Psychopharmacology (2017) 234:1439–1449
DOI 10.1007/s00213-016-4522-4

REVIEW

Feeding-modulatory effects of mu-opioids in the medial prefrontal cortex: a review of recent findings and comparison to opioid actions in the nucleus accumbens

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Received: 2 November 2016 / Accepted: 20 December 2016 / Published online: 4 January 2017

Abstract
Rationale Whereas reward-modulatory opioid actions have been intensively studied in subcortical sites such as the nucleus accumbens (Acb), the role of *cortical* opioid transmission has received comparatively little attention.
Objectives The objective of this study is to describe recent findings on the motivational actions of opioids in the prefrontal cortex (PFC), emphasizing studies of food motivation and ingestion. PFC-based opioid effects will be compared/contrasted to those elicited from the Acb, to glean possible common functional principles. Finally, the motivational effects of opioids will be placed within a network context involving the PFC, Acb, and hypothalamus.
Results Mu-opioid receptor (μ-OR) stimulation in both the Acb and PFC induces eating and enhances food-seeking instrumental behaviors; μ-OR signaling also enhances taste reactivity within a highly circumscribed zone of medial Acb shell. In both the Acb and PFC, opioid-sensitive zones are aligned topographically with the sectors that project to feeding-modulatory zones of the hypothalamus and intact glutamate transmission in the lateral/perifornical (LH-PeF) hypothalamic areas is required for both Acb- and PFC-driven feeding. Conversely, opioid-mediated feeding responses elicited from the PFC are negatively modulated by AMPA signaling in the Acb shell.
Conclusions Opioid signaling in the PFC engages functionally opposed PFC➔hypothalamus and PFC➔Acb circuits, which, respectively, drive and limit non-homeostatic feeding, producing a disorganized and "fragmented" pattern of impulsive food-seeking behaviors and hyperactivity. In addition, opioids act directly in the Acb to facilitate food motivation and taste hedonics. Further study of this cortico-striato-hypothalamic circuit, and incorporation of additional opioid-responsive telencephalic structures, could yield insights with translational relevance for eating disorders and obesity.

Keywords ACCUMBENS · Dopamine · Feeding · Hypothalamus · Motivation · Opiate · Opioid · Prefrontal cortex

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Introduction

In the spirit of this Special Issue, we discuss a topic that featured prominently in the acclaimed and highly impactful scientific career of the late Dr. Athina Markou: the neural substrates underlying reward function. Although Dr. Markou's interests cut across multiple domains of biological psychiatry, her work was unified by the idea that studying central reward function (often using the highly adaptable and informative brain stimulation-reward technique) could provide a "window" into challenging questions regarding the affective components of drug reward, withdrawal, or psychiatric conditions such as depression and schizophrenia. Here, we explore the network mechanisms underlying the feeding-modulatory actions of telencephalic opioids. Neither of these subjects (feeding or opioids) were particular foci of Dr. Markou's research. Nevertheless, we hope that this discussion can enhance understanding of general principles by which telencephalic networks modulate motivational function, which may have broad

relevance to the issues that Dr. Markou studied so productively and successfully in her career.

Feeding-modulatory opioid actions in the Acb

It has long been hypothesized that endogenous opioid function modulates some aspect of food reward, possibly the hedonic experience of eating preferred foods. Early studies showed that opioid receptor blockade reduces the perceived pleasantness of palatable foods, without significantly altering feelings of hunger, basic taste perception, or taste intensity (Drewnowski et al. 1992; Fantino et al. 1986; Yeomans and Gray 1996). Relatedly, systemic treatment with opioid agonists or antagonists in rats selectively increase, or decrease, respectively, consumption of palatable solutions and diets preferentially over standard chow (Apfelbaum and Mandenoff 1981; Cooper 1983; Giraudo et al. 1993; Levine et al. 1982), and systemic opioid antagonist administration was found to prevent the formation and expression of taste preferences (Cooper 1983; Cooper and Turkish 1989; Evans and Vaccarino 1990; Lynch 1986). Accordingly, Levine and colleagues demonstrated that the efficacy of naloxone at reducing food intake (1) is inversely related to the level of food deprivation the animal is subjected to (Levine et al. 1995; Rudski et al. 1994; Weldon et al. 1996) and (2) is dependent upon individual dietary preferences (Glass et al. 1996). Because food deprivation enhances palatability and food-reward valuation (Berridge 1991; Cabanac and Duclaux 1973; Cameron et al. 2014), both findings could be interpreted as indicating that endogenous opioid function modulates of the rewarding impact of the food.

Attempts to localize feeding-modulatory opioid actions in the brain have revealed opioid-responsive sites at neural levels ranging from the cortex to the brainstem (Giraudo et al. 1998; Kim et al. 2004; Leibowitz and Hor 1982; Mena et al. 2011; Wilson et al. 2003; Woods and Leibowitz 1985; Zhang and Kelley 2000). Among the most extensively studied site of feeding-modulatory opioid actions is the Acb, and drug manipulations in this structure have shed some light on the distinct motivational processes that contribute to the opioid modulation of feeding. Early studies found that intra-Acb morphine infusions (injections were located in the medial core) increased food intake and that naloxone reversed this effect (Majeed et al. 1986; Mucha and Iversen 1986). Furthermore, intra-Acb μ-OR stimulation increased intake of palatable solutions, regardless of taste modality or caloric content (sucrose, saccharin, or saline solutions) (Zhang and Kelley 2002) and a study employing specially formulated diets in which flavor varied but macronutrient content was held constant showed that intra-Acb μ-OR blockade reduced intake of the flavor preferred at baseline (Woolley et al. 2006). These findings converge on the interpretation that endogenous opioid function (at least in the Acb) modulates the rewarding impact of intrinsically preferred foods or tastes, rather than selectively affecting a particular taste, orosensory characteristic, or post-ingestive consequence.

In this context, it is important to note that "reward" is the emergent property of several interrelated yet partly dissociable processes: the learning and subsequent assignment of motivational significance to cues and goal objects in the environment, "energizing" of approach behaviors and instrumental acts directed at those cues, and generation of a positively valenced affective state during commerce with those cues and goal objects (Baldo et al. 2013; Berridge 2004; Salamone et al. 2007). Incentive-motivation theory, for example, posits that the feeding central motivational state (CMS) consists of multiple parallel processes working in tandem to produce coherent behavioral sequences; these include "instrumental" seeking-type processes that increase the likelihood of goal attainment and "transactional" processes (e.g., commerce with food) (Bindra 1974; Konorski 1967; Toates 1986). Relatedly, ethologically based frameworks propose distinctions between "preparatory/approach" vs. "consummatory" behaviors (Ball and Balthazart 2008; Craig 1917; Ikemoto and Panksepp 1999). These functions are highly interrelated, and they function cooperatively in the healthy brain to enable reward learning, generate adaptive goal-directed behavior, and facilitate the expression of basic consummatory action patterns when and where appropriate. Yet, evidence has accrued that these functional domains are mediated by partly dissociable neuromodulator systems and pathways. Some of this evidence has emerged from the analysis of similarities and differences in Acb-based opioid and dopaminergic actions upon various indices of food-reinforced behavior and unconditioned reactions to tasteants (Baldo et al. 2013; Barbano and Cador 2006, 2007). Intra-Acb dopamine manipulations, for example, are less effective at altering unconditioned, low-effort responses (e.g., simple ingestive behaviors or taste reactions), relative to conditioned food anticipation, cue-driven approach, hyperactivity, or effortful food-seeking actions (Baldo and Kelley 2007; Berridge 2007; Salamone et al. 2007). Rats treated with dopamine receptor antagonists or dopamine lesions in the Acb will display markedly diminished general activity in the presence of food and less switching among competing behaviors, while total food intake itself is unaffected (Bakshi and Kelley 1991; Baldo et al. 2002). Relatedly, Salamone and colleagues have shown in a variety of tasks that dopamine depletion in the Acb produces shifts in choice towards less effortful food-seeking behaviors, although overall food intake is unchanged (Aberman and Salamone 1999; Nowend et al. 2001; Salamone et al. 1994). The fact that intake itself is unchanged suggests that the "consummatory" motivational component (involving commerce with the food) remains relatively intact. This conclusion is further supported by the observation that Acb dopamine depletion does not eliminate orofacial taste reactions to passively

infused sucrose solutions, an index of the hedonic evaluation of foods and tasteants (Berridge et al. 1989).

Acb-based opioid systems, on the other hand, appear to play a role not only in invigorating instrumental behaviors, but also enhancing the primary rewarding aspects of eating. Systemic morphine increases and naloxone decreases the number of evoked hedonic taste responses to sweet sucrose solutions (Doyle et al. 1993; Parker et al. 1992; Pecina and Berridge 1995; Rideout and Parker 1996) and suppresses aversive reactions to bitter quinine solutions (Clarke and Parker 1995; Parker et al. 1992). It has been argued that these stereotyped, cross-species reactions to pleasant and unpleasant tastes are the manifestation of an internal evaluation of the hedonic quality of a taste stimulus (Grill and Norgren 1978). Meticulous mapping studies employing local μ-OR agonist injections coupled to the analysis of resultant "plumes" of Fos expression have revealed a highly circumscribed area in the medial AcbSh where μ-OR stimulation augments hedonic-like taste reactions (Pecina and Berridge 2005). Nevertheless, a wider zone, extending into the medial core, was found to mediate μ-OR-driven hyperphagia but not the enhancement of hedonic taste reactions. Furthermore, intra-Acb core μ-OR stimulation augments progressive ratio (PR) responding for sucrose (a schedule in which progressively more responses are required for each successive reinforcer) (Zhang et al. 2003) and opioid stimulation of either the Acb core or shell facilitates sucrose-associated Pavlovian-to-Instrumental Transfer (PIT), a reflection of the underlying process by which Pavlovian learning invigorates goal-seeking actions, (Pecina and Berridge 2013). Opioids influence reward-seeking behavior through interactions with the mesolimbic dopamine system (Fields and Margolis 2015; Zheng et al. 2007); however, unlike dopamine manipulations, μ-OR stimulation also facilitates hedonic reactions to taste. In the incentive-salience framework proposed by Berridge and Robinson (Berridge 2009; Berridge and Kringelbach 2015; Robinson and Berridge 2001), dopamine facilitates the "wanting" of rewards, whereas opioids facilitate both "wanting" and "liking", although the "liking" function is highly restricted to the anterior medial AcbSh.

This anatomical heterogeneity across sectors of the Acb agrees with the more general observation that there are gradients of opioid sensitivity spanning the entire striatal complex. Early morphine microinfusion mapping studies revealed an anatomical gradient of opioid-induced feeding, with strong hyperphagia evoked by infusion of D-Ala2, N-Me-Phe4, Gly5-ol]-Enkephalin (DAMGO), a specific μ-OR-subtype agonist, into the Acb and weaker responses in more dorsal, lateral, and posterior infusion sites (Bakshi and Kelley 1993). The most effective site for eliciting feeding was an area spanning the lateral aspects of the Acb core and the medial aspects of the shell. Nevertheless, opioid-driven feeding effects were not restricted to the Acb. Morphine infusions into the ventral aspects of dorsal and medial striatum also elicited feeding, albeit to a lesser degree compared to the Acb. A later microinfusion-mapping study using DAMGO confirmed that the strongest opioid-driven food intake effects were elicited from the Acb core (Zhang and Kelley 2000). Significant effects were also observed with placements in the ventrolateral striatum and in the lateral core and even in dorsal striatum (although opioid effects in this latter site were less consistent across subjects). Accordingly, a recent peptide-microdialysis study confirmed that enkephalins are released into the extracellular space of the anterior medial dorsal striatum during palatable feeding and that DAMGO infusion into this striatal zone elicits palatable feeding (DiFeliceantonio et al. 2012).

To summarize, the studies reviewed above suggest a sensitivity gradient for opioid-modulated behavioral functions spanning the anterior medial AcbSh to the dorsal striatum. This gradient is characterized by several features. First, food ingestion itself can be elicited by μ-OR agonist injections within a wide zone centered on the Acb core/shell boundary, but including lateral aspects of the core, shell, and the ventrolateral striatum. Opioid-driven feeding responses can also be elicited from select areas in dorsal striatum; these effects are more inconsistent and less robust relative to Acb-mediated effects. As injection placements move caudally away from ventromedial and ventrolateral striatum, the magnitude of opioid-driven feeding effects diminishes. Second, there appears to be an anatomical segregation of function with regard to opioid-driven pursuit of food goals and modulation of incentive salience (e.g., enhancement of progressive ratio responding and PIT) vs. opioid modulation of taste reactivity. The former can be elicited from sites both in the Acb core and medial shell, whereas the latter appears to be tightly restricted to the anterior medial shell. To the authors' knowledge, there have been no systematic mapping studies of opioid-modulated operant responding, PIT, or taste reactivity across the entire extent of dorsal striatum; this represents an interesting direction for future research, particularly considering the convergent microinfusion and microdialysis data indicating that there may be an important opioid-sensitive feeding zone in the anterior medial dorsal striatum.

Feeding-modulatory opioid actions in the PFC

Compared to the Acb, far less is known regarding the behavioral mechanisms underlying feeding-modulatory opioid actions in the PFC. Evidence thus far indicates that μ-OR stimulation in ventromedial sectors of frontal cortex induces a robust feeding central motivational state (CMS), although the mechanistic details of this state are not fully understood. μ-OR stimulation in the ventromedial prefrontal cortex (vmPFC), mainly the infralimbic region, engenders feeding both in food-deprived and ad libitum-maintained rats (Mena et al. 2011); the organization of this feeding response consists

of brief feeding bouts and abrupt switching between food-directed responses and responses directed away from food (e.g., "exploratory-like" ambulatory or rearing behaviors). This pattern is essentially the opposite of that engendered by GABA-mediated inactivation of the vmPFC (i.e., longer feeding bouts and less ambulation and rearing) (Baldo et al. 2016; Mena et al. 2011), suggesting that the net behaviorally relevant effect of μ-OR stimulation is to activate or disinhibit cortical output. Presently, the role of μ-ORs in regulating pyramidal neuron activity (and thus cortical output) is not well understood. It is interesting to note that μ-ORs mediate hippocampal pyramidal neuron disinhibition by suppressing local inhibitory interneurons (McQuiston and Saggau 2003; Zieglgansberger et al. 1979). These hippocampal interneurons are similar to μ-OR-bearing interneurons in cortex (Curley and Lewis 2012; Ferezou et al. 2007; Krook-Magnuson et al. 2011; Taki et al. 2000), lending some plausibility to the idea that cortical μ-OR stimulation may have net disinhibitory or activational effects upon cortical output.

In addition to driving feeding itself, μ-OR stimulation in vmPFC also robustly amplifies responding in a sucrose-reinforced progressive ratio (PR) task and promotes "impulsiveness-like" deficits in differential reinforcement of low response rate task (DRL) (Selleck et al. 2015). Together, these effects indicate that cortical μ-OR stimulation increases the motivational value of food and energizes food-seeking repertoires, as well as disrupting inhibitory control over food-seeking. The precise mechanisms underlying these effects are unclear, but a number of possibilities come to mind. For example, because electrophysiological studies have suggested that units in vmPFC encode information regarding food-associated taste characteristics (including taste hedonics) and reward valuation (Jezzini et al. 2013; Parent et al. 2015), the intra-PFC μ-OR-mediated increase in food intake could reflect an enhancement of the hedonic properties of the food. Nevertheless, the μ-OR stimulation-induced pattern of bout initiation coupled with the *shortening* of individual bouts indicates that commerce with the food does not sustain the relatively longer periods of consumption that might be expected with increased gustatory reward (Davis and Smith 1992; Ostlund et al. 2013; Spector et al. 1998). This could be interpreted as enhanced salience of the sucrose incentive in the absence of hedonic taste facilitation ("wanting" in the absence of increased "liking"). In this regard, an important question for future research is whether intra-vmPFC μ-OR stimulation modulates taste reactions to sucrose.

Alternatively, the changes in feeding-bout microstructure described above could reflect opioid-mediated perturbation of underlying response-selection functions of the PFC. In a general sense, medial PFC plays a prominent role in modulating ongoing behavior and inhibiting disadvantageous behavior, to match prevailing (and often changing) contingencies; examples include the regulation of set-shifting (Birrell and Brown 2000; Dalley et al. 2004; Floresco et al. 2008; Ragozzino et al. 1999) and the expression of extinction learning (Eddy et al. 2016; Peters et al. 2008; Quirk et al. 2006; Rhodes and Killcross 2007). With regard to ingestive behaviors, recent findings that inhibition of ventromedial PFC disturbs the temporal distribution of licking bouts in an incentive-contrast paradigm, "misaligning" licking bout durations to high and low concentrations of sucrose (Parent et al. 2015). This finding suggests a PFC-based operation that matches the temporal duration of licking bouts with the reward value of the food. It is interesting to hypothesize that, in a free-feeding context, this "supervisory" operation aligns the temporal duration of consummatory responses with contingencies of taste-reward valuation and the need for periodic environmental reconnaissance, enabling flexible, adaptive switching between the two competing response sets. Such a function would serve to keep food-directed and non-food-directed repertoires in balance, thereby optimizing intake while minimizing risk (Blanchard and Blanchard 1989; Dukas 2002; Krebs et al. 1996; Krebs et al. 1997; Onuki and Makino 2005). This purported switching function, combined with a facilitation of the incentive value of food (as reflected in the abovementioned effects on PR and DRL performance), could produce the observed μ-OR stimulation-induced changes in feeding approach and bout duration. As will be discussed below, it is possible that the modulation of and switching between food-directed vs. non-food-directed activity by PFC-based μ-ORs reflects the recruitment of distinct PFC efferent pathways.

From an anatomical perspective, recent studies have begun to map the effects of intra-tissue infusions of a μ-OR agonist in order to determine whether, as in striatum, there are heterogeneities in opioid sensitivity across different regions of frontal cortex. First, to define the basic effect, the μ-OR agonist, DAMGO, was infused directly into vmPFC. In this initial experiment, injections were placed near the dorsal border of infralimbic cortex, which some sites crossing into the ventral aspect of prelimbic cortex (Mena et al. 2011). These infusions dose dependently enhanced food intake in both food-deprived and ad libitum-maintained rats. A subsequent mapping experiment revealed that DAMGO infusions in the ad libitum condition also enhanced food intake when injections were placed in medial aspects of subgenual orbitofrontal cortex. DAMGO effects were weaker when infusions with infusions sited more dorsally in the medial wall (i.e., anterior cingulate cortex), dorsolaterally in anterior somatosensory cortex, or laterally in orbitofrontal cortex (i.e., lateral subgenual orbital cortex, anterior aspects of insular cortex) (Mena et al. 2011). Hence, a gradient of μ-opioid sensitivity is apparent in the frontal cortex. The strongest feeding-modulatory sites are located in a ventromedial zone comprising parts of medial PFC and orbitofrontal cortex; as infusions move dorsally and laterally from this zone, progressively weaker effects are observed. Presently, it is unknown whether opioid modulation of PR or

DRL can be elicited from frontal territories beyond the infralimbic cortex. This represents an important area for future research.

Motivational effects of telencephalic opioids: a cortico-striato-hypothalamic network model

Consideration of the topographic organization of cortical and striatal gradients of opioid sensitivity suggest possible efferent pathways through which telencephalic opioids modulate appetitive motivation. First, the frontal cortical sites from which the strongest μ-OR-induced feeding responses can be elicited are clustered in a "ventromedial corridor" consisting of sites both in medial and orbitofrontal cortex that innervate opioid-responsive zones in the Acb and dorsal striatum (Heilbronner et al. 2016; Schilman et al. 2008; Thompson and Swanson 2010; Vertes 2004). In particular, the infralimbic area projects strongly to the Acb shell (Heilbronner et al. 2016; Thompson and Swanson 2010), including the anteromedial zone that plays a specialized role in mediating taste hedonics (Pecina and Berridge 1995). Opioid-sensitive sites in frontal cortex have also been shown to project to the hypothalamus, including lateral and perifornical areas of tuberal hypothalamus from which intense feeding responses can be elicited by local infusions of glutamate agonists or neuropeptide Y (Floyd et al. 2001; Gabbott et al. 2005; Reppucci and Petrovich 2016; Vertes 2004). Similarly to the ventromedial PFC, the medial AcbSh projects to feeding-modulatory areas of hypothalamus both directly and indirectly via the ventral pallidum (Groenewegen et al. 1993; Haber et al. 1985; Heimer et al. 1991; Mogenson et al. 1983).

The anatomical relationships described above suggest a circuit for higher-order control of feeding behavior, consisting of telencephalic nodes in ventromedial frontal cortex and medial Acb shell outputting to a dienephalic node in tuberal hypothalamus. The functional relevance of this circuit has been confirmed in studies employing drug microinfusions and the analysis of immediate-early gene expression to "dissect" distinct pathways among those sites. Early studies focused on the functional relationship between the medial AcbSh "feeding hotspot" and the lateral hypothalamus in the control of food intake. Kelley and colleagues performed a series of dual-site microinfusion studies in rats in which the AcbSh and hypothalamus (in a zone spanning lateral and perifornical areas of tuberal hypothalamus; LH-PeF) were jointly targeted with infusion cannulae. Feeding responses were elicited either by AMPA receptor blockade, GABA receptor stimulation, or μ-OR stimulation in the Acb; in the same animal, a GABA agonist or glutamate antagonist was concurrently infused into the LH-PeF (Maldonado-Irizarry et al. 1995; Stratford and Kelley 1999; Will et al. 2003). For each orexigenic manipulation of the Acb, it was found that reducing neural activity in the hypothalamus (via either glutamate blockade or GABA stimulation) eliminated the Acb-mediated hyperphagia, indicating that intact hypothalamic function is necessary for the expression of Acb-driven hyperphagia. This conclusion is further bolstered by recent optogenetic studies showing that silencing the Acb shell increases consumption, stimulating that region decreases consumption and that these effects are mediated through projections of D1-bearing Acb neurons projecting to the hypothalamus (O'Connor et al. 2015; Parent et al. 2015). Further work indicated that either GABA receptor or μ-OR stimulation in the Acb shell provoked expression of the immediate-early gene, Fos, in several hypothalamic regions, including the LH-PeF (Baldo et al. 2004; Stratford and Kelley 1999; Zhang and Kelley 2000). Immunohistochemical co-labeling studies indicated that intra-Acb GABA-ergic or μ-OR manipulations provoke Fos expression in orexigenic neuronal populations including hypocretin/orexin (H/O)-containing cells in the LH-PeF (Baldo et al. 2004; Zheng et al. 2003). It is important to note that, in the abovementioned Fos mapping study, a number of sites in addition to the hypothalamus were activated by intra-Acb DAMGO. These included the ventral tegmental area (VTA) and nucleus of the solitary tract (NTS) (Zhang and Kelley 2000). Accordingly, local GABA-mediated inactivation of the VTA or NTS blocked intra-Acb DAMGO-induced amplification of sweetened-fat intake (Will et al. 2003). It is unknown whether Acb interactions with these mesencephalic and brainstem sites are enacted mainly through direct projections or through a hypothalamic relay. One study has identified a serial relationship among the Acb, to H/O-expressing hypothalamic neurons, to the VTA mediating intra-Acb DAMGO-driven feeding (Zheng et al. 2007). It is certainly possible that both serial and parallel projections are involved; pathway-specific optogenetic or chemogenetic manipulations could shed further light on this issue.

Recent findings have also demonstrated a role for a functional interaction between PFC and hypothalamus in the control of feeding. Infusions of the μ-OR agonist, DAMGO, directly into the vmPFC (infralimbic and ventral prelimbic territories) induced Fos expression in the LH-PeF, including within a group of medially localized H/O-containing cells (Mena et al. 2013). This finding suggests that intra-vmPFC DAMGO activates neurons in this hypothalamic area, possibly via glutamatergic afferents arriving from the vmPFC. Evidence for glutamate involvement in this functional relationship between the PFC and hypothalamus was provided by the finding that hyperphagia induced by intra-vmPFC DAMGO was reversed by intra-LH-PeF infusions of low doses of the glutamate NMDA receptor subtype antagonist, AP-5 (Mena et al. 2013). The LH-PeF subregion targeted in this study is similar to the zone from which strong neuropeptide-Y-induced feeding responses have been reported (Stanley et al. 1993) and also to the area where local inactivation or glutamate receptor blockade reduces hyperphagia

induced by intra-Acb μ-OR stimulation (Maldonado-Irizarry et al. 1995; Stratford and Kelley 1999). Further evidence for a PFC-hypothalamus functional relationship is provided by studies examining the control of Pavlovian-conditioned cues over food consumption. Displaying a stimulus previously paired with hunger-driven hyperphagia causes a subsequent increase in food intake in sated rats. Examination of activity-dependent gene expression during cue-induced overeating revealed activation in PFC and amygdalar inputs to the hypothalamus (as defined by labeling from a retrograde tracer placed in the hypothalamus) (Petrovich et al. 2005). Interestingly, the AcbSh➔hypothalamus projection did not seem to be involved. A lesion study confirmed that the PFC is required for the expression of cue-induced overeating (Petrovich et al. 2007). Hence, the hypothalamus appears to be an output node not only for drug-induced hyperphagia elicited from the Acb or PFC, but also for higher-order computations relevant for the modulation of intake by learned cues.

The vmPFC➔AcbSh projection also modulates feeding, but in the opposite direction. Thus, bicuculline-induced disinhibition in infralimbic cortex limits feeding responses engendered by intra-AcbSh AMPA blockade (Richard and Berridge 2013) and intra-Acb shell neural activation, including that engendered by AMPA receptor stimulation (Stratford et al. 1998), electrical stimulation (Krause et al. 2010), or optogenetic activation (O'Connor et al. 2015) arrests feeding and provokes competing behaviors such as intense motor activity (Ikeda et al. 2003). These results suggest a complex, glutamate-coded functional relationship among the PFC, Acb, and LH-PeF, whereby PFC-driven feeding is mediated by glutamate transmission in the LH-PeF, but negatively modulated by AMPA signaling in the Acb. These results can be interpreted as reflecting the activity of a cortico-striato-hypothalamic circuit, consisting of functionally opposed PFC and AcbSh efferents converging on a hypothalamus-based output node. It has been hypothesized that these putative PFC➔hypothalamus "feeding driver" and PFC➔AcbSh "feeding limiter" pathways counterbalance one another to maintain food-directed activity within adaptive limits (Baldo 2016). It is not yet known, however, to what extent these functional relationships are driven by monosynaptic glutamatergic projections originating from the PFC vs. polysynaptic routes of control; such a determination awaits the application of optogenetic or chemogenetic manipulations to dissect the individual pathways.

To summarize the major tenets of the network model, μ-OR activity in the PFC or Acb appears to drive feeding via an obligatory output node in the PeF-LH, albeit by distinct mechanisms. Glutamatergic PFC projections *stimulate* hypothalamic feeding systems, while the inhibition of GABA-ergic Acb efferents *disinhibits* those systems. Conversely, activation of the Acb via AMPA receptor stimulation (possibly arising from glutamatergic PFC projections) *inhibits* feeding, partly through descending inhibitory control over the hypothalamus, but also through the recruitment of non-food-directed behaviors. The incoherent engagement of these parallel "feeding-driver" and "feeding-limiter" pathways by opioid signaling could result in disorganized, impulsive food-seeking behaviors, such as those engendered by μ-OR stimulation in ventromedial PFC (Mena et al. 2011; Selleck et al. 2015). Figure 1 shows a schematic summarizing this model, along with possible feeding pathologies arising from different types of network dysfunction.

Finally, it is important to consider how additional opioid-responsive telencephalic sites can be incorporated into this cortico-striato-hypothalamic network hypothesis. Based upon hodological considerations and functional evidence, the amygdala is a prime candidate. This structure sends robust projections to Acb, PFC, and hypothalamus and, hence, is positioned to modulate PFC and Acb directly as well as to enact parallel regulation of Acb- and PFC-innervated zones of hypothalamus (Reppucci and Petrovich 2016). Sites within the amygdaloid complex support μ-OR-induced effects on feeding and food motivation; for example, μ-OR stimulation in the central amygdaloid region (CeA) causes hyperphagia (Kim et al. 2004) and strongly amplifies the activational effects of Pavlovian cues over food approach and other instrumental actions (Mahler and Berridge 2012). Furthermore, intra-CeA μ-OR stimulation-induced hyperphagia appears to interact in a complex, reciprocal way with opioid function in the Acb, as evidenced by the finding that opioid receptor blockade in amygdalar sites blocks opioid-driven feeding elicited from the Acb, and vice-versa (Kim et al. 2004). Along with the CeA, the basolateral area of the amygdala (BLA) plays an obligatory role in the amplification of palatable feeding induced by intra-Acb μ-OR stimulation (Parker et al. 2015; Will et al. 2004). Thus, pharmacological inactivation of either BLA or CeA eliminated the increase in sweetened-fat intake induced by intra-Acb infusions of DAMGO, without suppressing baseline levels of intake (Will et al. 2004). Finally, interactions between the PFC and amygdala may also participate in the regulation of food motivation. For example, a recent study demonstrated that optogenetic activation of PFC projections to the basolateral amygdala enhances feeding (Land et al. 2014). Finally, Pavlovian cue-induced overeating recruits both BLA➔ hypothalamus and PFC➔hypothalamus pathways (Petrovich et al. 2005), suggesting a route through which BLA and PFC processing can converge on a common hypothalamic output node.

Together, the studies discussed above suggest multiple pathways through which amygdalar processing can integrate with the feeding "driver" and "limiter" circuits described above, including but not limited to (1) parallel convergence onto a common hypothalamic effector node; (2) regulation of opioid responses at the level of the Acb and/or PFC, either via

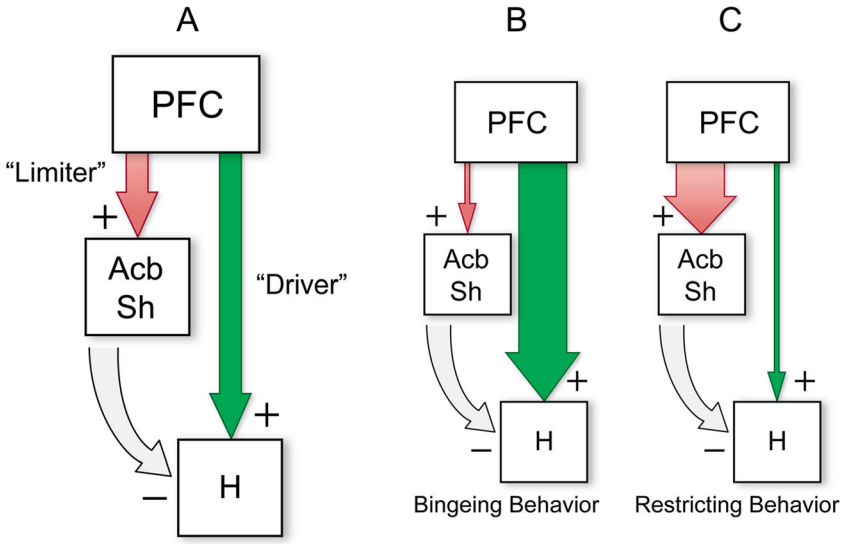

Fig. 1 Schematic depicting the proposed cortico-striato-hypothalamic feeding-modulatory network, along with possible feeding pathologies arising from different types of network dysfunction. Panel (**a**) shows the underlying organization of prefrontal cortical (*PFC*) projections to the nucleus accumbens shell (*AcbSh*) and feeding circuits in the hypothalamus (*H*). Excitatory PFC➔AcbSh glutamatergic projections (indicated by "+" signs) acting through AMPA-type receptors act as a "limiter circuit," restraining bouts of consummatory activity. PFC➔H projections elicit feeding, acting as a "driver circuit" that can be engaged by frontal activation, including that associated with local opioid release. The AcbSh, in turn, sends an inhibitory GABA-ergic projection ("–" sign) to the H. Panel (**b**) displays possible network alterations that would be predicted to cause bingeing behavior. These alterations include increased activity in the "driver" pathway, and/or diminished function of the "limiter" pathway. Influence of these pathways over their respective terminal fields is depicted by the width of the *arrows*. The opposite changes (i.e., overactive "limiter" and/or underactive "driver" pathways) would be expected to result in abnormal restriction of feeding behavior, as depicted in panel (**c**)

monosynaptic projections or multi-step pathways through intermediaries such as orexin neurons or VTA dopamine neurons; (3) descending control of amygdala function by the PFC. Teasing these network interactions apart using contemporary optogenetic and chemogenetic approaches represents an exciting direction for future research.

Clinical implications

Aberrant activity prefrontal cortex and nucleus accumbens contribute to deficits in impulse control in a number of psychiatric disorders characterized by excessive appetitive motivation, including disorders of food intake such as binge eating disorder (BED) (Dong et al. 2016; Karhunen et al. 2000; Schienle et al. 2009; Seo et al. 2013; Uher et al. 2004). Several studies have suggested that these deficits arise from supernormal opioid transmission (Blasio et al. 2014; Gorelick et al. 2008; Love et al. 2009; Mitchell et al. 2012; Morganstern et al. 2012; Selleck et al. 2015; Zubieta et al. 1996), and these studies are supported by clinical findings that opioid antagonists have at least some degree of efficacy across several disorders characterized by loss of control over goal-seeking behavior (Cambridge et al. 2013; Kim et al. 2001; Mitchell et al. 2007; Volpicelli et al. 1992). However, there is variability in the reports of opiate antagonist clinical efficacy (McElroy et al. 2013; Ziauddeen et al. 2013), suggesting that further studies are needed to more thoroughly delineate opioid actions within the brain and how normal brain function is influenced by opioid antagonists. The network model outlined in this article suggests that using poly-drug approaches may enhance the efficacy of opiate antagonists in treating disorders such as BED, as well as other conditions such as alcohol dependence, for which opioid antagonists represent one of the only FDA-approved treatments (Pettinati et al. 2006; Soyka and Rosner 2008; Volpicelli 1995). Because nodes in the network have been specified neurochemically (i.e., as described previously, μ-ORs in the PFC and Acb, as well as other sites including the CeA; orexin systems in the LH-PeF, AMPA receptors in the Acb shell), it is possible to identify combinations of treatments that together could have an additive or super-additive effect on network function. Specifically, co-administering opioid antagonists with treatments that target downstream nodes of the network (for example, orexin systems in the hypothalamus) may prove more effective than opioid antagonists alone. It has been suggested, for example, that orexin manipulations could represent an effective treatment for conditions such as drug addiction or relapse (Plaza-Zabala et al. 2012; Zhou et al. 2011) (Picetti et al. 2013). More generally, future studies aimed at enhancing our understanding of the neural networks through which opioids exert reward-modulatory effects will be crucial for developing better treatments for a wide variety of disorders, including drug dependence and withdrawal, psychiatric conditions that were the focus of Dr. Athina Markou's career.

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