidence from cognitive–behavioral and human neuroimaging studies strongly suggests that dysfunction in frontal cortical systems contributes to pathological behavior in eating disorders, drug or behavioral addictions, and other syndromes characterized by motivational dysregulation. For example, studies using tasks that probe frontal inhibitory control function have shown that individuals diagnosed with binge eating disorder or bulimia nervosa exhibit impulsivity deficits [39–42]. Furthermore, evidence of aberrant frontal

cortical activity in binge-type eating disorders [43–46], drug addiction [47], pathological gambling [48], and in response to a stressor in individuals with trait impulsivity [36] has been provided by human neuroimaging studies using functional magnetic resonance imaging (fMRI) or PET. This dysregulated frontal activity occurs in a set of functionally distinguishable yet interacting regions that, via integration with limbic structures, computes affective significance of cues, modulates emotional responses, and guides behavioral choice [49–51]. These regions include insular cortex, medial orbitofrontal areas (OFC), and rostral ventral aspects of anterior cingulate cortex (ACC). For example, in eating disorders with binge features, dysregulated food intake appears to be due in part to the exaggerated activation of frontal sites that normally responds to salient food cues, including the insular cortex, OFC, and ACC. More broadly, these regions [particularly the ventral medial PFC (vmPFC), comprising medial aspects of orbitofrontal and rostral ventral aspects of ACC] appear to encode the subjective value of rewards across multiple modalities and domains [52,53]. Within several of these regions, responses to food cues are enhanced by hunger, or when the cues presented are associated with calorie-dense or highly palatable foods [54–56]. In individuals with eating disorders and obesity, exaggerated activity within the same set of frontal subregions has been observed [43,46,57,58]. Conceptually similar findings have been obtained in human neuroimaging studies of drug addiction; for example, heightened responses in the vmPFC were found to correlate with high cue-induced alcohol craving and subsequent alcohol relapse [47], and heightened activity is present within OFC during cocaine craving [50].

Could dysregulated μ -OR signaling contribute to the exaggerated frontal cortical responses observed in binge-type eating disorders and other syndromes? There is evidence to suggest that this might be the case. In rat studies, μ -opioid peptide levels in the medial PFC were strongly elevated in animals exposed to a ‘binge’-inducing palatable feeding schedule [19], and intra-PFC μ -OR blockade reduced binge-like feeding [19]. Conceptually similar findings have been obtained in alcohol-drinking rats. In one study, rats characterized as ‘high drinkers’ were found to express significantly greater levels of μ -opioid peptides and their receptors in the medial PFC, and intra-PFC μ -OR stimulation was found to elevate alcohol drinking in these rats [21]. PFC-localized μ -ORs are also upregulated by binge-like cocaine administration patterns in rats [59]. In human neuroimaging studies, μ -opioid peptide release has been detected within orbitofrontal cortex in association with sweetened alcohol drinking, and in ACC with rewarding amphetamine doses [33–35]. Furthermore, μ -OR upregulation in frontal sites including the ACC robustly predicts the severity of craving and the rapidity of relapse in cocaine users [60–63]. This upregulation could reflect receptor numbers, affinity, or decreased availability of endogenous ligand; however, in a general sense, μ -OR upregulation could confer greater responsiveness to exogenously administered opiate drugs, and possibly to phasic ‘surges’ of endogenous μ -opioid release. This putative μ -OR-mediated cortical hyperresponsiveness could contribute to the disorders of motivational regulation described earlier.

Evidence from Preclinical Animal Studies that Intra-PFC μ -OR Signaling Modulates Inhibitory Control

Surprisingly few animal studies have investigated μ -ORs in formal tests of inhibitory control, but the few that have provide strong support for μ -OR involvement in this process. Genetically altered mice lacking μ -ORs show markedly decreased motor impulsivity in a signaled response task [64], implying that μ -ORs promote impulsive behavior. Naltrexone reverses morphine-induced impulsive choice in a delay-discounting task in rats, and reduces impulsive choice in a subset of alcoholics [65,66]. Notably, a recent ligand PET imaging study in humans showed an upregulation of PFC μ -ORs, and greater stress-induced endogenous opioid release in ACC and medial PFC, in individuals with trait-like impulsivity (defined as the tendency to act on cravings or urges) [36]. Together, these findings suggest that excess μ -OR signaling can degrade inhibitory control with a PFC locus of action.

A recent series of studies further supports this hypothesis. Infusions of the μ -OR-selective agonist, DAMGO, into rat vmPFC (a zone spanning of dorsal infralimbic and ventral prelimbic cortex; Figure 1) and medial aspects of OFC – areas roughly homologous to primate vmPFC described earlier [67–69], augmented feeding [37] (Figure 1). In a choice procedure, intra-vmPFC DAMGO selectively enhanced the intake of carbohydrate-enriched food, which is interesting given the reports that children exhibiting binge-like eating behaviors preferentially consume carbohydrates [70]. Together, these findings suggest that the motivational state engendered by intra-PFC μ -OR signaling has face validity for food bingeing. Next, construct validity was assessed by using targeted operant tasks to probe two defining, interrelated characteristics of motivational dysregulation syndromes: abnormally elevated appetitive motivation [assessed using a sucrose-reinforced progressive ratio (PR) task], and impulsivity-like loss of inhibitory control [indexed using a differential reinforcement of low response rates (DRL) task] [38]. In the PR task, intra-vmPFC infusion of DAMGO markedly increased the expenditure of effort to obtain sucrose reward. Congruently, in the DRL task, intra-vmPFC μ -OR stimulation with DAMGO dose dependently increased the number of ‘impulsive-like’, premature responses. Blocking vmPFC-localized opioid receptors, by contrast, reversed impulsive-like DRL performance deficits in very hungry rats, and also attenuated the hunger-induced amplification of PR responding. Together, these findings demonstrate that that μ -OR signaling within the vmPFC is both necessary and sufficient for the expression of abnormally strong food motivation and loss of control over food-seeking responses. In contrast to opioid manipulations, intra-vmPFC infusions of D-amphetamine were without effect – unlike in the Acb, where both DAMGO and amphetamine elevate breakpoint and promote impulsivity. Moreover, a wide variety of intra-PFC dopaminergic, serotonergic, and noradrenergic receptor agonists and antagonists have been tested in a free-feeding paradigm, and none of them mimicked the behavioral effects of intra-vmPFC DAMGO [37]. Indeed, to the author's knowledge, DAMGO is unique among pharmacological manipulations of the PFC in its ability to engender the ‘behavioral phenotype’ of disorganized feeding responses, increased carbohydrate preference, abnormally strong food motivation, and impulsivity.

Could Incoherent Recruitment of Functionally Diverse PFC Terminal Fields Account for Motivational Dysregulation Provoked by Intra-PFC μ -OR Signaling?

μ -OR-induced PFC network perturbations could conceivably result in the recruitment of diverse – and, perhaps, functionally opposed – PFC terminal fields in a dysregulated manner (Box 1). For example, multiple downstream projection targets could be simultaneously engaged that normally are not, or the normal balance of PFC-driven activity in two functionally opposed terminal fields could be thrown off. Such effects would be expected to confer a degree of incoherence to appetitively motivated behavior sequences. Accordingly, intra-PFC μ -OR-driven feeding response is characterized by significantly shortened short bouts that are often terminated by abrupt shifts into other behaviors such as rearing or grooming [37] (Figure 1). This pattern contrasts with the sustained feeding bouts observed under ‘normal’ motivational conditions, such as hunger. If the μ -OR-induced ‘fragmentation’ of the behavioral repertoire is indeed the outcome of dysregulated recruitment of distinct PFC terminal fields that mediate differing response tendencies, one might predict that inactivation of select PFC terminal fields would differentially affect subcomponents of the overall behavioral phenotype. To test this hypothesis, dual cannulation studies were carried out to assess the functional roles of the nucleus accumbens shell (AcbSh) and the lateral and perifornical hypothalamic area (LH-PeF), a feeding modulatory region of the **hypothalamus**, in the expression of PFC-driven feeding responses [71], because previous work suggests that PFC→AcbSh and PFC→LH-PeF circuits mediate opposing processes in appetitively motivated behaviors.

It has long been known, for example, that stimulation of the LH-PeF region with glutamate or neuropeptide Y engenders strong feeding responses [72,73]. More recently, it has been shown that feeding provoked by an appetitive Pavlovian cue activates PFC neurons marked by tracer infusions into the LH-PeF but not the Acb [74]. These results suggest that a medial PFC–hypothalamus interaction triggers appetitive behavior. In contrast, stimulation of AcbSh-localized AMPA-type glutamate receptors suppresses feeding [75], electrical stimulation of the Acb arrests consummatory sucrose licking [76], and, conversely, AMPA blockade or GABA-mediated inactivation of the AcbSh provokes feeding [77,78]. In general agreement with these pharmacological findings, several electrophysiology studies have provided evidence for a substantial population of Acb neurons that show inhibitions in conjunction with the anticipation and receipt of reward, or during the performance of motoric consummatory actions associated with food reward [76,79–82]. One study, for example, identified Acb units that show inhibitions that begin immediately before the onset of consummatory sucrose licking and persist during consumption [76]. Although the afferent control of these Acb neurons is not clear, one study showed that medial PFC lesions suppress the basal activity of these reward-inhibited Acb units, suggesting that these neurons can be modulated by excitatory vmPFC projections [83]. Together, these findings suggest that PFC projections to LH-PeF versus AcbSh may have opposing actions on appetitively motivated behaviors.

This hypothesis has been tested using a dual-site microinfusion approach [71]. Rats received two sets of infusion cannulae, aimed at either the PFC and AcbSh, or the PFC and the LH-PeF. Food intake elicited by intra-vmPFC administration of the μ -OR-selective agonist, DAMGO, was blocked by a subthreshold dose of the NMDA antagonist, AP-5, infused directly into the LH-PeF (Figure 2). This result demonstrates that a surge of glutamate release in hypothalamus is necessary for the expression of vmPFC μ -OR-driven feeding. Further confirming that intra-PFC μ -OR stimulation activates feeding modulatory hypothalamic substrates, intra-vmPFC DAMGO elevated Fos expression (a marker of neuronal activation) in the dorsomedial perifornical area – the same region targeted in the microinfusion study described earlier. A significant number of these Fos-expressing cells were found to contain the neuropeptide hypocretin/orexin (H/O), which modulates feeding and arousal, and which is hypothesized to couple arousal with motivational state (Figure 2). Essentially the opposite profile was seen in rats with dual vmPFC and AcbSh placements: intra-AcbSh glutamate receptor blockade augmented vmPFC–DAMGO-driven feeding, attenuated DAMGO-mediated hyperactivity, and markedly potentiated DAMGO-induced exaggerated motivation in the PR task [71]. These results demonstrate that, in contrast to the results of PFC→hypothalamus manipulations described earlier, glutamate transmission through AcbSh-localized AMPA receptors limits the degree of food motivation engendered by intra-PFC μ -OR stimulation.

Note that, although the dual cannulation studies described earlier can reveal functional interactions between two sites they cannot establish that the route of control is monosynaptic (indispensable information for a true understanding of network organization). To achieve a deeper level of insight, the distinct efferent pathways originating from vmPFC must be functionally isolated using methods such as optogenetics or pathway-specific expression of DREADD receptors. The use of such technologies represents an important next step for ‘dissecting’ and understanding the functional organization of PFC–Acb–hypothalamus interconnections. These technologies can also be used to assess whether, outside the vmPFC, there is some degree of anatomical segregation of appetitive versus inhibitory control (see Outstanding Questions).

Cortico–Striato–Hypothalamic Network Dysfunction in Syndromes of Motivational Dysregulation: A Working Hypothesis

Based on the results described earlier, the Baldo group has developed a network-based, testable model accounting for how abnormal μ -OR signaling in the PFC could provoke excessive and unrestrained appetitive motivation (Figure 3, Key Figure). A core feature of the model is the postulate that, under normal conditions, the PFC enacts input–output mappings that recruit subcortical ‘motivational driver’ and ‘motivational limiter’ systems in a flexible, adaptive, and contingency driven manner. These mappings are disrupted under conditions of excess μ -OR signaling. The specific tenets of the theory are as follows:

- i. Intra-vmPFC μ -OR signaling exerts a unique disinhibitory action (relative to the PFC-based monomine receptors tested thus far) on the local cellular network, resulting in enhanced PFC outflow and consequent glutamate release in multiple terminal fields including AcbSh and hypothalamus (Box 1).

- ii. Glutamate signaling in the hypothalamus engages a non-homeostatic appetitive drive, partly by activating specific peptide-coded substrates (including the hypocretin/orexin system).
- iii. At the same time, AMPA receptor signaling in the AcbSh acts to limit (but not eliminate) appetitive responses, preventing the animal from becoming 'locked' into goal-seeking repertoires and thereby enabling inhibitory control when such is needed to optimize performance.
- iv. Loss of frontal inhibitory control over appetitive behavior occurs either when vmPFC μ -ORs are hypersensitive, when the AcbSh 'limiter circuit' is subsensitive to vmPFC input, when the hypothalamus is hypersensitive to PFC drive, or a combination of these factors.
- v. Repeated experience with intense, reward-driven feeding enacts some set of neuro-adaptations described in (iv); in this manner, bingeing may produce a vicious cycle of worsening pathology in which balance between various feeding effector sites (i.e., the PFC–Acb circuit versus the PFC–hypothalamus circuit) is disrupted. Note that a functional imbalance in the other direction (i.e., a subsensitive 'driver circuit' and hypersensitive 'limiter circuit') would be predicted to cause an abnormal restriction of feeding, as is seen in anorexia nervosa.

It is important to distinguish between the 'normal' physiological role of cortical μ -ORs versus their putative role in pathological states. A recent ligand PET study showed that eating a meal when hungry caused μ -OR activation in the OFC and of lean, but not obese, subjects. Furthermore, in lean subjects, OFC μ -OR activation was associated with a meal-associated decrease in negative affect [84]. This finding suggests that cortical μ -OR signaling, and associated affective modulation, occurs in normal feeding. Nevertheless, this 'normal' μ -OR-mediated regulation could progress to dysregulation if μ -OR activation occurs in the context of a faulty efferent network; for example, if the motivational 'limiter' function of the circuitry has been compromised and can no longer hold cortically driven responses in check. Recent findings have begun to suggest that exposure to reward-driven feeding engenders adaptations within PFC terminal fields that could, in principle, result in a blunting of the proposed PFC→AcbSh 'limiter circuit' [85]. Rats that had gorged daily on sweetened fat displayed a markedly sensitized feeding response to a low-dose intra-AcbSh challenge of the GABA agonist, muscimol. This increased responsiveness to GABA-mediated inhibition could conceivably reflect a broader underlying change in the balance of inhibitory and excitatory transmission in the Acb, the net effect of which would be to attenuate the functional impact of glutamate-coded signals arriving from the PFC. If so, this GABA plasticity could engender a vicious cycle of abnormal binge-like feeding behavior, if the PFC→Acb projection indeed functions as a 'limiter' circuit. Whether additional types of neurochemical plasticity occur in the network remains to be determined (see Outstanding Questions).

Concluding Remarks and Clinical Implications

The network model outlined earlier can serve as a framework for understanding how pathological behavior can emerge from a cortico–striato–hypothalamic network designed to balance the expression of reward-directed and non-reward-directed actions. If repeated exposure to drugs or to certain foods/eating patterns enacts neuroplastic changes that attenuate or exaggerate the ability of the PFC to engage a particular subcortical system (e.g., either the ‘motivational driver’ or ‘motivational limiter’ circuits), dysfunctional behavior would emerge predictably based upon the direction of the change and the particular pathway affected. This model could suggest treatment strategies that enhance the effectiveness of opiate-blocking drugs by jointly targeting downstream neurochemical systems that are recruited by intra-PFC μ -OR signaling. In other words, manipulating the ‘apex’ along with lower levels of the network could lead to a synergistic reduction in PFC-driven motivational dysregulation. Such an approach could improve the efficacy, reduce response variability, and/or reduce the required dose of opiate antagonist drugs, potentially yielding a large improvement in treatment outcomes.

An interesting candidate for such a strategy would be the targeting of opioid receptors along with hypocretin/orexin (H/O) receptors, with the aim of dampening the exaggerated appetitive motivation induced by overactivation of the PFC→hypothalamus ‘appetitive driver’ circuit. The H/O system is involved in regulating and stabilizing arousal states [86], and in linking arousal and motivational states [87,88]. The etiology of narcolepsy, for example, appears to be a lack of hypothalamic H/O or a deficiency in the function of H/O receptors [89,90]. Moreover, evidence has accrued to suggest that H/O plays a role in psychostimulant- or alcohol-seeking behavior [91–94], and in generating patterns of binge-like eating [95–97]. Indeed, it has been suggested that H/O antagonists, which are currently FDA-approved for the treatment of narcolepsy [98], could represent a useful pharmacological treatment for drug relapse and other disorders of motivational regulation [99,100].

As described earlier, recent work demonstrates that intra-PFC opioid signaling activates a subpopulation of H/O neurons in the dorsomedial perifornical area of the hypothalamus (Figure 2). This observation suggests the possibility that H/O neurons play a role in the behavioral effects of intra-PFC opioid signaling, although further work with H/O antagonists needs to be done to fully test this hypothesis. Along similar lines, H/O neurons appear to act as a key relay in the circuitry linking striatal opioid function with mesencephalic motivational effector systems [101]. The work reviewed here suggests the additional possibility that combining the blockade of H/O receptors with blockade of opioid receptors could have additive or super-additive effects on dysregulated appetitively motivated responses (broadly construed) by simultaneously targeting opioid-driven PFC dysregulation along with the downstream sequelae of such dysregulation.

More generally, because the neurochemical identity of the nodes in the network model described earlier have been specified to some degree, it is possible to rationally predict and test drug combinations that would be particularly effective at quelling syndromes of PFC-based motivational dysregulation. Studies to further enhance our understanding of opioid-

modulated, PFC-based networks (see Outstanding Questions) will be crucial for developing pharmacological treatments for a class of disorders that exacts an enormous toll with regard to human lives and productivity.

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Glossary

Appetitive motivation

refers to the set of interacting processes by which organisms identify goals to pursue (e. g., food, water, sexual mate) and exert effort to obtain those goals.

Binge(ing)

appetitively motivated behavior that is excessive and unchecked by normal inhibitory controls. For example, clinical accounts of food bingeing describe a subjective sense of ‘loss

of control' over food intake. Binge-like behavior is a common feature of drug and behavioral addictions (e.g., binge eating, pathological gambling).

Endophenotype

an underlying biological process that produces core behavioral symptoms in one or more diseases. An endophenotype is thought to represent the manifestation of a specific, heritable mechanism controlled by a gene or cluster of genes.

Hypothalamus

this structure, located in the ventral part of the diencephalon, regulates core metabolic and behavioral functions necessary for survival. The hypothalamus enacts homeostatic control by detecting deviations from an adaptive range of physiological function, and adjusting hormone release and behavior to counteract the deviation. In the context of feeding behavior, the hypothalamus aligns food intake with energy balance needs by sensing blood-borne energy sensing hormones. This 'bottom-up' hormonal control can be modulated or overridden by 'top-down' signals from structures such as the Acb shell, PFC, or amygdala.

Inhibitory control

used here to refer collectively to the processes by which adaptive limits are set upon appetitively motivated behaviors. Breakdown in inhibitory control can result in bingeing, impulsive behavior (rapid, unplanned actions or suboptimal choices), and compulsive behavior (persistence in a particular motivated behavior despite adverse consequences).

Mu-opioid receptor (μ -OR)

a cell-surface receptor, belonging to the broad family of G-protein-coupled receptors, that binds certain endogenous opioid peptides (enkephalins, β -endorphin, endomorphins) as well as drugs of the opiate class (morphine, heroin, fentanyl). μ -OR signaling in the brain modulates the rewarding effects of opiate drugs, alcohol, and certain natural rewards (e.g., palatable food).

Nucleus accumbens (Acb)

a subcortical brain structure crucially involved in regulating the motivational effects of drugs and natural rewards (food, sex, etc.). Anatomically, the Acb is defined as the ventromedial aspect of the corpus striatum. Functionally, the Acb serves as a limbic-motor interface, connecting affective states to goal-directed behaviors. The Acb has two distinct subregions: the core and shell. The shell plays a specialized role in both initiating and arresting feeding-related behaviors.

Prefrontal cortex (PFC)

functionally distinguishable, yet interacting, subregions of the frontal lobes that optimize behavioral output by organizing information from lower levels of processing, and using this information to flexibly provoke or restrain behavioral responses. The PFC is the most highly elaborated part of the primate brain. Nevertheless, anatomical and/or functional homologs of primate PFC subregions exist in rodent species; for example, reward-modulatory sites in ventromedial PFC and medial orbitofrontal cortex, as discussed in this opinion article.

Trends

Abnormal opioid signaling in the brain is thought to contribute to motivational dysregulation in drug and ‘behavioral’ addictions (e.g., binge eating, pathological gambling). Opioid actions have been extensively studied in subcortical sites (e.g., the nucleus accumbens, Acb), but not in the cortex.

Recent studies suggest that the prefrontal cortex (PFC) is a key anatomical substrate for opioid-driven food and alcohol bingeing, and food impulsivity.

Recent findings suggest that dysregulated motivated behavior emerges when cortical opioid signaling disrupts the balance between PFC→hypothalamus ‘motivation driver’ and PFC→Acb ‘lim-iter’ circuits.

Improved knowledge of opioid-responsive cortical→subcortical circuitry could aid the development of poly-drug strategies that block opioid receptors along with PFC-targeted subcortical neurochemical systems.

Box 1 **μ -OR Regulation of PFC Neuronal Function**

Given the robust and unique behavioral effects of opioid manipulations in the PFC, the question arises as to how μ -opioids modulate neuronal function within this brain region. Evidence is accruing to suggest that μ -OR signaling acts at several points of the PFC cellular network to modify the response to excitatory input. Enkephalins, β -endorphin, and endomorphins are found within the PFC [27–29,102]. Single cell PCR and immunohistochemistry studies have shown that μ -ORs are synthesized exclusively within cells expressing glutamic acid decarboxylase (GAD) and several other known interneuron peptide markers and exhibiting interneuron-like morphologies and spiking dynamics [27,29]. μ -OR stimulation suppresses interneuron spiking [27] and diminishes GABAergic miniature inhibitory postsynaptic currents (IPSCs) onto pyramidal cells [27,32]. Presumably, these actions activate pyramidal cells (via disinhibition), thereby augmenting glutamate-coded outflow from the PFC to its terminal fields. This proposed mechanism is similar, in a general sense, to the well-characterized disinhibitory actions of μ -OR signaling in the hippocampus, a structure that contains interneurons very similar to those found in the PFC [103].

In addition to these local actions on intrinsic PFC interneurons, μ -ORs may also modulate thalamic input to the PFC through the modulation of glutamate release from presynaptic thalamocortical nerve terminals. A series of electro-physiology studies in cortical slices showed that μ -OR agonists suppress the increase in pyramidal neuron excitatory postsynaptic currents (EPSCs) that are engendered by 5-HT_{2A} agonists, an effect that appears to be due to an interaction between μ -ORs and 5-HT_{2A} receptors on presynaptic glutamate terminals [104]. An initial exploration into the subcortical source of these terminals showed that thalamic lesions, but not basolateral amygdala lesions, eliminated 5-HT_{2A}-receptor mediated PFC pyramidal neuron spiking [105]. This finding suggests the interesting possibility that the presynaptic effects of μ -OR stimulation are targeted more selectively to thalamic afferents relative to PFC inputs from other subcortical regions.

These multiple μ -OR-mediated effects have the potential to markedly reshape patterns of activation in the PFC. For example, intra-PFC μ -OR signaling could amplify evoked spiking in pyramidal output neurons by suppressing local inhibitory interneurons. At the same time, μ -OR stimulation could shift the proportional influence of amygdalar drive relative to thalamic drive by damping 5-HT_{2A}-evoked glutamate release from thalamocortical terminals. This combination of effects could render the PFC hyperresponsive to incoming limbic signals, which are then ‘passed along’ in a disorganized way to multiple downstream targets. At present, these hypotheses are speculative (but testable). In general, work reviewed in the present opinion article supports the hypothesis that the behavioral effects of intra-vmPFC μ -OR stimulation arise from increased glutamate release in multiple PFC projection targets, the combined effects of which engender disorganized appetitive responses.

Outstanding Questions

To what degree are inhibitory control and food intake regulation coextensive (or segregated) in subregions outside of the vmPFC? What other PFC terminal fields beyond the hypothalamus and Acb mediate the effects of μ -OR stimulation on motivation and inhibitory control? Which PFC afferents are crucial for μ -OR-mediated effects?

Can the divergent functions of PFC $\rightarrow$ hypothalamus and PFC $\rightarrow$ accumbens pathways be confirmed using optogenetic or chemogenetic manipulations? Will those techniques reveal monosynaptic or polysynaptic routes of control?

Does dysregulated food or drug bingeing cause plasticity in the circuitry reviewed herein (e.g., changes in cortical μ -ORs, Acb glutamate systems, or hypothalamic peptide systems targeted by PFC projections)?

Does the circuitry reviewed herein play a role not only in conditions of motivational excess but also in motivational restriction? Could exaggerated function of the proposed 'limiter circuit' underlie disorders such as anorexia nervosa?

What are the dynamics of endogenous opioid peptide release in the PFC? How is this release modulated by appetitive and aversive motivational states?

What are the electrophysiological effects of intra-PFC μ -OR stimulation in awake, behaving animals? How do PFC-localized μ -ORs regulate basal versus evoked firing?

Are μ -OR-mediated motivational effects unique to this receptor, or are the effects an exemplar of a broader class of yet-undiscovered peptide-mediated actions in the PFC?

Do PFC-localized μ -ORs mediate functions beyond food motivation and inhibitory control? Do these receptors govern parallel processes in drug addiction? Do they regulate PFC-based working memory processes?

Considering the established sex differences in opioid-mediated reward and analgesia, do the behavioral effects of intra-PFC μ -OR stimulation differ in males versus females? Is the function of PFC-localized μ -ORs modulated by steroid sex hormones?

Figure 1. Microinfusion Mapping of the PFC Sites Mediating μ -OR-Driven Feeding Responses

Bar graphs in panels (A–D) depict the feeding modulatory effects of intra-PFC infusions of the μ -OR agonist, DAMGO. Asterisks denote significant differences from saline controls. Intra-PFC DAMGO enhanced food intake, both in non-food-deprived rats ('Ad Lib') and in food-deprived rats ('Food Dep'), as reflected in total intake (A), number of feeding bouts initiated (B), and total duration of time spent feeding (C). Panel (D) depicts the effects of intra-PFC DAMGO infusions on mean eating bout duration. In the 'Food Dep' condition (which is associated with longer average feeding bouts), intra-PFC DAMGO significantly shortened mean bout duration, despite the fact that food intake was elevated. This effect is a reflection of the disorganized and 'fragmented' behavioral profile engendered by intra-PFC DAMGO, in which the rats abruptly terminated ongoing feeding bouts in order to engage in a non-food-directed behavior (e.g., locomotion or rearing). Panel (E) shows chartings of injector placements, coded with regard to the magnitude of the feeding effect at each site. Placements in the ventral prelimbic (PrL), dorsal infralimbic (IL), and ventromedial orbitofrontal (VO) areas were most effective; as placements moved dorsally and laterally from these zones, the feeding effect was lost. Abbreviations: Cg1, anterior cingulate; M1, M2, premotor and motor areas; AI, agranular insular cortex; LO, lateral orbitofrontal cortex; DP, dorsal peduncular cortex; Cl, claustrum; PFC, prefrontal cortex; μ -OR, μ -opioid receptor. Adapted from [37]; copyright with permission from the Society for Neuroscience.

Figure 2. Evidence that Intra-PFC μ -OR Stimulation Drives Appetitive Behavior through Glutamate-Mediated Activation of Hypothalamic Substrates

Line graphs in panels (A) and (B) show the results of a dual-site microinfusion study, in which the μ -OR agonist, DAMGO, was infused into a ventral portion of the PFC ('vmPFC'), while simultaneously, the NMDA-type glutamate receptor antagonist, AP-5, was infused into a feeding modulatory subregion of the lateral/perifornical hypothalamus ('LH-PeF'). Intra-hypothalamic AP-5 eliminated PFC–DAMGO-driven feeding (A). Furthermore, AP-5 failed to alter vmPFC–DAMGO-driven hyperactivity (B), demonstrating that the blockade of feeding was not the nonspecific consequence of motor incapacitation, and furthermore suggesting that separate neural pathways mediate hyperphagia versus hyperactivity effects of intra-PFC μ -OR stimulation. The remaining panels show that intra-PFC infusion of DAMGO activates medially localized hypocretin/orexin (H/O) neurons, as indexed by the expression of the activity marker, Fos, in those neurons. As described in the text, H/O modulates arousal state and plays a role in drug seeking and drug relapse. The photomicrograph shows immunohistochemical staining of H/O neurons in the LH-PeF, segregated into 'Lateral' and 'Medial' groupings for quantification. The chartings show that a greater number of medially localized H/O neurons are activated by intra-PFC DAMGO, relative to intra-PFC saline or exposure to a novel environment (a control for nonspecific activity/arousal effects). H/O-immunoreactive neurons are depicted with beige circles; H/O neurons also expressing Fos are depicted with red circles. Abbreviations: LH-PeF, lateral and perifornical hypothalamic area; PFC, prefrontal cortex; μ -OR, μ -opioid receptor; vmPFC, ventral medial PFC. Adapted from [71]; copyright with permission from the Society for Neuroscience.

Figure 3. DAMGO in the vmPFC activates output neurons; the mechanism is unknown, but may involve μ -OR-mediated suppression of inhibitory GABAergic cortical interneurons upon which μ -receptors are found

This loss of local recurrent inhibition translates into pyramidal cell disinhibition and consequent glutamate release in multiple terminal fields of vmPFC. In the lateral/perifornical area of the hypothalamus ('LH-PeF'), vmPFC-derived glutamate release drives appetitive behavior, including ingestion, perhaps partly through the activation of H/O-containing neurons. Also, activation of H/O neurons augments general arousal within the waking state. In the Acb shell, enhanced signaling through AMPA receptors activates the neuronal subpopulation that normally 'gates' the expression of goal-directed and consummatory behaviors, thus interfering with feeding and making it harder to remain 'locked' into feeding bouts. Relatedly, intra-Acb shell AMPA signaling elicits non-food-directed behaviors. The net result of this simultaneous activation of functionally dissociable terminal fields of vmPFC is disorganized appetitive behavior, as is seen after intra-vmPFC μ -OR stimulation. Abbreviations: Acb, nucleus accumbens; H/O, hypocretin/orexin; PFC, prefrontal cortex; μ -OR, μ -opioid receptor; vmPFC, ventral medial PFC.

Key Figure. Working Model of the Network that Subserves the Behavioral Actions of Intra-vmPFC μ -OR Stimulation