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Principles of motivation revealed by the diverse functions of neuropharmacological and neuroanatomical substrates underlying feeding behavior

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Abstract

Circuits that participate in specific subcomponents of feeding (e.g., gustatory perception, peripheral feedback relevant to satiety and energy balance, reward coding, etc.) are found at all levels of the neural axis. Further complexity is conferred by the wide variety of feeding-modulatory neurotransmitters and neuropeptides that act within these circuits. An ongoing challenge has been to refine the understanding of the functional specificity of these neurotransmitters and circuits, and there have been exciting advances in recent years. We focus here on foundational work of Dr. Ann Kelley that identified distinguishable actions of striatal opioid peptide modulation and dopamine transmission in subcomponents of reward processing. We also discuss her work in overlaying these neuropharmacological effects upon anatomical pathways that link the telencephalon (cortex and basal ganglia) with feeding-control circuits in the hypothalamus. Using these seminal contributions as a starting point, we will discuss new findings that expand our understanding of (1) the specific, differentiable motivational processes that are governed by central dopamine and opioid transmission, (2) the manner in which other striatal neuromodulators, specifically acetylcholine, endocannabinoids and adenosine, modulate these motivational processes (including via interactions with opioid systems), and (3) the organization of the cortical-subcortical network that subserves opioid-driven feeding. The findings discussed here strengthen the view that incentive-motivational properties of food are coded by substrates and neural circuits that are distinguishable from those that mediate the acute hedonic experience of food reward. Striatal opioid transmission modulates reward processing by engaging frontotemporal circuits, possibly via a hypothalamic-thalamic axis, that ultimately impinges upon

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hypothalamic modules dedicated to autonomic function and motor pattern control. We will conclude by discussing implications for understanding disorders of “non-homeostatic” feeding.

Keywords

Feeding; Reward; Motivation; Dopamine; Opioid; Acetylcholine; Nucleus accumbens; Amygdala; Hypothalamus

1. Authors’note

In the spirit of this Special Issue, we have prepared a review discussing the literature on telencephalic circuits and neuromodulator systems that subserve food reward, emphasizing Dr. Ann Kelley’s scientific contributions in this area. We also include recent work from our own labs that extends her research legacy. We do, however, confess to having an additional agenda. As former trainees, we hope in some small way to convey the “essence of Ann”—her infectious enthusiasm, selfless mentoring, bold, rigorous scientific work, and remarkable integrative thinking that was grounded in deep knowledge of physiological psychology and neuroanatomy. In this article, we borrow a favorite teaching device of Ann’s: the use of “classic” quotes from pioneers of the field, including individuals that had influenced her thought or inspired her scientific passion, to illustrate concepts upon which contemporary work is built. We have scattered several such quotes throughout this article, culled from old reprints and books and underlined by her own hand. And, we include a quote from Ann herself.

In crediting Ann’s enormous and lasting contributions to the field we honor her enormous and lasting impact upon us. We will always miss her deeply.

2. Aligning feeding-related motivational processes with discrete neuropharmacological substrates

2.1. Theoretical considerations

> “… In fact there is no one-to-one relation between a certain unique process-an instinct or a motivational state-and a single particular type of action. For example, eating on the part of a hungry animal depends not only on food-related motivation, but also on how familiar the animal is with the situation, what other opportunities or dangers lie therein, what effort is required to reach and ingest the food, and so on.” —D. Bindra (1979)

Feeding reflects the integration of a remarkable variety of behavioral processes. Consider a hungry rat that happens upon a store of familiar, palatable food. The rat approaches the food, flexibly adapting its goal-directed behavior as needed—overcoming physical obstacles, checking for predators—and then, once in contact with the goal, commences the relatively simple, and somewhat fixed motor repertoire of chewing, swallowing, etc. This consumatory repertoire is modulated by the sensory characteristics of the goal object (noxious-tasting food would be rejected, while palatable food might encourage extended contact), and can be flexibly and rapidly interrupted by an emergency (a hawk appears). According to classic incentive-motivation theory, this set of behavioral events is coordinated by a central motivational state (CMS), which derives from internal “organismic states”—in this case, energy deficit—combined with the incentive properties of the food (see Konorski, 1967; Bindra, 1974;Toates, 1986).Through network interactions, the CMS conjointly recruits effector systems for variegated “response components” that, together, enable the entire behavioral sequence (including commerce with the goal object). However, these response

components can be rapidly supplanted by other repertoires (for example, escape or defensive behavior) should the need arise. Hence, in principle, the CMS and its response components can be seen as the emergent property of coordinated action among functionally specialized subsystems; contemporary neuroscience states that this coordination reflects *network interactions among functionally distinct processing modules*. For example, it is widely appreciated that neural systems specialized to detect and respond to metabolic energy deficits are anatomically distinct from the networks that represent the learned incentive properties of food (for a review, see Berthoud, 2011). Under normal conditions these modules interact seamlessly to generate the feeding CMS. Importantly, this coordination permits feedback regulation from multiple sources and levels of the neural axis. The possibility arises, however, that in pathological conditions (e.g., eating disorders, addiction) these modules are functionally "pulled apart" such that the CMS emerges under maladaptive contingencies, or fails to emerge under adaptive ones. Hence, understanding the organization of the diverse sub-systems that together generate a particular CMS may be important for understanding psychopathology.

An important goal for neuroscientists has been to identify the relevant dimensions across which these distinct sub-systems are organized. For example, is the proper level of analysis anatomical (i.e., different brain regions mediate different processes), or neuropharmacological (i.e., different neuromodulators in the same region mediate dissociable functions)? As will be reviewed in this article, the answer is, "both." As a case study, we will consider the question of whether the systems that compute the incentive salience of reward-relevant stimuli, energize approach behaviors toward goals, and govern the hedonic experience that attends commerce with the goal object, can be functionally pulled apart. Indeed, some discussions of reward have combined processes of priming, reinforcement, and hedonism or "euphoria" (Wise, 1978; Kornetsky and Esposito, 1979). Nevertheless, considerable evidence has accrued to suggest that these reward sub-processes are mediated by modules that are dissociable both in terms of their anatomical organization and their neurochemical coding—although this dissection has been difficult to achieve and still engenders debate. Much insight derives from the study of feeding behavior, and, as described below, Dr. Kelley's work contributed fundamentally to this area.

2.2. Evidence that opioids and dopamine modulate dissociable aspects of food motivation

> "… of course, only humans can actually say whether something is pleasant. Much has been written, and no doubt even more will be written, on the vexed question of whether animals have such conscious sensations. I can contribute little to this debate. All I would like to say is that animals behave as if they experience pleasure in many situations that would be described as pleasurable by humans. Therefore, 'hedonism' should be seen as a useful heuristic and convenient shorthand"
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> "Even undeprived animals will eat substantial amounts if they are confronted with highly palatable foods… So, certain incentive properties are sufficient to instigate motivation in the absence of anything resembling a deprivation-induced drive. However, deprivation can powerfully enhance the ability of some incentives to instigate motivation." F. Toates (1986)

Anyone who has eaten a large piece of chocolate cake after completing a full meal can appreciate the prodigious motivational pull, beyond any conceivable metabolic need, exerted by palatable food. Introspection reveals that eating the cake makes us feel good, and furthermore, the "good feeling" associated with viewing the cake on the dessert tray seems different in nature from that associated with its actual consumption. Are these two processes mediated by functionally dissociable yet interacting subsystems, or are they manifestations of different facets of a unitary "reward substrate?" The discovery of electrical brain

stimulation-reward (BSR) prompted the idea that specialized reward systems are present in the brain (Olds et al., 1971; Olds and Milner, 1954), and the finding that chemical manipulation of the dopamine system powerfully modulates BSR in a manner dissociable from motor performance contributed to the idea that dopamine mediates the experience of primary reward, including hedonia and euphoria (Kornetsky and Esposito, 1979; Fouriezos and Wise, 1976; Liebman and Butcher, 1973; Lippa et al., 1973). Nevertheless, numerous studies have shown that dopamine antagonism or dopamine-depleting brain lesions drastically reduce food-related motivational arousal, approach, and effortful instrumental responding for food or food-associated incentive cues, while sparing actual feeding (for example, Ervin et al., 1977; Koob et al., 1978; Baldo et al., 2002; Cousins et al., 1994; Salamone et al., 1994). To elaborate on just one early example from Ann Kelley's work, Bakshi and Kelley showed that intra-nucleus accumbens (Acb) infusions of the dopamine receptor antagonist, haloperidol, significantly prolonged feeding bouts and increased food intake, while elevating latency to approach the food and diminishing exploratory-like motor activation seen in the context of feeding sessions; although some degree of motor impairment can arise from haloperidol administration, this does not explain these results because the number of feeding bouts that were initiated (reflecting the ability to locomote toward the goal object) were not affected by haloperidol and the total amount of food consumed was *increased* with haloperidol (Bakshi and Kelley, 1991). These and other conceptually related findings suggested that, at least in the case of feeding behavior, the functional modules governing consumatory or "transactional" response components (Bindra, 1974), or, perhaps, which generate hedonic reward during feeding, were functionally dissociable from those governing "instrumental" response components, including those generating approach behaviors.

Cador and colleagues conducted a series of elegant studies that further elucidate the lines along which the feeding CMS, and its associated response components, can be "pulled apart." Behavioral tests assaying food anticipation, consumption, and motivation (in the sense of response-invigoration), were carried out in food-sated and food-restricted rats offered two kinds of food differing in their palatability level (Barbano and Cador, 2005). The *consummatory* component was measured by the latency to eat and the amount of food eaten in a familiar environment. The *motivational* component was measured in two distinct paradigms: the runway paradigm in which rats had to run an alley to get access to food, and a progressive ratio task in which rats had to increase by 3 the number of lever presses to receive each successive pellet. The *anticipatory* component was measured through the development of conditioned locomotor activity in expectation of food delivery, which occurred a fixed time after rats being placed into activity cages.

Using these simple paradigms, it was possible to reveal interactions between palatability and homeostatic states. Regarding the consummatory aspect of feeding behavior, food restricted animals ate more and with a shorter latency than food sated animals. Animals given access to palatable food also ate more and with shorter latency than animals given access to less palatable food. For instance, sated rats can eat as much as food deprived animals, provided they are offered palatable food. Therefore, food restriction and food palatability can interact to control food intake, demonstrating that the perception of palatability is influenced by food-restriction but also that satiety can be overcome by food palatability. This agrees well with the basic structure of classic incentive-motivation theory, as well as the concept of "allesthesia" (Berridge, 1991; Cabanac, 1988; Cabanac and Lafrance, 1990). Similar interactions were found in the runway and the progressive ratio paradigms: food restricted animals ran the fastest and had the highest break-point. Nevertheless, food-sated animals seeking palatable food ran almost as fast as and had a similar break-point as food restricted animals, indicating that an enhancement of palatability level can be translated into a higher level of motivation for both food-sated and food-restricted rats (Hodos, 1961).

Regarding anticipatory activity (which belongs to the preparatory phase of feeding), a very different picture emerged. Food-restricted animals developed a conditioned anticipatory increase in locomotor activity across the training session, which was at the highest level during the last 15 min of the 30 min interval before the food presentation. Food palatability did not appear to differentially influence the development of anticipatory activity in restricted animals. Surprisingly, food-sated animals did not present any anticipatory activity to the presentation of palatable food despite the fact that these animals demonstrated avid consummatory behavior once the palatable food was presented, and exhibited levels of motivation quite similar to restricted animals in the runway and progressive ratio paradigms. This indicates that conditioned anticipatory activity is not controlled by the hedonic properties of the food, but rather by homeostatic state. This hypothesis has already been explored, and a double dissociation of two motivational mechanisms mediating food reward in food-deprived and sated animals has been shown (Bechara et al., 1992; Bechara and van der Kooy, 1992; Nader et al., 1997).

Although the neuropharmacological substrates of such dissociations remain unclear, evidence is accruing to support the following broad generalization: dopamine is more closely connected to generalized activational properties of a food CMS, which energizes the "vigor" of responding on effortful tasks, and opioids are connected to the hedonic state that attends commerce with palatable food. Evidence supporting this hypothesis, including distinctions between "wanting" (processes related to the salience of the incentive and effort expended in seeking the goal) and "liking" (unconditioned responses indicating hedonic valuation of the food) (see Berridge, 2009) is discussed below.

2.2.1. Dissociable roles of dopamine and opioids in the hedonic perception of food—One of the best demonstrations that dopamine is not involved in hedonic taste evaluation comes from studies in which rats with severe central dopamine depletion or rats injected with neuroleptics are still capable of exhibiting hedonic orofacial reactions in response to a sucrose solution (Treit and Berridge, 1990; Berridge and Robinson, 1998). Importantly, when a solution of saccharin/polycose was associated with an injection of lithium chloride, rats with mesolimbic dopamine depletion were able to switch their prior appetitive reactions into aversive ones (Berridge and Robinson, 1998). Moreover, genetically modified dopamine-deficient mice still preferred sucrose or saccharin to water (Cannon and Palmiter, 2003). Conversely, genetically engineered hyperdopaminergic mice did not show any difference in hedonic taste reactions to sucrose compared to wild-type mice (Peciña et al., 2003). D1 and D2 mutant mice did not show any modification on basal food intake compared to wild type mice when maintained on a palatable, fat-enriched or sucrose diet (Cannon et al., 2004; El-Ghundi et al., 2003). Together, these findings suggest that interfering with brain dopamine neurotransmission seems to be ineffective at "removing" the primary hedonic properties of food.

On the other hand, there is considerable evidence for opioid involvement in the amplification of hedonic perception. Systemic administration of opioid agonists increases, and of antagonists decreases, food intake in sated rats (Glass et al., 1999; Bodnar, 2004; Levine and Billington, 2004). Moreover, opioid antagonists, such as naloxone or naltrexone, preferentially decrease the intake of highly palatable, sweet, or fatty foods (Giraudo et al., 1993; Agmo et al., 1995; Cleary et al., 1996; Yeomans and Gray, 1997, 2002; Glass et al., 1999; Kelley et al., 2002; Barbano and Cador, 2005) while opioid agonists, such as morphine or DAMGO, preferentially increase it (Bakshi and Kelley, 1993; Doyle et al., 1993; Zhang and Kelley, 1997). As well, Barbano and Cador (2005) found that the amount of food eaten in sated or restricted rats is not modified after systemic injection of a dopaminergic antagonist (alpha-flupentixol), whatever the degree of palatability of the food and whatever the doses of the neuroleptic used (though these doses were devoid of motor-

debilitating effects). Indeed, an absence of dopamine antagonist effects was found for different kinds of food with different level of palatability. In one experiment (Barbano and Cador, 2005), habitual food was compared with highly palatable chocolate cereals, and in another (Barbano et al., 2009), manufactured pellets with different palatability levels were compared (test diet 'AI pellets' (low palatability)) and test diet 'P pellets' (high palatability), as demonstrated in a choice procedure. Using exactly the same tests, administration of the opioid antagonist naloxone decreased food intake, but only in sated rats, and this decrease was much greater in rats presented with palatable compared to normal food. Food restricted rats were almost insensitive to the effects of alpha-flupenthixol (a dopamine receptor antagonist). This suggests that blocking opioid receptors impacts the influence that palatability has on the amount of food intake.

Accordingly, it has been found that hedonic reactions elicited in rats by the administration of a bittersweet solution were higher after a systemic injection of morphine when compared with saline (Doyle et al., 1993). The same pattern of results has been observed in humans: naltrexone administration decreases the perceived pleasantness of food without modifications of the rated appetite (Yeomans and Gray, 1997, 2002). Indeed, the hedonic preference for sucrose or fat was respectively increased and decreased after the administration of butorphanol (an opioid agonist) and naloxone. Nonetheless, the subjects were still able to discriminate between a more or a less concentrated solution, indicating that the intrinsic ability to perceive taste intensities was functional in these subjects (Drewnowski et al., 1992).

2.2.2. Dissociable roles of dopamine and opioids in the motivational properties of food—Even if central dopamine seems not to be involved in food-palatability evaluation, it appears to be deeply involved in other aspects of feeding behavior (see below; Kelley et al., 2005a; Kelley et al., 2002; Baldo et al., 2002; Kelley, 2004; Salamone and Correa, 2002). Many reports in the literature show that interfering with dopamine transmission decreases food-reinforced operant responding (Wise, 1978; El-Ghundi et al., 2003, Cannon et al., 2004). Nevertheless, Barbano and Cador did not find any effect of alpha-flupenthixol administration in either sated or restricted rats using a straight-alley runway paradigm (Barbano and Cador, 2005) (although there was some suppression seen with this treatment in the progressive ratio paradigm). These data suggest that dopamine may be involved in translating a feeding "drive" into adaptive behaviors to obtain food, and that this computation is very sensitive to the cost of the work required. Accordingly, neuroleptic treated rats or rats bearing nucleus accumbens dopamine depletion show impaired performance in operant tasks to obtain food but are still capable of eating when food is available without constraints (Salamone et al., 1994). This is in line with the hypothesis proposed by Salamone and colleagues that dopamine is more specifically implicated in the evaluation of the cost/benefit of performing an action aimed to gain access to relevant stimuli (for a review, see Salamone and Correa, 2002).

If opioid agonists enhance and antagonists decrease the perceived palatability of food, we could predict a modification in the motivation to seek food after an experimental modification of the opioid system. As a matter of fact, Kelley and colleagues (Zhang et al., 2003) proposed that an opioid-mediated enhancement of food hedonic properties could be translated into a higher level of motivation to obtain that food (assayed in a progressive ratio paradigm). Furthermore, mice lacking β-endorphin, enkephalin, or both showed a decreased level of motivation to obtain food when sated but not when food deprived (Hayward et al., 2002). Accordingly, it was shown that sated rats also decreased their running performance for palatable food when injected with naloxone, while food-restricted animals were not sensitive to this drug in a runway paradigm (Barbano and Cador, 2005). The different results observed in sated versus restricted animals are highly relevant, inasmuch as palatability is

the primary controller of feeding in sated rats. Restricted animals will eat more, putatively in response to metabolic needs and therefore, their feeding behavior will be less affected by the administration of opioid antagonists (Hayward et al., 2002; Barbano and Cador, 2005). When animals were working on a progressive schedule of reinforcement to obtain a palatable saccharin solution without any caloric content (thus, working only for the pleasurable taste), naloxone decreased the total lever presses in both sated and restricted animals when compared with water. All these results point to an opioid regulation of food-motivated behaviors, through which food palatability "feeds into" distinct processing modules for response invigoration.

2.2.3. Dissociable roles of dopamine and opioids in anticipatory hyperactivity engendered by food expectation—Much of the evidence cited above, considered in conjunction with the very influential work of Schultz and colleagues, indicates that dopamine seems to signal the preparatory stages in order to obtain food (especially when they are preceded by cues) than to modulate the consummatory aspects of feeding behavior (Hollerman and Schultz, 1998; Schultz, 2002). In this framework, to interfere with dopaminergic neurotransmission should impair anticipatory actions. An interesting feature, very relevant to feeding behavior, is that dopamine depletion or antagonist administration was able to decrease food anticipatory behavior only when the presented food was palatable (Barbano and Cador, 2005; Blackburn et al., 1987, 1989; McCullough and Salamone, 1992; Weingarten and Martin, 1989). When animals were presented with normal chow (their "habitual" food), the interference with dopaminergic neurotransmission had no consequences on food anticipation (Barbano and Cador, 2005; Jones and Robbins, 1992; Mistlberger and Mumby, 1992). It is worth noting that in these same animals, after food presentation, the amount of food consumed was not modified by neuroleptic administration when compared with controls. In this framework, dopamine seems to be involved in the anticipation of highly relevant stimuli (such as palatable food) but not in its consumption. Regarding opioids, naloxone failed to decrease food anticipatory activity (Barbano and Cador, 2005), indicating again that the opioid system rather is involved in the coding of food palatability and does not participate in the preparatory aspect of feeding behavior.

2.2.4. Summary—Together, these findings provide important insights into the manner in which distinguishable motivation constructs map onto distinct, neurochemically coded brain substrates. First, it would appear that generalized hyperactivity associated with food anticipation represents a distinct type of response component that appears to be dopamine- but not opioid-mediated, and furthermore, that the dopaminergic mediation of this response component is dependent upon the nature of the food's expected stimulus properties and/or incentive value. That is, dopamine antagonism attenuates anticipatory activity with regard to palatable, but not standard, food. Note that dissociations between dopamine and opioid systems have also been reported for the establishment of flavor preferences (Touzani et al., 2010). Second, the above-mentioned findings support the idea that sensory inputs closely intertwined with "transactional" response components (behaviors that occur during actual commerce with the food), instantiate an affective state—hedonic in nature, if the food is palatable—which is closely connected to opioid but not dopamine transmission. The hedonic evaluation of food and the production of these consummatory acts are both highly resistant to dopamine-blocking manipulations, suggesting significant independence of both processes from dopamine transmission. Nevertheless, dopamine may be important for *learning* about certain types of hedonic evaluations; for example, flavor preferences associated with the post-ingestive effects of glucose (Touzani et al., 2008). Finally, it appears that opioid-modulated hedonic amplification feeds into a dopamine-dependent system that energizes subsequent goal-seeking behaviors directed at the palatable food; dopamine transmission is particularly important when the instrumental response-

components are effortful. The question then arises as to the nature and location of the brain circuits within which these dissociable opioid and dopamine-mediated processes act, which will be discussed below with particular emphasis upon opioid-mediated amplification of palatability-driven feeding, which was a major focus of Dr. Kelley's career.

3. Cortico-striatal-hypothalamic circuits that subserve the opioid-mediated amplification of food reward

> "Locomotor and oral motor responses are of special interest [in this article] because they are fundamental components of food-seeking and ingestive responses, vocalization, escape from predators and other behaviors essential for adaptation and survival. Limbic structures appear to have access to these pattern generators suggesting that the limbic system may have a direct role in the initiation of motor responses." —Mogenson, Jones, and Kim (1980)

> "The striatum, the main entrance portal for neural inputs to the basal ganglia, receives its most voluminous afferents from the entire expanse of the cerebral cortex… the afferents from the cerebral cortex are distributed in the striatum in an intricate stereometric pattern that by and large preserves the cytoarchitectural subdivison of the cortical mantle…" —WHJ Nauta (1989)

One of the important principles informing Ann Kelley's work was the idea that functional specialization of striatal sub-regions is determined, in part, by the type of information arriving via cortical afferents (Kelley, 2004). This view represents the synthesis of several groundbreaking insights in neuroanatomy; namely, the characterization of the basic cortico-striato-pallidal wiring diagram of the basal ganglia (for a review of early studies, see Nauta and Domesick, 1984); the insight that the nucleus accumbens, olfactory tubercle, and ventral pallidum were part of this wiring scheme (Heimer and Wilson, 1975; de Olmos and Heimer, 1999), and the development of models emphasizing functionally specialized, parallel circuits through the striatum (Alexander and Crutcher, 1990; Alexander et al., 1990). Within this general context, the observation that cortical afferents to the ventral striatum derived from older cortical areas associated with emotional processing and the classic "limbic brain," i.e., amygdala and hippocampus (Graybiel, 1976; Kelley et al., 1982) contibuted to the profoundly influential idea of the accumbens as a "limbic-motor interface" responsible for connecting emotional states with the motor effectors that generate goal-seeking behavior (Mogenson et al., 1980). Another crucial insight was that the nucleus accumbens can be divided into at least two sub-territories, the core and shell, based upon (mainly topographic) differences in the origins of cortical and thalamic afferents and a categorical difference in efferent projections (the shell sends direct projections to the lateral hypothalamus while the core does not) (Heimer et al., 1991; Brog et al., 1993), and the differential intra-accumbens distribution of a wide array of neurochemical markers (substance P, calbindin, orexin/hypocretin and noradrenergic nerve terminals, to name just a few) (Baldo et al., 2003; Berridge et al., 1997; Delfs et al., 1998; Jongen-Rêlo et al., 1994).

In agreement with this model of a "limbic-motor interface" with outputs to feeding effectors, stimulation of intra-accumbens mu-opioid receptors was found to elicit, and mu-opioid receptor blockade to suppress, food intake (Mucha and Iversen, 1986; Majeed et al., 1986; Bakshi and Kelley, 1993; Kelley et al., 1996; Bodnar et al., 1995; MacDonald et al., 2003). Opioid agonist-induced feeding-stimulatory effects were stronger and more consistent with intra-Acb infusions compared to infusions into the dorsal striatum (Bakshi and Kelley, 1993; Zhang and Kelley, 2003), although, very recently, a highly sensitive "hot spot" for opioid-stimulated feeding was identified in the anterior dorsal striatum (DiFeliceantonio and Berridge, 2012). Interestingly, the distribution of opioid-sensitive sites within the accumbens are distributed throughout the core and shell (Zhang and Kelley, 2003), in contrast to the

feeding-stimulatory effects of AMPA blockade or GABA receptor stimulation, which are strictly limited to anterior parts of the shell (Kelley and Swanson, 1997; Stratford and Kelley, 1997). This difference has been hypothesized to reflect the fact that ventral striatal opioid transmission, by modulating glutamate-coded, affect-relevant inputs that target striatal regions both within and beyond the shell, engage telencepalic networks (the "frontotem-poral system," Swanson and Petrovich, 1998) that regulate reward processing in a broad sense, and ultimately "feed into" feeding effector systems (Kelley, 2004; Baldo and Kelley, 2007). In contrast, feeding engendered by GABA or glutamate manipulations of the shell results from a more direct functional interaction with the hypothalamus, reflecting the disinhibition of feeding-specific control elements therein. A more extensive review of this hypothesis is provided in Kelley et al., 2005b, and Baldo and Kelley (2007).

Concordant with the systemic studies of opioid antagonist effects discussed above, behavioral analyses have revealed that effects of both opioid stimulation and blockade within the nucleus accumbens exhibit some degree of preferential sensitivity for palatable foods. For example, intra-accumbens infusions of opioid antagonists suppressed sucrose drinking at lower doses than those required to attenuate chow intake in hungry rats (Kelley et al., 1996; Ward et al., 2006), while intra-accumbens infusions of mu-selective agonists potently augment the intake of palatable foods, fat-enriched test diets, or liquid tastants (even those with no caloric content, such as sapid saline solutions) (Zhang et al., 1998; Zhang and Kelley, 2002). A recent study demonstrated that in rats presented with a choice of two palatable flavored pellets of identical macronutrient composition, intra-Acb mu-opioid stimulation selectively augmented intake of the option that was already preferred at baseline, although opioid stimulation amplified intake of each pellet when presented separately (Woolley et al., 2006). The emerging view is that intra-accumbens mu-opioid transmission "amplifies" the reward valuation of foods or flavors for which there is an intrinsic preference, regardless of macronutrient composition. Studies of taste reactivity are in general agreement with this hypothesis; it has been shown that hedonic taste reactions elicited by palatable sucrose solutions are augmented by mu-opioid stimulation, at least within a circumscribed zone of the medial accumbens shell (Peciña and Berridge, 2005). These studies are reviewed elsewhere in this Special Issue.

It seems reasonable to posit that this "reward computation" to which intra-accumbens opioid systems have access is aided by incoming glutamate afferents that convey relevant information about affective state. A prime candidate for the source of this information is the amygdala. A series of studies by Kelley and colleagues revealed a unique role for the basolateral amygdala in specifically mediating the opioid-induced amplification of palatability-driven feeding of fat- and sugar-enriched foods, as opposed to standard foods eaten when hungry. This dissociation between palatabilityvs. hunger-driven feeding accords well with the findings of Cador and colleagues discussed above. Temporary inactivation of the BLA completely abolishes the increased intake in high-fat diet produced following intra-Acb DAMGO administration, yet leaves baseline intake intact (Will et al., 2004; Will et al., 2009). This same treatment has no influence on increased high-fat intake following 24 h food deprivation (Baldo et al., 2005; Will et al., 2009). Interestingly, inactivation of the CeA prevents opioid- or GABA-driven palatable feeding elicited from the nucleus accubmens as well as hunger-induced chow intake (Will et al., 2009). This pattern of results fits well with the known connectivity of the BLA and CeA. While both regions share similar inputs from gustatory and prefrontal regions and provide direct input to hypothalamic regions, only the BLA has direct input to the ventral striatal (accumbens) region, suggesting a preferential role of the BLA in reward-driven feeding (Kelley et al., 1982).

As described earlier, the behavior of feeding can be conceptualized in terms of two distinct phases, the appetitive and the consummatory. In experiments investigating the role of the

BLA in mediating high-fat feeding driven by striatal opioid activation, a very interesting observation was made. While consumption of the high-fat diet was blocked by temporary inactivation of the BLA, approach behavior toward the diet (as measured by number of entries into the food hopper) continued for the remainder of the feeding session. This dissociation of feeding behaviors (consumption vs. approach) by BLA inactivation was shown to follow this exact pattern of sustained approach behavior in a subsequent experiment in which rats were treated with intra-Acb DAMGO but given limited (8g) access to the high-fat diet. While sustained approach behavior to an emptied food hopper may be understandable and expected, the sustained approach to a half-full hopper of high-fat diet with no consumption is harder to explain. Regardless, the pattern of results suggests that activation of the BLA is necessary for the phase of consumption, but that the expression of the approach phase of feeding behavior is BLA-independent. Again, this hypothesis is consistent with the idea that the BLA supplies the ventral striatum with information regarding the positive affective valence of palatable feeding, which is then amplified by opioid transmission in the nucleus accumbens.

What is the nature of the broader network in which the BLA-Acb circuit is embedded? Studies of this network employing targeted microinfusions and analysis of immediate-early gene expression have revealed crucial contributions of sites ranging across the entire neural axis. For example, intra-Acb administration of DAMGO to rats given limited access to a high-fat diet activates Fos expression in a variety of regions throughout hypothalamic, limbic, and brainstem areas (Zhang and Kelley, 2000). The activation of this distributed network, including the lateral and dorsomedial hypothalamus, ventral tegmental area, nucleus of the solitary tract, and the basolateral and central nucleus of the amygdala (Will et al., 2003; 2004), were all shown to be critical to observe the well characterized increased high-fat intake that follows opioid activation of the Acb. Thus, temporarily inactivating any one of these regions prior to administration of intra-Acb DAMGO completely blocked the exaggerated high-fat consumption. It is reasonable to posit that each region maps onto distinct motivational, motoric, or autonomic regulatory processes; however, it is the *coordinated* recruitment of these diverse network “nodes” that is essential for the expression of opioid-modulated behavior.

Finally, it is important to note that there are several telencephalic sites beyond the striatum that support opioid-driven feeding or related motivational processes. Mu-opioid peptide infusions into the central amygdala elicit strong feeding responses (Gosnell, 1988; Giraudo et al., 1998; Levine et al., 2004), and enhance appetitive behaviors directed toward Pavlovian cues (DiFeliceantonio et al., 2012; Mahler and Berridge, 2012) and muopioid receptors in the BLA appear to mediate positive shifts in the learned incentive value of food reward (Wassum et al., 2011). Recently, it was shown that mu-opioid stimulation in the ventral medial prefrontal cortex (vmPFC) markedly increased feeding but not drinking or gnawing behaviors, and directed food choice toward a sweet, carbohydrate-enriched test diet over a fat-enriched diet (Mena et al., 2011). Interestingly, there is evidence for reciprocal opioid-dependent interactions among sites (for example, feeding elicited by intra-CeA opioid infusions are blocked by intra-Acb opioid receptor antagonism, and vice versa) (Kim et al., 2004), perhaps suggesting coordinated opioid release at least within certain key forebrain “feeding nodes,” although it is presently unknown whether these reciprocal interactions seen between the central amygdala and nucleus accumbens extend to other telencephalic opioid-sensitive sites, such as the vmPFC. It is noteworthy that these sites all project strongly to the hypothalamus. It is interesting to speculate that opioid release may be coordinated among these sites during appetitive motivational states, which could orchestrate joint “top-down” control over hypothalamic feeding circuits. Refinements in methodology for recovery and detection of endogenous opioid peptides (for example, see DiFeliceantonio et al., 2012) may provide a stronger test of this hypothesis, and, more generally, improve our

understanding of the range of physiological conditions that engender telencephalic opioid release.

3.1. Intra-striatal neuromodulators that influence opioid-induced feeding

Crucial insights into the separable neural systems within the ventral striatum that are involved in appetitive and consummatory behavior can be gleaned from examining the interactive effects of other striatal neurotransmitters upon the mu-opioid induced enhancement of palatable food intake. An important method of examining this within the nucleus accumbens has been to give preor co-treatments of drug agents that act as agonists or antagonists upon other neurotransmitter receptors along with DAMGO injections, and then to compare the effects of the pretreatment on food intake patterns as compared to infusions of DAMGO alone. Such experiments have led to intriguing results; consistent with the separable effects of dopaminergic and mu-opioid receptor agents upon appetitive and consummatory food-directed processes, respectively, neither the blockade of D1 nor D2 receptors affected baseline intake of a sweetened fat diet, nor did they impact the enhancement of food intake seen following DAMGO treatment of the nucleus accumbens (Will et al., 2006). Antagonism of glutamate AMPA receptors similarly failed to impact food intake following DAMGO treatment of the nucleus accumbens, although, interestingly, there is evidence for a reciprocal interaction between μ-opioid agonists and GABA-B receptors in the Ach shell (Znamensky et al., 2001). Other intra-accumbens pretreatments to date that have been shown to affect subsequent DAMGO-induced feeding are the blockade of muscarinic (but not nicotinic) acetylcholine receptors (Will et al., 2006), the stimulation or blockade of the cannabinoid CB1 receptor (Skelly et al., 2010), or the blockade of the adenosine 2A receptor (Pritchett et al., 2010). Each of these effects shall be considered in turn below.

3.1.1. Cholinergic muscarinic receptors—Initial insights about cholinergic regulation of feeding-related motivational processes were gleaned by examining the effects of muscarinic or nicotinic receptor blockade upon the learning of an operant response for sugar reinforcement; it was found that antagonism of muscarinic receptors (but not nicotinic receptors) within the nucleus accumbens core or shell blocked learning of the operant response, and also reduced performance of the operant task after the task was learned (Pratt and Kelley, 2004). In separate tests in which food-restricted rats were offered free access to sugar pellets, the muscarinic receptor antagonist scopolamine was shown to increase locomotor behavior and reduce the intake of sugar across a 30-min test session (without affecting number of feeding bouts). Together, these data suggested that the learning impairment following muscarinic receptor antagonism might result from a reduction of the motivational incentive of the reward, rather than from a learning impairment per se. Subsequently, it was shown that a single injection of scopolamine methyl bromide into the nucleus accumbens core (or the anterior dorsal striatum) potently reduced ad libitum food intake over a 24-h period; locomotor activity tests demonstrated that in the absence of food, measures of locomotion returned to normal within 60 min of the drug treatment (Pratt and Kelley, 2005).

This study also suggested a potential link between Acb muscarinic receptor blockade and the striatal mu-opioid system. Prior reports had demonstrated that systemic administration of muscarinic agonists upregulated preproenkephalin (PPE) expression in the striatum (Weisinger et al., 1992, 1998), whereas systemic antagonism of muscarinic receptors increased preprodynorphin (PPD) expression (Wang and McGinty, 1996) and reduced the up-regulation of PPE mRNA resulting from amphetamine administration or 6-OHDA lesions of striatal dopaminergic fibers (Nisenbaum et al., 1994; Wang and McGinty, 1996); whether these effects involved Acb cholinergic receptors remained unclear. Hence, after the

food intake test in the study by Pratt and Kelley (2005), brains were collected from rats that had received either saline or scopolamine injections into the nucleus accumbens, and were processed via in situ hybridization to examine the expression of endogenous opioid mRNAs; PPE expression within striatal tissues was reduced 24 h post-scopolamine injection into Acb. Therefore, Acb muscarinic blockade produced changes in striatal opioid gene expression (i.e., reduced PPE) that were consistent with a putative 'reduced opioid transmission' hypothesis at both the behavioral (i.e., feeding reduction) and temporal (i.e., at 24 h post infusion, when the feeding reduction was observed with scopolamine) levels. Thus, it may be that muscarinic cholinergic receptor blockade within Acb produces its feeding-inhibitory effects via a downregulation of striatal opioids.

These data suggested an important link between acetylcholine and opioid systems of the nucleus accumbens in modulating food intake, and led to a direct test of the aforementioned hypothesis by examining the effects of Acb scopolamine pre-treatment on the feeding elicited by Acb DAMGO injections. As noted above, muscarinic receptor antagonism of the nucleus accumbens blocked DAMGO-elicited feeding of a sweetened fat diet, and also reduced baseline intake when given alone (Will et al., 2006). It should be noted, however that this initial test was done immediately after scopolamine infusion, and thus the increased locomotion observed following scopolamine treatment may have reduced feeding due to response competition. Thus, Perry and colleagues (2009) tested the effects of scopolamine when injected 30 min, 4 h, 10 h, or 24 h prior to DAMGO injection and behavioral testing. Significant reduction of the intake of the sweetened fat diet was observed at both the 30 min and 4 h time point, well after the time that scopolamine infusions no longer affected ambulation or rearing in an open field (Pratt and Kelley, 2005).

Such a striking opposition of muscarinic receptor blockade upon both striatal mu-opioid mRNA expression and the feeding activated by mu-opioid receptor stimulation led us to question whether the behavioral effects of muscarinic blockade of the nucleus accumbens were dissociable in terms of its effects on appetitive versus consummatory behavior. In short, given the strong evidence that striatal acetylcholine and mu-opioid function were interlinked, were the effects of muscarinic receptor blockade of the nucleus accumbens limited to consummatory measures (as appears to be the case for opioids, see above), or did they impact both phases of motivated behavior? In the initial examination of the effects of nucleus accumbens scopolamine on lever-pressing (Pratt and Kelley, 2005), it was shown that scopolamine treatment caused a modest but significant decrease in the break point on a progressive ratio schedule of reinforcement, suggesting that the treatment might impact appetitive behavior as well as food consumption (Pratt and Kelley, 2004). However, although the progressive ratio paradigm does allow for an assessment of the incentive value of a reinforcer, it does not separate appetitive processes from reward valuation of the food once consumed, as rats ultimately earn sugar pellets within the paradigm.

To address this question more directly, a series of experiments was conducted to examine the effects of a 10-μLg infusion of scopolamine into the nucleus accumbens 3 h prior to behavioral tests designed to discriminate between the appetitive and consummatory phases of food-directed motivation (Perry et al., 2010). The 3-h pretreatment interval was used to minimize the impact of motor-hyperactivity confounds (prior work had shown that scopolamine-induced hyperactivity abates by 3 h, but the feeding suppression is still present; Perry et al., 2009). At this 3-hr time point, scopolamine treatment reduced sucrose pellet consumption in hungry rats by reducing the size of a feeding bout but *not* by altering the number of bouts initiated. In the presence of food, ambulation and rearing measures increased, though this was not the case when rats were tested without food in the chamber. This might have suggested that the hyperactivity in the presence of food was the result of a drug–environment interaction (e.g., the presence of an appetitive goal "releasing"

heightened activity in scopolamine-treated rats) or simply a consequence of altered competition between time spent eating and time spent locomoting. To test this more directly, separate rats were tested in 45-min sessions, three hours after intra-accumbens injections of saline or scopolamine. During the first 15 min of behavioral testing, they were able to approach a screen behind which food was present but not accessible. In the final 30 min, the screen was removed, and sucrose intake was measured for the remainder of the session. Rats in this condition approached the screen an equal number of times whether treated with saline or scopolamine, suggesting that there was no impairment in the appetitive value of the sugar reward. Once the screen was removed, however, rats ate less sucrose following nucleus accumbens muscarinic receptor blockade. Furthermore, scopolamine treatments had no effect on lever-pressing for a sucrose-associated Pavlovian conditioned cue, nor did scopolamine affect the potentiation of conditioned reinforcement by intra-accumbens amphetamine injections. Together, these data suggest that, while muscarinic receptor antagonism of the ventral striatum clearly impacts food consumption, it does so while leaving the appetitive phase of food-seeking intact. That muscarinic receptor inactivation of these regions has quite the opposite effect of mu-opioid receptor stimulation within similar behavioral paradigms suggests that the two neurotransmitter systems play a vital role in consummatory behavior as it is regulated within striatal circuitry.

Before expanding upon this further, two points should be noted. First, we have reported that pairing a flavor or a location with nucleus accumbens scopolamine leads to its subsequent avoidance (Pratt et al., 2007). Thus, the food reward devaluation that occurs following scopolamine treatment is associable with environmental cues. These effects, however, are not likely due to a general malaise caused by the treatment for several reasons. Such malaise (for example, that induced by LiCl) is typically characterized by relative inactivity of the rat following treatment, and scopolamine treatments do not cause a locomotor reduction. Additionally, for none of the experiments detailed above was water intake affected by treatment. Specifically, Perry et al. (2010) demonstrated that scopolamine treatment of the nucleus accumbens does not affect water intake in water-deprived rats, suggesting that the motivational impact of muscarinic blockade is relatively selective to food. Finally, that the appetitive components of food motivation are not reduced as a function of treatment argues against malaise being a factor, as these measures would also be affected by general motivational decline.

Evidence from the laboratory of Bart Hoebel has shown that striatal acetylcholine levels rise as animals finish a meal (Mark et al., 1992). Those findings, in conjunction with similar increases occurring following exposure to a flavor that has been conditioned for aversion (Mark et al., 1995), has led this group to suggest that striatal acetylcholine is a marker of both satiety and aversion. This leads to an apparent difference in interpretation of striatal acetylcholine in feeding behavior, as in one case it is an increase of striatal acetylcholine that is argued to lead to satiety/aversion, whereas in the other it is a blockade of action of acetylcholine on muscarinic receptors that has been found to reduce consummatory behavior. It has been suggested that the apparently contradictory effects of the pharmacological versus microdialysis approaches may result from the fact that scopolamine increases acetylcholine output as a result of blockade of the M2/M4 autoreceptors (Avena and Rada, 2012; Pratt et al., 2007). This subsequent high acetylcholine output may then be the culprit for the effects of the drug treatment, rather than the blockade of post-synaptic muscarinic receptors acting upon projection neurons. However, two reported findings make this interpretation implausible. First, direct injections of an acetylcholine/physostigmine cocktail into the nucleus accumbens has no impact on the intake of a sweetened fat diet (Will et al., 2006), as might be predicted if high acetylcholine levels signal the end of a meal. Second, we have shown that blockade of the nucleus accumbens M2 receptors with the selective antagonist AFDX-116 has no effect upon the intake of rat chow in food-

deprived rats, whereas stimulation of M2 receptors with the M2-receptor preferring oxotremorine sesquifumarate reduces the food intake in a manner consistent with that of scopolamine treatment (although with a divergent locomotor profile; Pratt and Blackstone, 2009). The M2 receptor has been argued to serve as an autoreceptor in striatal tissues (Billard et al., 1995). Notably, AFDX-116 and oxotremorine sesquifumarate have been shown (at similar concentrations to those used by Pratt and Blackstone, 2009) to increase and decrease striatal acetylcholine outflow, respectively, presumably through their actions at autoreceptors (Billard et al., 1995; Murakami et al., 1996; Ragozzino et al., 2009). If increased striatal cholinergic outflow due to autoreceptor blockade mediated scopolamine-induced inhibition of feeding (as suggested by Hoebel and colleagues), then selective blockade of the M2 receptors at concentrations that increase striatal acetylcholine should also have caused feeding inhibition (and did not). However, M2 receptor stimulation reduced food intake, at doses of oxotremorine sesquifumarate that were previously shown to be effective in lowering acetylcholine levels within striatal tissues. It is possible, in the latter case, that oxotremorine activated other muscarinic receptor classes as well, as the drug has some affinity for all the muscarinic receptor classes (Brauner-Osborne and Brann, 1996). Nonetheless, the findings of Will et al. (2006) and Pratt and Blackstone (2009) suggest that intra-Acb scopolamine blocks feeding by decreasing, rather than increasing, muscarinic receptor tone within ventral striatal feeding circuitry. It should be noted that the latter data do not argue that increased striatal acetylcholine is not involved in satiety processes, but they do suggest that disruption of the normally high cholinergic tone on nucleus acccumbens muscarinic receptors (as caused by scopolamine treatment or the activation of M2 autoreceptors) inhibits feeding at some point prior to satiety onset (see Pratt and Blackstone, 2009). Clearly, additional research is needed to expand our understanding of the functional role of striatal acetylcholine in regulating food-directed motivation.

Collectively, these data suggest that there is an important role for striatal acetylcholine in the regulation of food motivation during the consummatory phases of food intake (in contrast to during the appetitive phases of food-seeking). Furthermore, that muscarinic receptor blockade blocks the increase in food intake that occurs during mu-opioid receptor stimulation of the nucleus accumbens, and also down-regulates the expression of the mRNA precursor to the enkephalin peptide in conjunction with this food intake decline, suggests that the cholinergic interneurons of the striatum are in a critical position for regulating mu-opioid influences on the intake of foods. The corpus striatum receives its acetylcholine from its own population of large aspiny neurons. Although these neurons account for only a small proportion of the striatal milieu, each cell exhibits extensive arborizations of processes that extend into a full cubic millimeter of tissue (Graveland and DiFiglia, 1985; Zhou et al., 2001), and they have been shown to be responsive to food reward and food-predictive cues (e.g., Matsumoto et al., 2001; Ravel et al., 2003; Sardo et al., 2000). Furthermore, striatal cholinergic interneurons are heavily innervated by midline thalamic structures that themselves receive dense inputs from orexin-containing neurons of the lateral hypothalamus (Baldo et al., 2003; Lapper and Bolam, 1992; Meredith and Wouterlood, 1990). It has been argued previously that this “hypothalamic-thalamic-striatal” axis may be an important pathway by which the homeostatic and circadian circuitry of the hypothalamus regulates the rewarding and hedonic value of food within mesolimbic circuitry (Kelley et al., 2005b). This hypothesis is discussed, in further detail, later in the present article.

3.1.2. Endocannabinoids and adenosine—Although the mechanisms underlying their effects have not been as well categorized as those of muscarinic acetylcholine receptors, manipulations of both cannabinoid and adenosine receptors have also been shown to affect food intake following nucleus accumbens mu-opioid receptor stimulation. Regarding the former, there is an extensive literature connecting the endocannabinoid system with the regulation of food intake and energy metabolism (Silvestri et al., 2011; Li et al., 2011; Di

Marzo et al., 2009; Kunos et al., 2008; Nogueiras et al., 2008). Previous research has shown that systemically co-administered cannabinoid and opioid agents interact to modify feeding on both pabulum and palatable foods (Kirkham and Williams, 2001; Rowland et al., 2001; Tallett et al., 2008; Williams and Kirkham, 2002). A number of manuscripts have reported that the stimulation of cannabinoid receptors within the ventral striatum, and particularly within the nucleus accumbens shell, enhances food intake and affects the hedonic response to sapid solutions (Deshmukh and Sharma, 2012; Kirkham et al., 2002; Mahler et al., 2007; Shinohara et al., 2009; Soria-Gómez et al., 2007). Given the similar profile to that of mu-opioid receptor stimulation, it is tempting to suggest that the two systems may interact within the nucleus accumbens to promote feeding. As a first step in examining this potential interaction, Skelly et al. (2010) systematically examined the effects of co-manipulations of both systems on the intake of a sweetened fat diet. In contrast to prior reports, neither stimulation nor blockade of CB1 receptors in the nucleus accumbens shell (with WIN 55,212-2 and SR141716, respectively) affected intake of the fat diet when administered alone. However, co-stimulation of mu-opioid and CB1 receptors enhanced intake above that of DAMGO treatment alone, and CB1 receptor antagonism with SR141716 attenuated the effects of DAMGO on feeding. This suggests a clear interaction between nucleus accumbens muopoiod and cannabinoid receptor systems upon the promotion of food intake.

Adenosine is also a major neuromodulator within the striatum, altering both neurotransmitter release and intracellular functioning (Dunwiddie, 1985; Schiffmann et al., 2007). Both A1 and $A2_A$ receptor subtypes are distributed throughout the striatum with $A2_A$ receptors particularly abundant (Ferré, 2007; Ongini and Fredholm, 1996; Schiffmann et al., 2007). Within the striatum, adenosine receptors are localized upon enkephalinergic GABAergic neurons where they interact with the striatal opioid system, that, as others have suggested, serve a significant role in regulating feeding mechanisms (Ammon-Treiber and Höllt, 2005; Brundege and Williams, 2002; Franco et al., 2007; Halimi et al., 2000; Kaplan and Coyle, 1998; Schiffmann et al., 1991). Pritchett et al. (2010) examined the effects of adenosine A1 and A2 receptor manipulations upon the intake of a sweetened fat diet with or without co-stimulation of nucleus accumbens mu-opioid receptors. Neither stimulation of A1 nor $A2_A$ receptors impacted baseline or DAMGO-induced feeding. Antagonism of nucleus accumbens $A2_A$ receptors with MSX-3 increased feeding of the high-fat by itself, and also augmented the normal feeding increase produced by intra-accumbens DAMGO. Interestingly, the effect of $A2_A$ receptor antagonism on increasing fat intake was blocked by co-administration of naltrexone, suggesting that its effects may have been regulated through opioid-receptor systems.

4. New directions

One of the most interesting observations regarding the modulation of feeding by intra-striatal opioid infusions is that injection placements that elicit significant feeding responses sometimes fall far outside the classical “limbic-motor interface” of the nucleus accumbens (Zhang and Kelley, 2000; DiFeliceantonio et al., 2012). This could suggest some degree of functional homogeneity across ventral and dorsal striatum with regard to opioid-mediated feeding responses. Throughout her career, Dr. Kelley made profound contributions to our understanding of the physiological basis of striatal functional *heterogeneity*, many of which are discussed above. However, later on she became interested in conditions under which the striatal complex acts in a *homogeneous* way—as a unified whole—thereby coordinating activity in both the ventral and dorsal striatum. An important impetus for this line of thought was the observation that several physiological challenges that provoke global changes in reward function alter the transcriptional control of opioid peptide gene expression throughout the striatal complex. Dr. Kelley’s work in this area focused on the effects of different schedules of palatable food exposure, although generally similar effects have been

found for drugs of abuse. In one study, Kelley and colleagues found that 3-h daily exposure to a highly palatable, sugar- and fat-enriched chocolate drink for 2 weeks produced a downregulation of enkephalin gene expression throughout widespread areas of striatum (Kelley et al., 2003). Furthermore, as discussed previously, an intra-Acb infusion of scopolamine (which greatly reduced food intake) depressed striatal enkephalin gene expression (Pratt and Kelley, 2005); again, effects were seen in areas far beyond the Acb. Finally, in a study designed to dissect the influence of energy-balance state from food anticipation, it was found that striatal enkephalin was upregulated by food expectancy regardless of whether or not the rats were food-restricted (Will et al., 2007). Again, transcriptional effects were seen in striatal regions beyond the accumbens. Together, these results led to the hypothesis that overall levels of striatal enkephalin across the striatal complex track acute environmental contingencies that signal opportunities to eat; according to this model, the down-regulation of enkephalin signals a global motivational condition (such as short-term satiety) for which feeding is not "required" (in other words, low levels of striatal enkephalin represent a motivational "off switch," indicating that sufficient feeding has already occurred). Further studies are needed to test this hypothesis. Nevertheless, the question arises as to the mechanism underlying the coordination of enkephalin gene expression across wide striatal areas. If the topographic organization of glutamate-coded cortico-striatal afferents contributes to regional heterogeneity in the striatum (as discussed above), what is the functional principle underlying this *coordination* of gene expression *across* the striatal complex?

One theory, proposed by Kelley and colleagues (2005), involves the modulatory influence of striatal cholinergic interneurons. These cells have extensive processes that interact across wide striatal territories, providing the structural basis for functional integration. Indeed, there is evidence that "tonically active neurons," presumptive cholinergic interneurons, are functionally synchronized across wide areas of the striatum in various learning paradigms (Aosaki et al., 1995). Hence, it is possible that these interneurons act in a web-like, "reticular" fashion, coordinating opioid gene expression across wide striatal areas. The relevant inputs to cholinergic interneurons may come from thalamostriatal projections originating in midline or centromedial thalamic nuclei (Matsumoto et al., 2001; Tan and Bullock, 2008), which have access to energy-sensing systems in the hypothalamus (Kelley et al., 2005a; Risold et al., 1997; Cornwall and Phillipson, 1988). This model is speculative; however, in recent years evidence has accrued to support the anatomical basis of the model (Gautron et al., 2010).

The implications for psychopathology may be profound, perhaps most obviously with regard to food craving, obesity, and binge eating. These topics has been reviewed elsewhere (Kelley et al., 2002; Berner et al., 2011; Mercer and Holder, 1997; Nathan and Bullmore, 2009). Another set of clinical implications comes from a perhaps unexpected domain, sleep biology. It has been suggested that the recent societal trends toward chronic sleep loss in humans is contributing significantly to the "obesity epidemic." Polls conducted by the CDC, National Sleep Foundation (NSF), as well as large scale epidemiological studies have indicated that Americans may be chronically sleep deprived because of voluntary bedtime curtailment (Bonnet and Arand, 1995; Morbidity and Mortality Weekly Report, 2005; National Sleep Foundation, 2008). More than 50 cross-sectional studies originating from multiple countries have found a significant association between short sleep and elevated BMI (reviewed in Knutson, 2010). Several studies in healthy lean adults showed that when sleep is restricted in the laboratory (4–6 hrs/night for multiple nights), adverse effects on components of the metabolic syndrome, including increased insulin resistance, are evident; along with alterations in plasma leptin and ghrelin, peptides involved in modulating feeding, that favor stimulation of hunger and appetite (Spiegel et al., 1999; Spiegel et al., 2004; Nedeltcheva et al., 2009a; Spiegel et al., 2005).

Interestingly, the increased hunger and appetite induced by sleep restriction leads to increased energy intake in the presence of ad libitum feeding, particularly for high-carbohydrate palatable snacks (Brondel et al., 2010; Nedeltcheva et al., 2009b). These data are consistent with observations from animal studies that have shown that sleep deprivation produces an increase in food intake (Everson et al., 1989; Hanlon et al., 2005; Kushida et al., 1989; Rechtschaffen et al., 2002). For example, in one study, sleep-deprived rats preferentially increased intake of a carbohydrate-rich diet over other available diets (Bhanot et al., 1989). Similarly, in laboratory studies of sleep-restricted humans, appetite and hunger ratings were most increased for palatable, carbohydrate-rich nutrients (Spiegel et al., 2004). Although 2 weeks of sleep restriction in sedentary humans increased consumption of high-carbohydrate snacks, it did not reveal an increase in energy (Nedeltcheva et al., 2009b). Thus, increased hunger and food intake did not occur as the result of a normal response to a negative energy balance.

Based on these considerations, non-homeostatic mechanisms must be involved in the dysregulation of feeding behavior in conditions of sleep loss, and an interesting candidate substrate is the striatal opioid system. Interestingly, recent evidence indicates that sleep loss in rodents dramatically increases striatal enkephalin gene expression, and that this profound transcriptional regulation occurs across wide areas of the striatum (Baldo et al., 2011). This change would be predicted to engender a motivational state strongly favoring the consumption of palatable foods (i.e., the enkephalin-coded feeding “switch” cannot be turned “off”). This hypothesis accords with the escalation in food intake seen in sleep deprived rats, as well as the palatable-food preferences seen in sleep-deprived humans. Interestingly, although sleep-deprived rats eat more, they are less willing to work for food in operant lever-pressing tasks. Microanalysis of their response topography suggests a motivational rather than a motoric impairment (Hanlon et al., 2005; Hanlon et al., 2010). REM sleep-deprived rats that displayed an escalation of feeding behavior in their home cages responded less avidly in a sucrose-reinforced progressive ratio lever-pressing task, resulting in lower break-points; this deficit was reversed by intra-accumbens amphetamine infusions (Hanlon et al., 2010). Hence, the behavioral deficits in the sleep-deprived rat (i.e., increased feeding along with a deficit in goal-seeking behavior) resembles one in which the dopamine-coded “response-invigoration” module is underactive while the opioid-coded “taste-hedonics” processing module is overactive, resulting in a dysfunctional state characterized by global motivational deficit, but augmented food intake when the food is readily available—not inconsistent with the increased “junk food” intake seen clinically after sleep loss.

Thus, in a general sense, striatum-wide coordination of opioid peptide gene expression under pathological conditions may engender a situation in which the feeding CMS is expressed inappropriately (at least its transactional response components), leading to obesity; studies of sleep loss may provide a crucial window into this process.

5. Summary and Conclusions

> “Specific and phylogenetically ancient motivational systems exist in the brain that have evolved over the course of millions of years to ensure adaptation and survival. These systems are engaged by perception of environmental events or stimuli, and when so engaged generate specific affective states (positive or negative emotions) that are powerful drivers of behavior.. .Their elaboration and expression, when elicited by appropriate stimuli, are instantiated in complex but highly organized neural circuitry.” – A.E. Kelley (2005)

In this paper we have reviewed evidence for the neurochemical and anatomical segregation of discrete processes that together promote adaptive motivated behaviors. One important

insight—for which Ann Kelley's work provided crucial evidence—is that the distinct neural processing modules that, through their coordinated actions, mediate the feeding CMS can be understood both in terms of their neurochemical coding as well as their anatomical organization. A generalization supported by the work reviewed here is that opioid transmission in the ventral striatum mediates the hedonic state associated with palatable feeding, through the modulation of glutamate-coded amygdala afferents that perhaps convey specialized information about the affective valence of palatable food. Dopamine transmission, in contrast, is important for the generalized activational effects of food anticipation, and for the invigoration of effortful goal-seeking activities. One important (and perhaps surprising) insight is that these two chemically coded functions are instantiated within overlapping zones of the ventral striatum. The precise physiological basis for divergent opioid and dopamine actions within the same brain tissue is unclear—and represents an important avenue for future inquiry—but coordinated opioid/dopamine release events may underlie the close linkage between the "wanting" and "liking" of rewards in the intact brain. Evidence was also reviewed to suggest that, although there are clear zones of functional heterogeneity throughout the striatum, there is also evidence that under certain conditions the striatum can act as a functionally unified whole (at least with regard to coordinated opioid peptide gene expression) to modulate appetitive motivational states. Understanding both the *segregation* and *coordination* of striatal function may be crucial for understanding the role of the striatum in various "disorders of appetitive motivation" (to use a phrase of Dr. Kelley's).

In conclusion, the insights into the mechanistic basis of appetitive motivation gleaned from studies conducted and inspired by Ann Kelley may have profound implications for the alleviation of human suffering in psychiatric disease—the pursuit of which was always Ann's guiding CMS.

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