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Review

Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning

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Abstract

The nucleus accumbens is a brain region that participates in the control of behaviors related to natural reinforcers, such as ingestion, sexual behavior, incentive and instrumental learning, and that also plays a role in addictive processes. This paper comprises a review of work from our laboratory that focuses on two main research areas: (i) the role of the nucleus accumbens in food motivation, and (ii) its putative functions in cellular plasticity underlying appetitive learning. First, work within a number of different behavioral paradigms has shown that accumbens neurochemical systems play specific and dissociable roles in different aspects of food seeking and food intake, and part of this function depends on integration with the lateral hypothalamus and amygdala. We propose that the nucleus accumbens integrates information related to cognitive, sensory, and emotional processing with hypothalamic mechanisms mediating energy balance. This system as a whole enables complex hierarchical control of adaptive ingestive behavior. Regarding the second research area, our studies examining acquisition of lever-pressing for food in rats have shown that activation of glutamate *N*-methyl-D-aspartate (NMDA) receptors, within broadly distributed but interconnected regions (nucleus accumbens core, posterior striatum, prefrontal cortex, basolateral and central amygdala), is critical for such learning to occur. This receptor stimulation triggers intracellular cascades that involve protein phosphorylation and new protein synthesis. It is hypothesized that activity in this distributed network (including D1 receptor activity) computes coincident events and thus enhances the probability that temporally related actions and events (e.g. lever pressing and delivery of reward) become associated. Such basic mechanisms of plasticity within this reinforcement learning network also appear to be profoundly affected in addiction.

Keywords: Ventral striatum; Appetite; Ingestion; Instrumental behavior

Contents

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1. Introduction

In recent years a great deal of progress has been made in advancing our understanding of the neural mechanisms underlying reward and motivation. Much of this knowledge has arisen from research funded by the National Institute on Drug Abuse (NIDA). The primary mission of NIDA within the context of its neurobiology research program has traditionally focused on mechanisms underlying the neurochemical and behavioral effects of drugs and addiction. However, NIDA has also emphasized that knowledge of the basic processes controlling appetitive motivation and natural reward processes (such as those regulating ingestive and sexual behaviors) can provide critical insights into the addiction process. Roger Brown, my program director for many years at NIDA, was a strong supporter of this philosophy and was always very supportive of our research, which mainly focuses on neural systems involving natural reward processing and learning, rather than directly addressing mechanisms of addiction. In the present review I will highlight several of the major areas of research that our laboratory has undertaken, funded by NIDA, over the past decade or so. It should be emphasized that this paper, which was presented at a special symposium honoring the life and work of Roger Brown, is not a comprehensive overview of these fields but rather focuses specifically on our own NIDA-funded research, in line with the spirit of the symposium.

2. The nucleus accumbens: functional specialization of subregions

The nucleus accumbens, a brain region located within the ventral aspects of the basal ganglia, has long been conceptualized as an essential interface between 'motivation and action'. Mogenson first proposed this forebrain structure as a key element in the integration of affective and cognitive processing with voluntary motor actions [1]. He emphasized the connectivity of the nucleus accumbens, in that it received a convergence of information from brain regions involved in emotional learning, memory, and complex cognition, such as amygdala, hippocampus, thalamus, and prefrontal cortex. Most of these projections are now known to contain glutamate as their transmitter. He noted that, in turn, neurons within the nucleus accumbens projected out to basal ganglia motor circuits via the pallidum and ventral midbrain (primarily GABAergic in nature) and presumably were involved in somatic motor control. This general theory has been supported through the past two decades of experimentation. The nucleus accumbens is a brain region that appears to play a crucial role in behaviors related to natural reinforcers, such as ingestion, sexual behavior, incentive and instrumental learning (reviews, [2–4]. Its major dopaminergic innervation, arising from the ventral tegmental area, plays a key role in many of these functions [5,6]. Moreover, it is well established that the nucleus accumbens is a critical substrate for the rewarding and reinforcing properties of addictive drugs [7].

Although the nucleus accumbens has long been considered a ventral striatal territory with prominent similarities to the overlying caudate-putamen, in the early 1990s there was a major anatomical re-conceptualization of this brain region. Refined analysis of connectivity as well as its histochemical profile revealed that the accumbens was composed of two major subterritories, the core (tissue surrounding the anterior commissure) and the shell, a region extending medially, ventrally and laterally around the core. The core and shell subregions show striking differences in their afferent input and efferent projections [8,9]. For example, although both core and shell receive input from hippocampus, the ventral subiculum projects primarily to the shell while the dorsal subiculum projects to the core. Different regions of prefrontal cortex project to different zones; the prelimbic area projects to core, while the infralimbic and piriform cortices project to shell [10]. Specific subcompartments of the amygdala also reach distinct subregions within accumbens core and shell [11]. In terms of outputs, the core subregion connects extensively to classic basal ganglia output structures, such as the ventral pallidum, subthalamic nucleus, and substantia nigra. The shell subregion, in contrast, projects preferentially to subcortical limbic regions, such as the lateral hypothalamus, ventral tegmental area, ventromedial ventral pallidum, and brainstem autonomic centers.

On the basis of these distinctive anatomical profiles, functional specialization of these two subregions and their associated circuitry has been proposed [8,9,12]. The general notion put forth was that the accumbens core has similarities to the overlying caudate-putamen and is more allied with voluntary motor functions, whereas the shell, having close ties to the 'extended amygdala' [13] lies more in the domain of visceral or motivational mechanisms. Our work over the past decade has provided strong support for this general hypothesis [14]. Simply stated, our experiments suggest that the accumbens shell (AcbSh) in part functions as a critical link between cortical circuits and hypothalamic/brainstem circuits with regard to the control of food intake, while the accumbens core (AcbCo) and its connected circuitry is involved in the learning and execution of adaptive instrumental actions.

3. Connectivity related to control of food intake

The nucleus accumbens is well positioned to participate in neural control of food intake. It is useful to examine how internal and external food- or appetite-related information gains access to this structure, and how it can influence output effector pathways controlling feeding (Fig. 1). First, the accumbens receives brainstem information related to taste and visceral functions through a direct input from the nucleus of the solitary tract (NTS; to the medial shell), as well as an indirect input from gustatory cortex via parabrachial (PB) projections to gustatory (VPO) thalamus (to lateral shell and core) [15,16]. Taste and visceral information can also influence the accumbens via two amygdala pathways: the NTS–PB–central nucleus of amygdala–ventral tegmental area connection, and gustatory cortex–basolateral amygdala–accumbens pathway [17]. The central nucleus is particularly interesting as one of its major cortical inputs is from gustatory cortex [18]. Pathways signaling internal homeostasis that eventually reach nucleus accumbens include projections from lateral hypothalamus (LH, which has direct access to the arcuate nucleus, a critical central command area for metabolic sensing), to the medial accumbens shell. With regard to behavioral effector routes, much of the output of the accumbens core reaches classic basal ganglia motor control circuits, while the shell's main effector systems appear to involve medial ventral pallidum and lateral hypothalamus. The downstream outputs from the LH involve structures that directly control brainstem pattern generators for the motor actions of eating as well as autonomic structures. In summary, both the shell and core subregions of nucleus accumbens communicate extensively with circuitry that is well established to control taste perception, energy balance, and viscero/autonomic and somatomotor effectors.

3.1. The medial accumbens shell contains neurons, regulated by GABA and glutamate, that directly control feeding via the lateral hypothalamus

Our laboratory has found that certain neurons within the medial accumbens shell are critically involved in certain aspects of feeding behavior One of the earliest studies found that infusion of a glutamatergic AMPA receptor antagonist, DNQX (but not the NMDA antagonist AP-5), potently increased food intake in non-food deprived rats [19], a highly site-specific effect and selective for food [20]. Thus, removal of excitatory input to accumbens shell AMPA receptors (presumably deriving from corticolimbic or thalamic regions), results in robust, immediate-onset feeding. A study investigating the behavioral specificity of the DNQX effect found that water intake and wood-chip gnawing were not affected; however, palatable sucrose solution intake was increased by the treatment [20]. The feeding response bore remarkable resemblance to electrically induced feeding from the LH, and we tested the hypothesis that activation of the LH is critical for the feeding effect. Indeed, this effect is blocked by concurrent

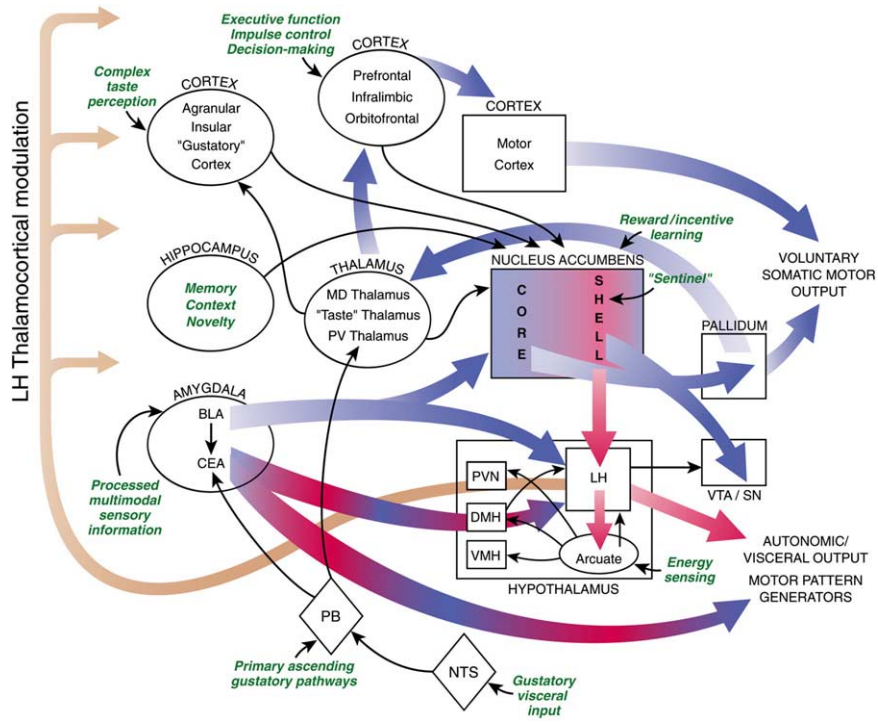

Fig. 1. Pathways that link the nucleus accumbens/ventral striatum with circuits involved in the control of taste perception, energy balance, and food intake. Red pathways are preferentially involved in amino acid coded feeding; blue pathways are more closely linked to opioid-induced feeding. All possible connections are not shown for purposes of simplicity. See text for discussion of details.

inactivation of the LH with muscimol, suggesting that the ingestive behavior is mediated through activation of cells within the LH. This was a novel demonstration of a specific behavioral role for the accumbens shell, and suggested an important functional link between two major brain regions involved in reward, the accumbens and lateral hypothalamus. Further studies showed that inhibition of the AcbSh with the $GABA_A$ agonist muscimol or the $GABA_B$ agonist baclofen also induces feeding [21–23]. A compound that causes increases in endogenous GABA, gamma-vinyl-GABA, by inhibiting GABA-transaminase, also markedly increased feeding. Both the glutamate- and GABA-mediated effects are dependent on activation of cells in the perifornical lateral hypothalamus. For example, utilizing expression of the immediate early gene c-*fos* as a marker for neuronal activation, we found that intra-shell muscimol markedly activates Fos expression throughout the LH [24]. When LH cells are activated by glutamate agonists, feeding also occurs [25]. We and others have recently reported that infusion of muscimol into the shell activates hypocretin/orexin-labeled LH cells, but not melanin-concentrating hormone-labeled cells and this treatment also causes strong Fos expression in the arcuate nucleus [26,27]. We have postulated that the accumbens shell-lateral hypothalamic pathway, which has been clearly demonstrated anatomically [8,28], constitutes an important communication route between striatal and hypothalamic mechanisms controlling motivated behavior [29].

These findings suggest that the medium spiny neurons within the shell, which contain GABA as their major transmitter, may release GABA in association with normal feeding, which by self-inhibition (through recurrent collaterals) would result in disinhibition of LH or perhaps other downstream cells involved in feeding. Moreover, they suggest that converging corticolimbic input to the AcbSh, coded by glutamate, restricts this mechanism and exerts inhibitory control over downstream feeding circuits. We have proposed that this mechanism may be necessary to override strong, metabolically driven feeding signals when an animal, engaged in feeding, directs its attention to novel or potentially dangerous signals in the environment. Thus, the accumbens shell acts as a kind of sensory 'sentinel', enabling adaptive switching and shutting off downstream feeding motor pattern generators, via the lateral hypothalamus.

3.2. Opiate receptors in widespread regions of ventral striatum regulate palatability and the affective response to food

Further work in our laboratory has focused on the role of endogenous opioid peptides within the ventral striatum in the control of food intake. Brain opioids play a fundamental role in reinforcement processes. Animals and humans self-administer opiate drugs, and they exert a powerful positive affective state [30]; even in neonatal rat pups preferences for stimuli associated with opiates can be demonstrated [31]. Opioids also play a central role in control of food intake; in many human and animal experiments, opiate agonists stimulate food intake and antagonists depress it. It has been theorized that opioids specifically mediate palatability or the hedonic evaluation of food [32]. For example, in the 'taste reactivity test', morphine enhances taste palatability [33], and opiates seem to have preferential effects on fat and sugar intake [34]. Our work and that of others has shown that the ventral striatum is one key region where opioids modulate palatability. Opioid stimulation of the ventral striatum, which contains dense amounts of enkephalin, as well as mu, delta and kappa opiate receptors and also beta-endorphin [34–36], results in robust stimulation of feeding in non-deprived animals [37–39]. It is of interest to note that in contrast to the muscimol-induced effect described above, opioid-induced feeding within the accumbens is found in relatively widespread regions of the ventral striatum and to some extent even in the dorsal striatum [40]. We have used the synthetic, long-lasting, mu selective enkephalin analog D-Ala2, NMe-Phe4, Glyol5-enkephalin (DAMGO) to show that mu receptor stimulation of the nucleus accumbens increases intake of sucrose, salt, saccharin but not water in water-deprived animals [41]. This treatment also selectively increases fat intake when rats are given a choice between carbohydrate and fat [42]. Indeed, rats treated with accumbens opioids often consume 2–3 times as much fat as they normally would. Recent investigations show that this 'bingeing' on fat is mediated by a broadly distributed network of structures, including the nucleus of the solitary tract (important as a major taste and visceral relay), lateral and dorsomedial hypothalamus, and ventral tegmental area [43]. It is very interesting that the amygdala also appears to play an important role in the opioid-mediated enhancement of palatability and food consumption. Inactivation of the basolateral amygdala completely prevents the opioid-induced enhancement of fat intake, although the baseline levels of fat intake remain unchanged (M. Will, unpublished findings). The central nucleus also plays a role; in this region inactivation completely blocks fat intake, as has been shown previously for chow intake in food-deprived rats.

A further aspect of our recent work concerns alterations in enkephalin gene expression within striatal regions. We have found that daily consumption of a highly palatable food (for a limited period, 3 h/day) results in downregulation of striatal enkephalin gene expression, an effect not observed upon acute ingestion of fat [44]. What is intriguing is that others have shown that chronic morphine or ethanol consumption results in the same profile [45–47], further suggesting a shared substrate for the brain's adaptive response to highly palatable foods and drugs.

3.3. Comparison of opioid- and amino-acid coded neural systems in nucleus accumbens

The hypothesis driving the ongoing experiments in our laboratory related to feeding behavior is based in part on differentiating two key elements of striatal-hypothalamic circuitry, one mediated by opioids and the other by GABA/glutamate systems. Thus, it is useful to draw comparisons between the feeding profile elicited by mu opioid stimulation of the nucleus accumbens to that induced by $GABA_A$ receptor stimulation (or AMPA receptor blockade). The commonalities and dissimilarities provide a framework for this hypothesis. First, muscimol-induced feeding is highly anatomically selective, being confined to an anteroposterior corridor of medial shell (the only sector of striatum that projects directly to the lateral hypothalamus). DAMGO-induced feeding, on the other hand, displays a broad anatomical gradient; feeding can be elicited throughout core, shell, ventromedial and ventrolateral striatum and even in the dorsal striatum in high doses [40,48]. Second, muscimol infusion increases intake only if the stimulus is caloric (chow, sucrose, not salt or saccharin) and is not specific for the type of food based on macronutrients or palatability (muscimol increases carbohydrate and fat intake equally). DAMGO, in contrast, causes increased intake of all palatable substances and preferentially affects high-palatability foods such as fat and sugar. Third, DAMGO strongly increases bar-pressing and break point for palatable food in a progressive ratio test, whereas $GABA_A$ stimulation leaves this unchanged [49]. Fourth, muscimol-infusion into accumbens shell induces Fos expression in arcuate and PVN neurons [26,27], whereas DAMGO infusion does not affect these medial hypothalamic regions involved in energy balance and neuroendocrine/autonomic signaling [40] (although both treatments activate LH cells). DAMGO-induced feeding is blocked by temporary inactivation of the basolateral amygdala, whereas muscimol-induced feeding is not (unpublished). Finally, several similarities are striking; both types of feeding responses are completely blocked by inactivation of the central nucleus of the amygdala and or the lateral hypothalamus, suggesting some shared circuitry.

3.4. Dopamine plays an incentive motivational role in food intake ('wanting', exploration, learning)

Although the majority of our experiments with regard to food intake do not focus on dopamine, it is useful to consider its role within the ventral striatum in the context of food-related behavior. Dopamine, in the striatum and other critical forebrain regions such as prefrontal cortex, mediates incentive learning and reinforcement mechanisms associated with positive rewards (such as food in a hungry animal) [50]. This role is not selective for food but rather for signaling the salience of a variety of potential biological rewards, and cues that predict rewards, in the organism's environment [51]. Empirical work shows that activation of DA systems enables or increases behavioral responses necessary for obtaining a goal object, and antagonists of DA depress this goal-directed behavior. However, DA manipulations do not appear to modify the immediate hedonic impact of stimuli such as food, in contrast to opioid systems. Lesions of the DA system, neuroleptics, and amphetamine do not modify affective responses on the taste reactivity test, nor do they affect food intake per se, but they do potently affect the willingness of the animal to engage in behavioral actions aimed at anticipating or foraging for food [52]. For example, we have recently found that infusion of selective DA D-1 or D-2 antagonists into the accumbens core or shell has no effect on food intake in food-restricted rats, but potently suppresses locomotor responses associated with the motivational state of hunger [53]. Thus, DA appears to play a broad role in adaptive motor behavior and learning, rather than a specific role in food intake. As noted below, we do find a key role for dopamine, and particularly D1 receptors, in acquiring the instrumental response to gain food—in accordance with the general theory of D1 receptors being involved in learning processes.

3.5. Integrative role of striatal-hypothalamic circuits in the control of food intake

It is interesting to consider the role of the ventral striatum within the context of peripheral–central integration of food-related signals at the level of the hypothalamus. Long-term adiposity signals such as leptin and insulin, and intermediate-term signals such as ghrelin, glucose, CCK and other hormones or metabolites, are released from peripheral tissues and primarily affect hypothalamic nuclei known to be involved in energy homeostasis, such as the arcuate nucleus and paraventricular nucleus. However, circulating signals to the brain that are meant to eventually influence behavior must be, in the words of Mogenson, 'translated into action'. Thus, energy sensing systems must engage higher order motivational systems, instantiated in cortico-limbic and basal ganglia circuits, in order to enable adaptive behavioral responses. It is likely that pathways involving the amygdala, prefrontal cortex, and ventral striatum, together with these structures' links to the lateral hypothalamus, play a critical role in control of food motivation and feeding behavior. However, relatively little is known about how cortically based circuitry ('frontotemporal system' in the words of Swanson) [54] interacts with the hypothalamus in the control of appetite and food reward, and what precise role the ventral striatum has within this system. This is an important area of obesity and food intake research, as cognitive control, decision-making, and modulation of emotional responses in relation to the desire to eat are major determinants for the control of appetite in humans. Our current ideas involve the notion of 'behavioral control columns'—hypothalamic subsystems that have developed in evolution to specifically control different motivated

behaviors critical for survival—social (defensive/reproductive), ingestive, (feeding/drinking) and locomotor/exploratory behavior (Swanson). We propose that both opioid- and GABA/AMPA-mediated feeding responses eventually gain access to the feeding behavioral control column, but via different routes. Amino acid-driven feeding directly engages the ingestive behavioral control column (involving both medial and lateral hypothalamus, and also central nucleus of the amygdala). Here, certain ventral striatal neurons bearing GABA receptors and AMPA receptors, in a restricted medial ventral striatal region, are able to directly control brainstem feeding motor pattern generators. These cells act as 'sentinels' for the ingestive behavioral control column, and enable an animal to rapidly switch its behavior (and interrupt or turn off feeding) even as strong metabolic signals drive this column. Thus, an animal in negative energy balance will vigorously feed if food is obtained and the conditions are appropriate—but if the sensory context is suddenly altered (i.e. a hawk appears overhead), the animal needs to quickly alter its behavior. Opioids also eventually engage the ingestive behavioral control column, but via a different route. It is proposed that ventral striatal opioids specifically regulate 'food affect' or the positive subjective state derived from tasty high-calorie food (fat, sugar). This system in evolution ensured that pleasurable/rewarding motivational states would be associated with finding relatively scarce high-energy food sources. Striatal opioids, activated by hedonically driven eating, may broadly engage frontotemporal cortical circuits that contribute to the conscious perception of taste and positive emotion associated with certain foods, and this process may by-pass arcuate nucleus-based energy-balance set point control (thus explaining why some foods are consumed purely for taste or pleasure). Our recent work suggests that opioid-mediated feeding involves basolateral/frontal striatal circuits and eventual engagement of voluntary motor responses, and also indirectly engages the behavioral control column via the LH and central amygdala. Thus, both the opioid-based and amino-acid based striatal systems enable cortical information to gain access to and influence basic vegetative feeding circuits, but in different ways.

4. Neurons within the nucleus accumbens core are critical for plasticity related to motor learning

A second broad area of our research has focused on the role of the nucleus accumbens and its connected circuitry in appetitive instrumental learning. These experiments derived from earlier findings implicated the core subregion of accumbens in exploration and learning [55,56]. We have found, as discussed in detailed below, that glutamate, dopamine, and their respective receptors of the NMDA type and dopamine D1 type play a key role in initiating intracellular plasticity underlying adaptive motor learning, within the accumbens but also within key regions connected to the accumbens. Many studies have implicated the nucleus accumbens and its dopaminergic innervation in reward learning [2,6], and the basal ganglia in procedural learning and memory (the learning of actions, skills, or habits) [57–59]. Our work has contributed to this body of work and has aided the elucidation of the cellular mechanisms underlying striatal-based learning.

4.1. Instrumental learning: adaptive motor behavior

Before reviewing the main results, it is useful to consider the type of learning involved. Instrumental learning, in which an organism learns a new motor response in order to obtain a positive outcome (procurement of food when hungry, avoidance of danger or pain), is one of the most elementary forms of behavioral adaptation [60]. Through interchange with its environment, animals learn about the consequences of their actions, and thereby modify the current environment through new behaviors to produce more favorable conditions [61]. In a philosophical view of this ability, Yakovlev [62] wrote of the 'sphere of the motility of effectuation which creates changes in the world of matter about the animal, i.e. produces work through which the animal impresses itself upon the world of matter, e.g. locomotes, shapes and handles matter using his own body and parts of it as tools'. The law of effect, formulated by Thorndike [63], postulated that the probability of a response being made is increased when followed by a reward (called 'satisfaction' by Thorndike), and decreased when followed by 'discomfort.' This was to be somewhat distinguished from classical conditioning or Pavlovian learning, in which an animal made associations not between actions and outcomes, but rather between environmental stimuli and outcomes [64]. In reality, and in modern interpretations of learning theory, these processes are closely intertwined, both neurally and conceptually [3,65,66].

Imagine a hungry rat in a Skinner box. For the purposes of this discussion, I will present this scenario based on the way that our operant learning paradigm is scheduled. The rat goes in the box for 15 min/day for 10 or more days. During the first few sessions, a free food pellet is delivered, randomly, every so often. During this delivery there are auditory cues provided by the reinforcement dispenser and the 'ping' of the pellet dropping. Casual observations reveal that the rat displays a number of behaviors, and is motivationally and motorically activated (sniffs, rears, locomotes, in effect, 'forages,') because of its deprivation state and the arousing effects of the occasional reward. On the third session a lever is introduced into the box, never have been experienced by the rat before. During the next few sessions, the animal engages in foraging activities, continues to nose-poke for pellets but also randomly bumps into the lever. This action also produces delivery of the reward. Somehow, over the next few sessions, the animal comes to 'realize' (or so it seems) that its action produces

a good outcome. Once it registers this contingency, it improves its performance, focusing keenly on the lever at the expense of other extraneous activities.

Despite nearly a century of animal learning research and a quarter century of neurobiology research, very little is known about how such fundamental, novel adaptive actions develop. For the brain to accomplish this type of new learning, neural synapses must be modified, and the trace of action–outcome relations instantiated within brain circuitry. Although the neural and molecular basis of other forms of learning and memory has received much attention, such as Pavlovian fear conditioning and formation of declarative memories, relatively little is known about how memories of new voluntary motor actions (e.g. procedural memories) are formed at the systems and molecular level. Our work has addressed this question.

4.2. NMDA receptor activation in accumbens core, basolateral amygdala, and prefrontal cortex is required for instrumental learning

We were first interested in the behavioral role of glutamate, and AMPA and NMDA receptors, within accumbens subregions The work on AMPA antagonists in the shell led to the experiments on feeding described above. We found no effects on feeding with glutamate receptor manipulations in the core subregion. However, our earlier studies revealed quite profound learning deficits with AMPA or NMDA antagonists infused into the core [56,67]. Specifically, infusion of AP-5, a selective competitive NMDA receptor antagonist, into the nucleus accumbens core blocked acquisition of appetitive instrumental learning. We extended these findings and wondered whether the requirement for NMDA receptor activation was specific to the accumbens core or whether other associated brain regions were also involved. Somewhat to our surprise, we found that NMDA receptor blockade in both the lateral/basolateral amygdala and medial prefrontal cortex (mPFC) also strongly disrupts acquisition of lever-pressing for food [68]. Injections into dorsal or ventral hippocampus had no effect. Several important features of the AP-5-induced impairment should be noted: first, it is only early in learning that AP-5 has any effect; infusions into active sites once learning is established have no effect. This profile suggests that NMDA receptor activation is required for plasticity *only early in the learning process*. Further, control experiments show that AP-5 infusions that disrupt learning *have no effect on general motor behavior or on motivation for food*. These data have provided novel evidence for an essential role of NMDA-receptor mediated plasticity in several key brain regions in the acquisition of new motor learning, and suggest that disruption of glutamatergic activity in any part of a distributed network is enough to prevent learning. They complement an important literature implicating NMDA-receptor mediated mechanisms in the cellular basis of learning and memory and in long-term potentiation [69].

4.3. A key feature of plasticity within this network is coincident activation of D1 and NMDA receptors

Since there has been growing evidence both in cellular and molecular models for D1-NMDA interactions in the control of learning-related plasticity, we decided to investigate the potential role of such a putative interaction in our instrumental learning model. Our first objective was to assess the effects of intra-accumbens core infusion of the D1 receptor antagonist SCH-23390 in acquisition. However, a major obstacle to investigating the role of DA receptors in learning and to interpreting effects on behavior is the considerable motoric impairment that often results with DA receptor blockade (unlike with AP-5). Because we indeed found evidence for a motor impairment, we examined the effects of infusion of very low doses of the D1 antagonist as well as combinations of low doses of AP-5 and SCH-23390 [70]. Bilateral infusion of a relatively high dose of SCH-23390 (3 nmol or 1 μg) significantly impaired learning but also disrupted performance after the response was learned. Infusion of a much lower dose of SCH-23390 (0.3 nmol) or a much lower dose of AP-5 than used in the previous studies (0.5 nmol or 0.1 μg) had no effect on acquisition or performance. Most interestingly however, *co-infusion of the low doses of the NMDA and D1 antagonist strongly disrupted acquisition of instrumental learning*. Although in control tests infusion of the higher dose of the D1 antagonist reduced spontaneous motor behaviors as might be expected, the co-infusion of low doses had no effect on motor activity or feeding.

Given that the mPFC, like the striatum, receives a convergence of dopaminergic and glutamatergic inputs, we hypothesized that a similar interaction in the mPFC might underlie neural adaptation during learning. An experiment similar to the previous one was carried out with cannulae aimed at the mPFC [71]. In this study it was necessary to employ three doses of SCH-23390 as we found the mPFC to be exquisitely sensitive to D1 blockade. Both the 3.0 and 0.3 nmol doses of SCH-23390 infused into the mPFC impaired acquisition of the bar-press response, and the highest dose also reduced performance of the learned response. We then infused the lowest dose of SCH-23390 with a low dose of AP-5, 0.5 nmol, which had no effect on its own. The co-infusion markedly impaired acquisition of instrumental responding. This study represents the first direct test of the effects of PFC dopamine D1 receptor antagonism and concurrent D1 and NMDA receptor antagonism on acquisition of instrumental responding. We believe these results have broad implications for the cellular basis of neuronal adaptation during motor learning, and in light of the similar profile with the nucleus accumbens, provide evidence for parallel cellular mechanisms within discrete regions of the proposed distributed network. We are

currently investigating possible similar mechanisms within the amygdala.

4.4. Intracellular signaling mechanisms in both the accumbens and mPFC are necessary for initiation of molecular events leading to established instrumental learning

The proposed convergence of dopamine D1 and glutamatergic NMDA receptors suggests that these extracellular signals, perhaps conveying both motivational information and temporal information pertaining to sensory and motor events, trigger second messenger cascades that eventually affect transcription and translation. We have particularly focused on protein kinase A (PKA), which interacts with a number of transcription factors as well as other second messenger systems. PKA is implicated in many forms of plasticity, including long-term potentiation [72,73]. For example, intra-amygdala infusion of the selective PKA inhibitor Rp-cAMPS impairs long-term memory for contextual fear conditioning [74]. We conducted a series of experiments in which drugs interfering with protein kinase activity were infused into the nucleus accumbens in conjunction with the instrumental learning task [75]. It was demonstrated that treatment with the PKA inhibitor Rp-cAMPS impaired learning. Interestingly, infusion of an activator of PKA, Sp-cAMPS also impaired learning, suggesting that an optimal level of PKA within the accumbens is required. It was also shown that post-trial infusion of the broad-spectrum kinase inhibitor H7 dose-dependently impaired acquisition, indicating that long-term kinase activity lasting minutes or hours may be at least one important mechanism related to the plasticity involved in this type of learning.

In the recent study involving the mPFC, we also conducted an experiment with infusions of Rp-cAMPS into this region [75]. Here too we found a similar profile, in that bilateral infusion of the PKA inhibitor also impaired learning. Although not directly shown in our experiments, these results together with much data in the literature suggest that PKA may be an intracellular substrate for the D1-NMDA interaction. An example of supportive evidence is provided by the work of Gurden et al. [76], who showed that LTP at hippocampal–prefrontal synapses is dependent on NMDA and D1 receptor coactivation and on intracellular PKA.

4.5. Early consolidation of instrumental learning requires protein synthesis in the nucleus accumbens

It is well established that long-term memory formation is a temporally dynamic process requiring the activation of specific genes and de novo protein synthesis [77,78]. For example, infusion of the protein synthesis inhibitor anisomycin into the amygdala prevents consolidation of fear memories [79]. However, no studies have addressed the role of de novo protein synthesis within specific brain structures for consolidation of positively motivated instrumental behaviors. Given our work with D1-NMDA interactions and protein kinases, we hypothesized that post-trial blockade of protein synthesis within the nucleus accumbens would disrupt the consolidation of 'instrumental memory'. We recently found that post-trial infusions of anisomycin into the core but not the shell after the first 5 of 12 test sessions prevent the consolidation of long-term memory for the task [80]. Post-trial core infusions delayed by 2 or 4 h had no effect. Once the task was learned, behavior was no longer sensitive to intra-accumbens anisomycin. Our data provide the first demonstration that a form of procedural or 'habit' learning is dependent on translational events in a specific brain region. However, once the animal learns these associations and the behavior becomes firmly established, protein synthesis within accumbens is no longer required for the expression of the behavior, a profile that exactly mirrors the role of NMDA and D1 receptor activation.

4.6. Post-trial blockade of NMDA or D1 receptors does not affect acquisition of instrumental learning

Throughout the course of our studies, we have often wondered whether post-trial infusion of AP-5 or SCH-23390 would affect acquisition of instrumental responding. According to the main hypothesis driving the work, glutamate and dopamine within the distributed network are encoding current state—that is, the temporal pattern and context of events necessary for reinforcement learning. If this were true, post-trial blockade of D1 or NMDA receptors should have no effect on learning (unlike interference with kinases or protein synthesis, whose activity has a longer time-course). We have very recently conducted these experiments and have clear evidence that immediate post-trial infusion of AP-5 or SCH-23390 does not affect acquisition (results not yet published). These results fit nicely with the notion that dynamic and interactive activity of glutamatergic and dopaminergic circuits, only during the relevant contextual situation, is required for new learning. In contrast, within a constrained temporal window just following the context, intracellular transcription and translation contributes to long-term synaptic remodeling that is not dependent on context.

4.7. Investigation of other striatal and limbic sites suggests a broadly distributed network

Several recent sets of data have added evidence that a broadly distributed network subserves instrumental learning. First, we have been investigating the role of the central nucleus of the amygdala in this learning task. Since we previously found that AP-5 infusion into the basolateral amygdala impaired learning, it was of interest to ascertain any involvement of the closely adjoining central nucleus.

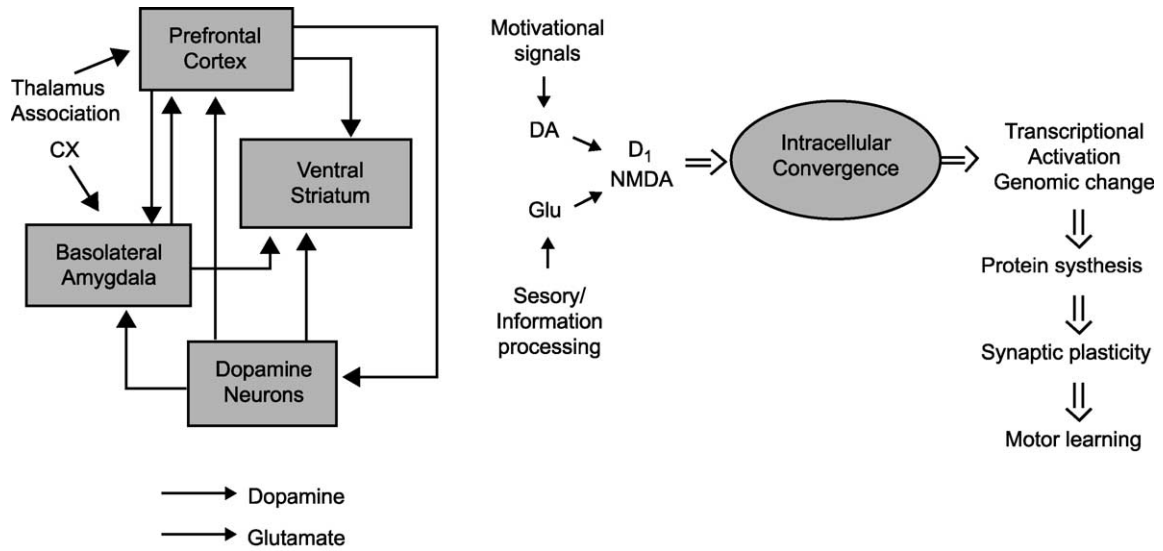

Fig. 2. A proposed model of glutamate–dopamine interactions within a distributed corticostriatal network in the control of appetitive instrumental learning. Activity and plasticity in this network are hypothesized to mediate synaptic alterations at nodes in this network during learning.

An experiment was carried out in which central nucleus infusions of AP-5 were made [81]. We indeed found that the AP-5 infusions prevented acquisition of responding. Interestingly, in contrast to all previous studies, performance was also markedly impaired by the AP-5 infusions given after the animals had acquired the task. A control experiment, however, revealed that central nucleus AP-5 infusions also affected spontaneous motor behavior and patterns of food intake; the drug actually augmented motor behavior and shortened feeding bouts. We have interpreted these data in the context of the proposed role for the central nucleus in attentional functions [82]. Recent studies also show that D1 receptors in the central nucleus play a role in the network [83].

Finally, several recent experiments examined the effects of AP-5 infusions into additional striatal subregions, in particular in the dorsolateral sector and a posterior region. The posterior region was originally chosen as a site control for the work with the amygdala. Much to our surprise, posterior, laterally placed striatal injections markedly impaired learning, and again, there was no effect on later performance of the learned response or on motor activity or feeding behavior [81]. In contrast, infusion of AP-5 into the dorsolateral sector of striatum had no effect on learning. What could possibly explain the difference in sensitivity to NMDA receptor blockade in these two sites? One hypothesis is that the critical regions within striatum involve only those regions innervated by amygdala, allocortex (prefrontal and perirhinal cortex) or mesocortex (piriform, entorhinal and hippocampus); in effect 'limbic-innervated striatum'. The negative result with the dorsolateral striatum, which receives afferents only from neocortex [84], may be very informative in this regard. In any case, our accruing results suggest that disruption of glutamatergic synapses anywhere in this network is enough to disrupt the plasticity processes that are necessary for learning. This very broad distribution suggests that glutamate-driven network synchrony or some sort of global cortico-striatal population code (perhaps necessary for assessing the temporal relationship of sensory and motor events) is a critical factor underlying this form of adaptive learning. Several neural computational models emphasize the suitability of cortico-striatal networks for such learning [85–88]. A schematic model of the potential interactions between glutamate and dopamine pathways within this network is shown in Fig. 2.

5. Conclusions

The above account summarizes the work of this laboratory over the past decade or so, which has helped to elucidate the functions of the nucleus accumbens and its related circuitry in reward-related behavior. Work with a number of different behavioral paradigms has shown that accumbens neurochemical systems play specific and differentiable roles in different aspects of food seeking and food intake, and part of this function depends on integration with amygdala and lateral hypothalamus. We propose that the nucleus accumbens integrates information related to cognitive and emotional processing with hypothalamic mechanisms mediating energy balance. This system as a whole enables complex hierarchical control of adaptive ingestive behavior. It is noteworthy that striatal opioid peptides appear to regulate the affective responses to food; this mechanism may provide insights into addiction, as many drugs of abuse (e.g. opiates, cannabinoids, alcohol) exert their effects through activation of the endogenous opioid system. We have also studied acquisition of lever-pressing for food in rats and shown that activation of

glutamate NMDA receptors, within broadly distributed but interconnected regions (nucleus accumbens core, posterior striatum, prefrontal cortex, basolateral amygdala), is critical for such learning to occur. This receptor stimulation triggers intracellular cascades that involved protein phosphorylation and new protein synthesis. It is hypothesized that activity in this distributed network (including D1 receptor activity) computes coincident events and thus enhances the probability that temporally related actions and events (e.g. lever pressing and delivery of reward) become associated. Such basic mechanisms of plasticity within this reinforcement-learning network also appear to be profoundly affected in addiction. Further work will explore the cellular and systems role of the nucleus accumbens in appetitive behavior.

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