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REVIEW

Discrete neurochemical coding of distinguishable motivational processes: insights from nucleus accumbens control of feeding

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Abstract
Background and objectives The idea that nucleus accumbens (Acb) dopamine transmission contributes to the neural mediation of reward, at least in a general sense, has achieved wide acceptance. Nevertheless, debate remains over the precise nature of dopamine's role in reward and even over the nature of reward itself. In the present article, evidence is reviewed from studies of food intake, feeding microstructure, instrumental responding for food reinforcement, and dopamine efflux associated with feeding, which suggests that reward processing in the Acb is best understood as an interaction among distinct processes coded by discrete neurotransmitter systems.
Results In agreement with several theories of Acb dopamine function, it is proposed here that allocation of motor effort in seeking food or food-associated conditioned stimuli can be dissociated from computations relevant to the hedonic evaluation of food during the consummatory act. The former appears to depend upon Acb dopamine transmission and the latter upon striatal opioid peptide release. Moreover, dopamine transmission may play a role in 'stamping in' associations between motor acts and goal attainment and perhaps also neural representations corresponding to rewarding outcomes. Finally, evidence is reviewed that amino acid transmission specifically in the Acb shell acts as a central 'circuit breaker' to flexibly enable or terminate the consummatory act, via descending connections to hypothalamic feeding control systems.
Conclusions The heuristic framework outlined above may help explain why dopamine-compromising manipulations that strongly diminish instrumental goal-seeking behaviors leave consummatory activity relatively unaffected.

Keywords Appetite · Reward · Opioid · Motivation · Glutamate · GABA · Food intake · Dopamine · Basal ganglia · Arousal

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Introduction

The role of dopamine in the neural mediation of reward is well accepted; indeed, this idea has been called "one of the most ubiquitous and popular hypotheses in the history of neuroscience" (Salamone and Correa 2002). Nevertheless, as is often the case with influential scientific paradigms, the actual component propositions of this idea have engendered intense controversy extending to the fundamental definitions of concepts such as reward and reinforcement. This literature is prodigious, and there have been many excellent reviews and theoretical articles promulgating different approaches to the understanding of dopamine's role in reward (for example, see Beninger and Miller 1998; Berridge and Robinson 1998; Ettenberg 1989; Horvitz 2002; Ikemoto and Panksepp 1999; Kelley et al. 2005b; Koob and Le Moal 2001; Salamone and Correa 2002; Schultz 2002; Smith 2004; Wise 2004). The present article is not an exhaustive review of this literature but rather outlines the conceptual roots and evidentiary support for what is gaining acceptance as a prevailing heuristic framework regarding dopaminergic function. This framework holds that 'reward' is best understood, from a

neurobiological perspective, as a construct encompassing several diverse motivational processes, including those conferring direction and vigor to goal-directed instrumental behaviors and those associated with affective evaluations of commerce with the goal object that contribute to the maintenance of unconditioned consummatory behavior sequences. The latter process also influences the organization of subsequent behavior in relation to the same goal, which is a defining characteristic of 'reinforcement'.

Although the idea that reward consists of several potentially dissociable components is not new, in recent years, evidence has accumulated suggesting that these discrete functions are subserved by distinct brain sites and neurotransmitter systems and, perhaps most surprisingly, by distinct neurochemical systems within the *same* brain site, the nucleus accumbens (Acb). While it is true that current competing theories of dopaminergic function diverge on several points, a generally agreed-upon theme has emerged in which dopamine is ascribed a role in mediating motor activation and response vigor associated with seeking after goals, although the mechanism underlying this function is under debate. Evidence has also accrued suggesting that the link between dopamine transmission and the ability of commerce with the goal object to sustain unconditioned consummatory behavior, such as eating, is far weaker. Dopamine may also play a role in learning/plasticity-related processes that facilitate action–outcome associations and the formation of internal representations related to the experience of the consummatory act. Much of the support for these views derives from studies of feeding behavior and food reward. The aim of this review is to provide an overview and evaluation of this evidence and to propose new frameworks for further investigations into the neural basis of appetitive motivation.

Historical perspective

Two of the most influential findings relevant to current theories of appetitive motivation were the discovery of brain sites that would support electrical self-stimulation (brain stimulation reward or BSR) and the identification of the ascending monoamine projections. These discoveries, particularly the former, contributed to a shift in theories of appetitive motivation in which older models centering on drive-reduction gave way to incentive motivation theories. In this regard, the recollections of P. Milner (the codiscoverer, along with J. Olds, of BSR) are telling (note the implicit linkage between the concept of reinforcement and internal affective states):

> Jim's [James Olds'] first thought was that he had a perfect refutation of the drive-reduction theory of reinforcement, which was dominant at that time. His argument was that stimulation increased the level of brain activity, and was at the same time reinforcing. Reinforcement could therefore hardly be due to the reduction of anything; it must involve an increase of positive affect, pleasure in fact (Milner 1989).

Thus, the discovery of central BSR substrates provided strong impetus for the idea that 'reward' could be understood in terms of the activation of a specialized brain substrate, even in the absence of an identifiable physiological drive (Olds et al. 1971; Olds and Milner 1954).

The next logical step was to hypothesize that this central reward substrate was accessed by 'naturalistic' stimuli, such as those associated with eating, drinking, and sexual behavior, which serve as powerful reinforcers of instrumental behavior. That a correspondence existed between the capacity of BSR to reinforce various types of instrumental responding, such as lever pressing and maze running, and the ability of BSR to elicit spontaneous locomotion, feeding responses, and other 'fragments' of appetitive behaviors did not escape the notice of Olds, Milner, or numerous BSR researchers that followed (for example, see Blundell and Herberg 1973; Hoebel and Teitelbaum 1962; Margules and Olds 1962; Mogenson 1969; Stephan et al. 1971; Valenstein and Cox 1970). This correspondence between the brain sites that support BSR, and those at which stimulation elicits specific patterns of unconditioned motivational arousal and appetitive-like responses, influenced subsequent ideas regarding the biological aspects of reinforcers. Here was evidence for a link between the spontaneously emitted behaviors that presumably increased the chances of obtaining the goals required for survival and the process by which the acts leading to successful goal attainment were reinforced. Thus, two distinct classes of phenomena, appetitive behaviors and instrumental learning, could now be linked under the same, biologically based, explanatory framework (Glickman and Schiff 1967). This synthesis profoundly influenced the evolution of incentive-based models of motivation.

The second major development, which occurred not long after the discovery of BSR, was the characterization of monoamine systems in the brain (Anden et al. 1964; Carlsson et al. 1965; Hillarp et al. 1966). It became known that Parkinsonism resulted from the loss of the ascending nigrostriatal dopamine projections (Hornykiewicz 1966); thus, the role of dopamine in governing extrapyramidal motor function became a dominant paradigm with which to understand the role of this monoamine in CNS function (Fuxe et al. 1977; Ungerstedt and Arbuthnott 1970). The appreciation of dopamine's role in motoric processes, along with the elegant studies tracing the trajectories of the ascending monoaminergic projections, led to a major

challenge to E. Stellar's dual center model of hypothalamic function, which was, at the time, a fundamental heuristic model with which to understand and investigate the neural basis of motivational processes. This theory posited the existence of discrete hypothalamic control centers for the initiation and termination of distinct categories of motivated behavior, such as feeding, drinking, sexual behavior, etc., as supported by early observations concerning the profound aphagia resulting from electrolytic lateral hypothalamic (LH) lesions and hyperphagia resulting ventromedial hypothalamic lesions (Stellar 1954). Upon the realization that the LH lesions were typically placed directly in the path of the monoamine projections along the medial forebrain bundle, several studies were undertaken to evaluate the possible contribution of the destruction of these pathways to the LH syndrome. It was soon determined that lesions of the ascending dopamine system or pharmacological blockade of dopamine receptors recapitulated many (but not all) of the features of this syndrome, raising a serious challenge to the idea of intrinsic hypothalamic centers as originally conceptualized by Stellar (Fibiger et al. 1973; Marshall et al. 1974; Ungerstedt 1970; Zis and Fibiger 1975). As will be discussed later, Stellar's view has been replaced with models focusing on distributed forebrain networks modulated by the ascending monoamines, with a recent important hypothesis that specific nodes within the diencephalon and brainstem, under regulation by corticolimbic output, act as controllers for coordinating the motoric, autonomic, and endocrine 'building blocks' of motivated behavior (Swanson 2000). Thus, Stellar's basic idea of functional hypothalamic domains retains great significance for modern motivational theories, although not exactly as originally conceptualized.

It is at the convergence of these two great neuroscience discoveries, BSR and the role of dopamine in processes of forebrain sensorimotor control, that the roots of current dopamine theories of motivation can be discerned. It was clear from early studies that many effects of dopamine loss could be attributed to gross sensorimotor deficits (Fibiger et al. 1976; Marshall et al. 1974; Ungerstedt and Ljungberg 1974). However, it was also found that dopamine-blocking drugs significantly depressed operant responding for BSR, leading to an additional (but not mutually exclusive) idea: that dopamine played an important role in governing the function of the central reward substrate (Fouriezos and Wise 1976; Liebman and Butcher 1973; Lippa et al. 1973). How, though, to prove the latter hypothesis, given the clearly evident motor impairments associated with interrupting dopaminergic function? The quest to separate 'reward' from 'motor' processes came to dominate the study of dopaminergic function for at least a decade, and many investigators contributed to this extensive literature. One of the seminal observations in this regard was made by Wise et al. (1978a,b). These investigators undertook detailed analyses of dopamine antagonist-induced depression of operant responding for food or BSR. Careful analyses of within-sessions response patterns revealed that while there was a clear decrement in total operant responding for the whole session, the time-course of responding exhibited a pattern whereby response rates were normal (or higher than normal) at first and then decreased progressively over the course of the sessions (Fouriezos et al. 1978; Wise et al. 1978a,b; Yokel and Wise 1975). Moreover, between-session responding progressively declined in a manner that could not be accounted for by pharmacokinetic factors (such as accumulation of residual drug). These effects strongly resembled those seen under conditions of extinction, and because under certain conditions, response rates were indistinguishable from controls, were difficult to explain as pure motor deficits. That dopamine receptor antagonism produced extinction-like effects contributed to the formulation of the profoundly influential 'anhedonia hypothesis' of dopamine function, which posited that central dopaminergic substrates played a crucial functional role in the central reward system and thereby mediated the reinforcing effects both natural and artificial (i.e., drugs, BSR) rewards (Wise et al. 1978a).

Perhaps because of the prevailing theoretical paradigm linking the incentive properties of goal objects and the process of reinforcement under the common umbrella of a unified biological reward substrate, the concepts of reinforcement, reward, and even the subjective experience of pleasure are somewhat conflated in the original formulation of the anhedonia hypothesis. Note, for example, that the term 'anhedonia' (lack of pleasure) is used to designate a theory concerning the biological basis of *reinforcement*, and in its original inception, the anhedonia hypothesis posits that the effects of dopamine antagonism "take the 'goodness' out of food. (Wise et al. 1978a)." Although in more recent revisions of the anhedonia hypothesis the putative role of dopamine in hedonic-like reward processes has been de-emphasized (Wise 1982, 1985), the originally postulated linkage between reward (in the sense of those brain functions that mediated the reinforcing properties of appetitive goal objects and were linked to internal hedonic states) and dopamine raised the question of whether effects consistent with removing the "goodness" of food or other goal objects could be seen in behavioral tests assaying unconditioned consummatory responses, such as free food intake or the consummatory aspects of the sexual response. Inquiries along these lines have indicated that the answer is 'no', or, at least, 'not nearly as much', and over the years, the relative sparing by dopamine-compromising manipulations of consummatory responses has become sufficiently well accepted as to be incorporated into many current theories of dopamine function.

Relative insensitivity of consummatory feeding responses to dopamine-compromising manipulations

Even in the early years in which a strong case for dopaminergic involvement in reward-related process was forming, data were emerging to suggest that neurobiological ideas of 'reward' and 'reinforcement' required reformulation in a manner that could account for the fact that dopamine-compromising manipulations, which strongly diminished (in a purportedly extinction-like fashion) learned operant behaviors such as lever pressing for food reward, seemed to at least partially spare unconditioned consummatory behaviors[1] such as eating (for a discussion about conceptual differences between reinforcement and reward, see White 1989). The list of such studies is extensive; what follows represents just a small sampling with an emphasis on studies of the mesolimbic dopamine system and Acb. An early study showed that hypothalamic 6-hydroxydopamine (6-OHDA) lesions that interrupted the ascending dopaminergic projections did not produce aphagia beyond an initial 1-week recovery period (Ervin et al. 1977). In a later study, Koob et al. (1978) showed that Acb 6-OHDA lesions in rats did not alter food intake in the home cages and actually *increased* food intake (while decreasing locomotor activity) in food-deprived rats tested in discrete activity monitoring sessions. These effects have been replicated in studies employing injections of dopamine antagonists directly into the Acb; specifically, intra-Acb infusions of either haloperidol or subtype-selective dopamine antagonists either had no effect on or increased food intake and lengthened feeding bouts while decreasing the heightened locomotor activation associated with food deprivation (Bakshi and Kelley 1991a; Baldo et al. 2002). Similarly, Tombaugh et al. (1979) showed that systemic treatment with the dopamine antagonist, pimozide (the drug used most extensively in earlier studies of the extinction-like effects of dopamine blockade), increased the latency to initiate feeding in food-deprived rats, but did not alter total consumption, although see an experimental rebuttal in Wise and Colle (1984). It was also shown that that doses of pimozide, which markedly reduced feeding preparatory responses (conditioned stimulus-cued entries into a feeding niche), failed to diminish food intake once food was contacted (Blackburn et al. 1987). Another feeding preparatory behavior, food hoarding, was eliminated by mesolimbic 6-OHDA lesions that produced little effect on total food consumption (Kelley and Stinus 1985). A striking demonstration of the dissociable effects of dopamine-compromising manipulations on food-seeking vs consummatory behaviors was provided by the 'concurrent choice' paradigm in which rats are given a choice between lever pressing for a preferred food, or eating a less-preferred, but freely available food available on the cage floor (Cousins et al. 1994; Nowend et al. 2001). Dopamine-specific lesions of the Acb decreased the preference to lever press for the preferred food, yet animals readily ingested *even more* of the freely available food than controls. Finally, in contrast to results from operant responding-based tests of extinction-like dopamine antagonist effects, Gramling et al. (1984) reported that a pimozide dosing regimen, similar to that used by Wise et al. (1978a), failed to produce within-session or between-session declines in licking for sucrose, as did replacing the sucrose solution with water for vehicle-treated rats, although pimozide tended to decrease somewhat overall licking rate and increase inter-lick intervals in a manner consistent with a mild motoric impairment. The authors concluded that "...there was little evidence that the pattern of responding was 'extinction-like'" (Gramling et al. 1984, p 623). Note that in all these studies, effects of dopamine lesions or antagonist treatments affected parameters other than actual consumption, thereby providing a positive control for the effectiveness of the dopamine-compromising manipulations. While it is true that massive 6-OHDA lesions or very high doses of dopamine antagonists can reduce consummatory measures of intake, it has been cogently argued that these deficits are likely due to profound performance impairments, perhaps arising in non-accumbens striatal territories controlling aspects of skilled motor function (Bakshi and Kelley 1991a; Salamone and Correa 2002). For example, local dopamine receptor blockade or 6-OHDA lesions in the ventrolateral striatum, a site governing oral motor control, strongly diminish feeding (Bakshi and Kelley 1991a; Jicha and Salamone 1991; Salamone et al. 1993).

[1] For the purposes of this review, we will use the terms 'appetitive' and 'consummatory' to distinguish behaviors leading up to goal attainment from those that involve actual commerce with the goal object (Craig 1918). Unless otherwise specified, the term 'appetitive phase' is meant, in a broad sense, to include specific preparatory behaviors, instrumental goal-seeking behaviors, as well as the spontaneous investigatory responses characteristic of motivational arousal. The term 'consummatory phase' is used in the spirit of Craig's "phase II" of a motivated behavior "cycle" in which the "reception of the appeted stimulus" is followed by a "consummatory reaction in response to that stimulus" (see Craig 1918, p 101). The appetitive/consummatory distinction can refer to the temporal organization of behavior in which the consummatory reaction is that which terminates the behavioral sequence but can also refer to qualitative differences between the flexible behaviors leading up to goal attainment vs the relatively stereotyped action patterns observed during commerce with the goal (Craig 1918). Our usage conforms more to the latter theme. Hence, we use 'consummatory phase' to designate the period in which repetitive, relatively inflexible motor acts occur during actual contact with the food; chewing, licking, swallowing, etc. In the context of ingestive behavior (which involves actual consumption), the term 'consumatory' is sometimes preferred to 'consummatory' (see Smith 1995), but we will use the latter term simply to imply the generalizability of our proposed framework to other motivated behaviors, such as sexual behavior.

Even experimental paradigms that have yielded results favorable to the anhedonia hypothesis have failed to show a dopamine antagonist-induced reduction in actual food intake. For example, studies of the partial reinforcement extinction effect (PREE) by Ettenberg and Camp (1986a,b) have been cited as representing some of the strongest evidence in support of extinction-like effects of dopamine receptor antagonism (Smith 1995; Wise 2004). In this paradigm, animals learn to traverse a runway to receive food pellets and are then tested under extinction conditions. Subjects trained under a partial reinforcement contingency (i.e., food availability on some trials but not others) require more trials to develop the marked increases in latency to reach the goal box that are characteristic of extinction. Rats that are given food on each trial during training, but receive dopamine antagonist treatments before the onset of some of these trials, show a resistance to extinction similar to that seen in animals receiving partial reinforcement. This finding has been interpreted as demonstrating a similarity between 'no reward' and 'reward under dopamine receptor antagonism'. Nevertheless, these investigators have repeatedly observed that rats under dopamine receptor antagonism typically eat all the food available in the goal box (Ettenberg and Camp 1986a; Horvitz and Ettenberg 1988; McFarland and Ettenberg 1998). This dissociation highlights a crucial difference between processes related to the maintenance of consecutive responses *within* a consummatory behavior sequence (i.e., eating), and those aspects of the consummatory act that serve to influence *future* behavioral responses directed toward acquiring the same goal object. The PREE results described above would suggest that dopamine transmission is involved in the latter but not the former. A conceptually related result was obtained by Wise and Raptis (1986), who showed that systemic pimozide administration affected food intake only very slightly on the first of several test days but strongly reduced feeding on subsequent days. Control experiments ruled out a progressive accumulation of drug. This extinction-like pattern suggests that consummatory behavior per se is not dependent upon intact dopamine transmission in an obligatory way but that dopamine mediates the ability of experience with food to influence future ingestive behavior. The finding that dopamine receptor blockade fails to diminish food consumption while producing other motivational effects in the runway paradigm has been replicated in several studies. For example, it was shown that intra-Acb infusions of the dopamine receptor antagonist, *cis*-flupenthixol, at a dose that significantly decreased running speed, failed to reduce sucrose consumption in the goal box (Ikemoto and Panksepp 1996) and that a low dose of systemic *cis*-flupenthixol, which diminished anticipatory rearing associated with scheduled food delivery, altered neither the speed to traverse the runway nor total food consumption (Barbano and Cador 2006).

A noteworthy exception to this position has been provided by G. Smith and colleagues, who showed in several studies that dopamine antagonist treatments altered aspects of sucrose sham feeding in a manner consistent with an antagonist-induced decrement in the rewarding properties of sucrose taste. Nevertheless, additional experiments demonstrated that a dose of the dopamine D2 receptor antagonist, raclopride, which reduced sucrose intake by 50%, failed to alter licking cluster size and local licking rate (Schneider et al. 1990). This result was interpreted as ruling out motor impairments as an explanation for the reduction in sucrose intake, although it should be noted that dopamine receptor antagonism impairs parameters such as lick force, tongue extension, and lick duration (Fowler and Das 1994; Jones and Mogenson 1979). In contrast, other studies demonstrated that very high doses of raclopride or the dopamine D1 receptor antagonist, SCH 23390, failed to diminish intra-oral sucrose intake in neonatal rat pups (Tyrka et al. 1992; Tyrka and Smith 1991). Significant decreases in intake were obtained with these two drugs in a different paradigm, the independent ingestion test; however, even at very high doses, intake was not completely abolished (at least at an early prenatal time point). Taken together, these results suggest that, at the very least, several important features of the consummatory act of licking are preserved under severe dopamine receptor antagonism.

Neurochemical techniques assaying dopamine release have yielded complex and often contradictory results with regard to dopamine's role in the context of appetitive and consummatory feeding behaviors (Hajnal et al. 2004; Hernandez and Hoebel 1988; Kiyatkin and Gratton 1994; Phillips et al. 1993; Radhakishun et al. 1988; Roitman et al. 2004; Wilson et al. 1995). Yet, in accordance with the results from the dopaminergic lesion and antagonist studies described above, evidence is emerging (particularly with more recent methods possessing high temporal resolution) that, at least in certain Acb territories, phasic dopamine release is more closely linked to the appetitive phase than the consummatory phase of feeding. One early study demonstrated that dopamine turnover in the Acb, as indexed by ratios of dopamine to the dopamine metabolite, 3,4-dihydroxy phenylacetic acid, was increased by exposure to a food-related conditioned stimulus, but not by feeding itself (Blackburn et al. 1989). A microdialysis study by Salamone et al. (1994b) demonstrated an important dissociation between augmented Acb dopamine release during FR1 responding for food reward and a lack of enhanced release during consumption of freely available food. This group also showed increased Acb dopamine release during schedules of periodic food presentation that were accompanied by high levels of locomotor activity; however, elevated dopamine levels were not observed with schedules associated with lower levels of activity or during

massed food presentation, although all the food was eaten in every condition (McCullough and Salamone 1992). In contrast, other microdialysis studies have revealed substantial increases in dopamine efflux in association with the feeding consummatory act, but not during periods of food anticipation. For example, one study showed markedly augmented dopamine release during the consumption of a palatable chocolate liquid in rats, but little or no increase during the pre-feeding period in which the animals were placed behind a screen partition that led into the testing chamber (Wilson et al. 1995). Note that these animals displayed considerable levels of anticipatory behavior while waiting behind the screen ("...sniffing, locomotion, and rearing, as well as nose-poking through the mesh of the screen partition"; Wilson et al. 1995, p 5171). Using similar testing procedures, it was found that intra-Acb dopamine levels were elevated during both the anticipatory and consummatory stages of the experiment, with larger increases seen during the consummatory phase (Ahn and Phillips 2002).

These discrepancies are difficult to resolve, but potential directions for a solution are provided by an important series of experiments by Di Chiara and colleagues (Bassareo et al. 2002; Bassareo and Di Chiara 1999), which demonstrate important differences in dopamine dynamics in the Acb core vs shell (note that the earlier microdialysis work did not attempt to distinguish these subregions and likely sampled mainly the core). These investigators have shown that feeding-associated dopamine release differs markedly in the Acb core compared to the Acb shell with regard to several key parameters including palatability and familiarity. Specifically, significant increases in dopamine efflux were detected in both the Acb core and shell when rats sampled a palatable chocolate solution for the first time, but large increases were noted *only in the Acb core* when the solution was resampled 24 h later (Bassareo et al. 2002). Similar results were obtained with a palatable salty snack food. These results indicate that phasic elevations in dopamine levels, at least in the Acb shell, are not a necessary condition and/or concomitant of the feeding consummatory act. The importance of novelty vs predictability of reward in determining functional responses of the dopamine system has also been demonstrated in an influential series of ventral tegmental area (VTA) electrophysiological recording studies in primates (Fiorillo et al. 2003; Hollerman and Schultz 1998; Mirenowicz and Schultz 1994; Schultz et al. 1993). For example, it was demonstrated that the activity of purported dopaminergic VTA neurons appears to track actual ingestion in the early stages of training (Schultz et al. 1993). As training progresses, increased firing of VTA units becomes associated with conditioned stimuli predicting juice delivery (Schultz et al. 1993), or with unexpected reward delivery (Hollerman and Schultz 1998), rather than with consumption itself. These findings are in good agreement with data suggesting that while the Acb is recruited in early motor learning, over-learned motor habits or aspects of skilled motor function depend more upon striatal territories outside the Acb (Bakshi and Kelley 1991a,b; Hernandez et al. 2005; Lehericy et al. 2005; Robbins and Everitt 2002; Salamone et al. 1993). Taken together, the microdialysis findings of Di Chiara and colleagues and the electrophysiological results of Schultz and coworkers highlight the possibility that differences in dialysis probe placements in the Acb core vs shell, and/or the degree of acclimation to testing procedures, may have contributed significantly to conflicting findings in the literature on Acb dopamine release during the appetitive and consummatory phases of feeding. Wilson et al. make a similar point when attempting to reconcile their observed selectivity of dopamine release to the consummatory phase of feeding with a previous result demonstrating increases in dopamine turnover specifically during the anticipatory phase (i.e., Blackburn et al. 1987). The authors argue that their results could be "...viewed as being consistent with Schultz's hypothesis if it is assumed that rats were at a relatively early stage of training at the time of microdialysis" and that it could be hypothesized "...that with continued training the increase in accumbal dopamine release would gradually shift from the consummatory to the anticipatory phase of the test session" (Wilson et al. 1995, p 5176) Note that this interpretation implies that elevated dopamine levels (at least in the Acb) are not a necessary correlate of the consummatory act, in contrast to what one might predict if dopamine transmission mediated the rewarding aspects of ingestion.

Another issue to consider is that the relatively low temporal resolution of the dialysis technique relative to the individual behavioral components of ingestion may cloud interpretations regarding the link between phasic dopamine release and performance of the consummatory act. More recent studies that employ in vivo voltammetry to detect dopamine release on the order of seconds or fractions of a second suggest that intra-Acb dopamine release is not elevated, and indeed may actually be depressed, during food consumption. For example, it was shown that, in experienced rats, dopamine levels in the Acb (with electrode placements mainly in the core) peaked at the point at which rats emitted a lever press for condensed milk reward, but rapidly decreased to *below* baseline levels during the period in which the animals were ingesting the milk (Richardson and Gratton 1996). Similarly, a recent study employing fast scan cyclic voltammetry, in which dopamine signals were sampled every 100 ms, showed that dopamine levels rose rapidly upon presentation of discriminative stimuli in an intra-oral sucrose self-administration

paradigm and that a lever press response was emitted at the peak of this phasic increase in dopamine levels (Roitman et al. 2004). However, the dopamine signal quickly declined to baseline levels during the actual consumption of the sucrose. Although the authors suggest that the dopamine decrease to below baseline levels observed in the Richardson and Gratton study may have been an artifact related to local tissue pH changes, both studies are in remarkable agreement that although food-seeking behavior is accompanied by a tightly time-locked (on the order of seconds) increase in the dopamine signal, actual food consumption is characterized by a return of the signal to baseline or below baseline levels.

Interpretations of the resistance of feeding consummatory responses to dopamine-compromising manipulations

The observation that interrupting dopamine transmission appears to produce a much smaller effect on feeding behavior relative to preparatory activities or instrumental food-seeking behaviors has achieved such wide acceptance that many current theories of dopamine function make either implicit or explicit reference to this idea (e.g., Berridge and Robinson 1998; Ikemoto and Panksepp 1999; Kelley et al. 2005b; McFarland and Ettenberg 1998; Salamone and Correa 2002; Schultz 2002). For example, in a recent article defending aspects of the anhedonia hypothesis, R. Wise states that "...[dopamine antagonists] do not immediately compromise the initiation of well-learned response habits, or even consummatory behavior" (Wise 2004, p 1). Inquiries into the dopaminergic control of sexual behavior have arrived at essentially the same conclusion, i.e., that the consummatory phase of the sexual response is affected to a far lesser degree by dopamine-compromising manipulations than the appetitive phase (Everitt 1990; Pfaus and Phillips 1991). However, this relative sparing of consummatory responses by dopamine-compromising manipulations raises an important question, namely, how can dopamine receptor blockade produce effects reminiscent of attenuated reinforcement, such as, for example, the PREE, and yet leave the consummatory act relatively unaffected? If, for example, bites of food are no longer reinforcing, why is this not reflected as changes in the amount of food that the animal actually eats?

Relevant to these questions is the previously mentioned distinction between two processes: the maintenance of consecutive behavioral responses within a given sequence of consummatory behavior and the ability of the consummatory act to affect the organization of future behaviors toward the goal object being sampled. There is little disagreement that the latter process represents an important aspect of reinforcement, but what about the former? Is the topography of individual motor acts during the consummatory phase organized such that each behavior is contingent upon preceding responses? The answers to these questions have important implications not only for understanding the role of dopamine in neurobiological processes of reinforcement and reward but also the manner in which the hierarchical control of motivated behaviors is instantiated in the brain. Current theories of dopamine function address these questions in various ways; however, two overarching perspectives have emerged. One emphasizes the quantitative differences between the automatic, patterned ingestive behaviors comprising the feeding consummatory act and more complex instrumental food-seeking behaviors, in terms of motoric requirements of effort. This is the anergia hypothesis of Salamone and colleagues (Salamone and Correa 2002; Salamone et al. 1997), also see Neill and Justice (1981), which holds that dopamine's role in motivational processes can be seen as the 'energizing' of motor output, such that the animals' willingness to expend effort in goal-seeking behaviors is increased. This idea is supported by several important findings. First, food-deprived rats given a choice to climb over an obstacle for a large food reward, or traverse an open alley for a fewer pellets, will typically choose the former. Intra-Acb 6-OHDA lesions produced a shift toward the 'easier' option; importantly, however, when lesioned animals were given a choice between climbing the obstacle for a small food reward vs receiving no reward in the open alley, the lesioned rats chose to climb the obstacle (Salamone et al. 1994a). In each of these circumstances, the lesioned animals ate all available food pellets. Second, as previously discussed, lesioned animals displayed a preference for eating a less-preferred food scattered on the floor, instead of lever pressing for a preferred food (as do control subjects), in a concurrent choice paradigm (Cousins et al. 1994). Finally, intra-Acb dopamine lesions strongly diminished lever pressing in operant tasks with large response requirements, but not in tasks with low requirements (such as a continuous reinforcement schedule), in a manner resembling ratio strain (Aberman and Salamone 1999; Correa et al. 2002; Mingote et al. 2005; Salamone et al. 2001). These findings were interpreted as indicating that Acb dopamine mediates a computation resembling a *choice* between different behavioral options with varying cost/benefit ratios, with 'cost' referring to effort requirements, and 'benefit', the rewarding properties of the goal. Implicit in this hypothesis is the idea that the feeding consummatory act represents a type of behavior with a low cost in terms of motor effort; thus, just as lesioned animals choose to respond under low but not high fixed ratio schedules, so they also choose the motorically less demanding act of free-

feeding over lever pressing or obstacle climbing. This perspective stresses what the consummatory act is *not* (i.e., it is not a complex motor act demanding the expenditure of great effort), rather than what it is.

More ethologically based frameworks emphasize qualitative differences between the appetitive phase and consummatory phase, with the idea that these differences make it intuitively appealing to hypothesize mediation by distinct brain circuits and neurotransmitter systems. Perhaps most obviously, behaviors during the appetitive phase are guided by internal representations of the goal (or the expected characteristics of the goal), while the consummatory phase is influenced by the sensory feedback and internal signals accompanying actual commerce with the goal. As discussed previously, this framework applies to the classic distinction of 'appetitive' and 'consummatory' phases of behavioral sequences (Craig 1918) and, on a priori principles, would strongly suggest that the two phases are governed by at least partially nonoverlapping neural substrates. A recent influential theory of dopamine function, the incentive salience hypothesis (Berridge and Robinson 1998), is in general accord with this idea. This hypothesis posits that dopamine transmission is involved in assigning motivational significance to stimuli, enabling them to 'grab attention' and, thereby, muster the motor output and response-selection mechanisms relevant to goal-seeking behavior (in colloquial terms, "wanting"). This theory also states that dopamine is *not* involved in computations relevant to the hedonic evaluation ("liking") of stimuli coming in contact with the gustatory sensory apparatus during feeding or, by extrapolation, the hedonic experience associated with the effects of other appetitive goals, such as drugs of abuse. Central to this account is the important finding that severe 6-OHDA lesions do not alter unconditioned 'hedonic-like' oromotor reactions to a palatable saccharine/polycose solution in a taste reactivity test; importantly, these lesions also fail to alter the shift from hedonic-like reactions to aversive-like reactions that occur when exposure to the palatable solution is paired with lithium chloride administration (Berridge and Robinson 1998). Because conditioned shifts in taste reactivity are thought to depend on forebrain mechanisms (as opposed to the generation of the orofacial movements themselves, which are governed by hindbrain pattern generators), these findings have been interpreted as indicating that dopamine transmission in the Acb does not mediate forebrain computations relevant to the hedonic evaluation of taste that serve to guide the feeding consummatory act (Berridge and Robinson 1998; Berridge et al. 1989).

Also relevant to understanding the dopaminergic control of feeding are the mutually incompatible ways in which motor output is organized during the appetitive and consummatory phases. The appetitive phase, especially in situations of relative novelty, is characterized by heightened ambulation and investigatory responses (rearing, nosepoking, etc. in a rodent) and switching among these various forms of motor output in a manner that presumably increases the probability of contact with the goal. Subsumed under the category of the appetitive phase are preparatory behaviors that involve contact with the goal object without actual ingestion, such as food hoarding in which food is actively transported to a place where consumption can occur later. Recall that anticipatory locomotion, rearing, nosepoking, and food hoarding are all strongly diminished by dopamine-compromising manipulations that spare actual food intake (e.g., Bakshi and Kelley 1991a; Baldo et al. 2002; Blackburn et al. 1987; Kelley and Stinus 1985; Koob et al. 1978). During commerce with the goal object, however, the animal 'trades off' exploratory or preparatory behaviors to *stay in one place* while emitting the repetitive basic motor patterns associated with the consummatory act. The well-established behavioral effects of pharmacologically augmenting dopamine release, particularly in the Acb, suggest that heightened dopamine transmission, in and of itself, produces a state not amenable to staying in one place. For example, administration of indirect dopamine agonists (such as cocaine or amphetamine), either systemically or into the Acb, is well known to augment ambulation and presumed investigatory responses such as rearing or nosepoking (for example, see Delfs et al. 1990; Fray et al. 1980; Geyer et al. 1987; Kelley et al. 1986, 1989; Pijnenburg et al. 1976). Mathematical analyses of spatial characteristics of the locomotor path associated with systemic administration of dopamine uptake inhibitors and releasers indicate that at doses that do not produce motor stereotypies, these drugs increase the unpredictability (quantified as an increase in entropy) of movement sequences (Paulus et al. 1990, 1993). Indeed, a classic view of Acb dopamine function holds that increased dopamine transmission mediates behavioral flexibility and switching between competing behaviors (Lyon and Robbins 1975; van den Bos and Cools 1989), with an augmentation (at non-stereotypy-producing doses) of the number of behavioral categories in which motor effort is expended (Lyon and Robbins 1975). These behavioral features of pharmacologically augmented dopamine release are compatible with the observations that the firing of presumed dopaminergic units in the VTA (Hollerman and Schultz 1998), or the efflux of dopamine in the Acb shell, (Bassareo et al. 2002), exhibit sensitivity to novel or unpredicted experimental contingencies but are not closely correlated with the consummatory act itself. It is under novel or unexpected conditions that heightened investigatory responses and behavioral flexibility would be expected and would serve an appropriate adaptive function. Hence, there are behavioral effects of enhanced dopamine transmission in

the Acb per se that seem incompatible with the manner in which consummatory responses are organized. This observation seems consistent with the previously discussed voltammetry findings demonstrating a decline in dopamine levels to baseline or below baseline levels during ingestion (Richardson and Gratton 1996; Roitman et al. 2004).

Related to this point, certain aspects of the appetitive and consummatory phases can be viewed as mutually incompatible from a behavior–ecology perspective, based on their incompatible demands upon attention and vigilance. Because the consummatory act mandates a certain degree of diminished vigilance and capability to respond to threats, the time spent in commerce with the goal object can be seen as 'expensive', warranting a cost/benefit computation informed by internal drive states vs the perceived need to maintain engagement with the environment (Blanchard and Blanchard 1989; Dukas 2002). For example, exposure to a threatening aversive noise during feeding increased the number of times that feeding bouts were interrupted by bouts of investigatory behavior (Krebs et al. 1996, 1997); moreover, when food-deprived rats were tested in the presence of a conditioned stimulus for foot shock, their behavior switched from feeding to food-carrying behavior (Onuki and Makino 2005). Interestingly, several early studies showed that cortical electroencephalogram (EEG) patterns shift suddenly from desynchronized to synchronous patterns upon the onset of ingestive licking behaviors (Buchwald et al. 1964; Clemente et al. 1964; Hackett and Marczynski 1969) and, strikingly, that during the consummatory act, sensory evoked potentials show a pattern of facilitation reminiscent of that seen during spindle slow-wave sleep (Hackett and Marczynski 1969; Schwartzbaum et al. 1972). These findings are consistent with the interpretation that the consummatory act is accompanied by a neural state indicative of decreased vigilance. Consideration of these trade-offs between the mutually incompatible motor behaviors and attentional requirements of the appetitive vs consummatory phases suggests the possibility that goal-directed behavior sequences, in an ethological sense, emerge from the flexible switching between distinct neural circuits vying for expression. In the context of theories of dopamine function, this idea is elaborated perhaps most explicitly by Ikemoto and Panksepp, who proposed that dopamine exerts positive modulation on an "approach motor generator," a neural subsystem generating the 'seeking-like' motor responses associated with the anticipatory phases of feeding, sexual behavior, etc., or under situations in which flexible strategies to flee threats are needed. Consummatory responses, on the other hand, are governed by "consummatory motor generators" not under direct control by the dopamine system and which participate in reciprocal inhibitory interconnections with the seeking system (Ikemoto and Panksepp 1999).

It should be noted that some caution is warranted in using the 'appetitive/consummatory' dichotomy to inform inquiries into neural function. It has been cogently argued that while these categories may represent a convenient way to split apparently distinguishable aspects of highly complex sequences of motivated behavior, these investigator-imposed distinctions are merely descriptive and may actually serve to obscure the complex and heterogeneous nature of the consummatory act. In other words, it is difficult or impossible to tell where the appetitive phase ends, and the consummatory phase begins, or whether it is even valid to draw such a line. For example, Smith (1995) points out that "...the consummatory phase of eating is more complex than has been assumed. It requires appetitive and ingestive movements and it involves incentive control," and Berridge and Robinson (1998) state that the consummatory phase "...is not a coherent single category in which to classify a response." We strongly agree with these viewpoints. Nevertheless, when analyzing the complexities of feeding behavior, it is valid to examine correlations and dissociations among distinct behavioral processes (as long as these can be assayed objectively) as revealed by discrete neural manipulations. Perhaps the semantic labels of 'appetitive' and 'consummatory' are inadequate to depict these complexities, and new terminology is needed; however, we argue below that these terms remain serviceable (with the appropriate caveats) to the extent that they appear to capture groupings of behaviors that are mediated by common neural mechanisms.

To summarize, the numerous complex, interactive processes that together comprise appetitive and consummatory feeding behaviors appear to be governed by distinct and, in some cases, likely reciprocally inhibitory, neural circuits and transmitter systems. These component processes of feeding include (but are not limited to) computations regarding the expenditure of motor output in 'seeking-like' goal-directed behaviors (likely dopamine-dependent), the hedonic evaluation of food during the consummatory act (likely not), and the degree of vigilance appropriate to the environment at hand (presently unknown). Because any of these mechanisms could potentially influence the initiation and termination of feeding, they must all be taken into account when evaluating the degree to which dopamine-mediated reward processes influence the feeding consummatory act. In the past several years, evidence has accrued to suggest that these component processes of feeding are instantiated in distinct, yet interacting, neurochemically coded systems at the level of the Acb. Much support for this view derives from observed dissociations between food-reinforced instrumental responding vs feeding consummatory behaviors as revealed by pharmacological manipulations of discrete transmitter systems in the Acb, as reviewed below.

Manipulations of intra-Acb dopamine, opioid, and amino acid transmitter systems reveal multiple dissociations between feeding behavior, operant responding for food, and responding for food-associated conditioned reinforcers

Of direct relevance to the question of whether responses in a food-reinforced instrumental task, and sequential licks or bites occurring during the consummatory phase of feeding, are mediated by similar dopamine-dependent processes is the issue of whether licks or bites can be seen as instrumental behaviors in the same sense as pressing a lever or traversing a runway. While the qualitatively different nature of appetitive 'seeking-like' responses (including instrumental goal-seeking behavior) and the simple, repetitive motor acts of the consummatory phase are clearly apparent, it is also true that updated evaluations of taste, satiety processes, and other incentive-related factors impinge upon these somewhat inflexible consummatory responses. In other words, as discussed above, it is difficult to draw an objective line separating the appetitive and consummatory phases of feeding. Hence, when evaluating results from free-feeding studies, the question arises as to the best level of behavioral resolution with which to glean the influence of incentive motivational processes. One option is to view the individual bites or licks of the consummatory phase as instrumental responses subject to incentive control; this idea has been implied by several investigators (Smith 1995; Wise and Colle 1984), but perhaps most explicitly by Berridge and Robinson in their incentive salience theory of dopamine function, in which they state

> ...active re-engagement with the external food requires the attribution of incentive salience to that food. The recurrence of 'wanting' is required to initiate each successive bout or lick, and is dopamine-dependent. In order to claim that consummatory behavior is not dopamine-dependent, one would have to posit that the individual fluctuates rapidly back and forth between appetitive and consummatory phases, as many times as there are bites in a meal (Berridge and Robinson 1998, p 354).

An alternative possibility is that because chewing or licking within a feeding bout is controlled by hindbrain pattern generators, the appropriate level of analysis with regard to forebrain control may be the *switching in or out* of a neural state that is permissive for these activities to occur rather than the control of each individual act. Thus, the set of behaviors leading up to a switch into consummatory activity may be governed by the same dopamine-dependent incentive processes that also control the initiation of, for example, instrumental lever pressing. Although something of a fine distinction, this latter perspective leads to different predictions regarding the ability of neural manipulations to differentially influence instrumental responding vs actual feeding responses. If, for example, the initiation of each bite or lick is governed by incentive processes in the same way as the initiation of each lever press in an operant task, then these two types of behavior should tend to track each other in response to common neural manipulations. We have already reviewed evidence that, at least in the case of Acb dopamine manipulations, this is not entirely the case. Further evidence in a similar vein is provided by a series of studies conducted over the past several years on the ability of discrete manipulations of intra-Acb dopaminergic, opioid, and amino acid systems to influence free-feeding, food-reinforced operant responding, and operant responding for food-associated conditioned stimuli. These findings can be summarized as follows (and are also shown in Table 1):

Dopaminergic manipulations As previously discussed, intra-Acb administration of dopamine receptor antagonists either fails to reduce chow intake or actually increases intake slightly and lengthens the duration of feeding bouts, but dramatically reduces ambulatory responses and rearing in food-deprived rats (Bakshi and Kelley 1991a; Baldo et al. 2002, see Fig. 1a–c). Conversely, intra-Acb administration of the indirect dopamine agonist, amphetamine, markedly increases locomotor activity while diminishing food intake (Bakshi and Kelley 1991b, Fig. 1f). With regard to food-related instrumental responding, intra-Acb amphetamine administration elevates breakpoint in a progressive ratio task (Zhang et al. 2003, Fig. 1d), and markedly augments lever pressing for a Pavlovian conditioned stimulus for food (e.g., Cunningham and Kelley 1992; Kelley and Delfs 1991; Phillips et al. 1994, also see Fig. 1e), while intra-Acb dopamine depletions diminish food-reinforced progressive ratio responding (Aberman et al. 1998), and intra-Acb dopamine receptor antagonism reduces food-associated conditioned reinforcement (Wolterink et al. 1993).

Amino acid manipulations Blockade of α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA)-type glutamate receptors, or stimulation of gamma-aminobutyric acid (GABA) receptors (both of which are presumed to reduce functional output of the Acb), results in dramatic increases in free-feeding in ad libitum-maintained rats; intake of chow is increased by as much as 600% compared to vehicle-treated animals, while prandial drinking is unaffected (Maldonado-Irizarry et al. 1995; Reynolds and Berridge 2001; Stratford and Kelley 1997, 1999; Stratford et al. 1998, see Fig. 2b,d). This effect is localized specifically to the Acb shell; similar treatments in the Acb core do not influence feeding (Kelley and Swanson 1997;

Table 1 Summary of intra-Acb dopaminergic, opiatergic, and amino acid manipulations on feeding and food-reinforced operant responding

	Food intake	PR breakpoint	CR responding	Macronutrient/taste selectivity	Anatomical specificity of effects on food intake
Amphetamine	⇓	⇑	⇑	N.A.	Acb core, shell
DA antagonists	⇔ or ⇑	⇓	⇓	?	Acb core, shell
Mu-opioid agonists	⇑	⇑	⇔	⇑ Intake of fat, sugar, noncaloric palatable tastants	Widespread throughout striatum, particularly strong in Acb
AMPA antagonists	⇑	?	⇔	?	Acb shell
GABA agonists	⇑	⇔	?	Nonselective, but ⇔ on noncaloric palatable solutions (e.g., saccharin)	Acb shell

(*Upwards double arrow*) increase, (*downwards double arrow*) decrease, (*left right double arrow*) no change, *PR* progressive ratio, *CR* conditioned reinforcement, *DA* dopamine, (*question mark*) not tested. See text for details and references

Stratford and Kelley 1997, see Fig. 2c). The hyperphagia associated with these manipulations is of a rather general nature; the intake of palatable sucrose solutions, different macronutrient-enriched foods, or standard rat chow is equally affected, although the intake of noncaloric palatable solutions (such as saccharin) is unchanged (Basso and Kelley 1999, see Fig. 2f). However, in striking contrast to what one might expect given the voracious nature of the hyperphagia, intra-Acb shell GABA receptor stimulation does not augment breakpoint in a progressive ratio task and actually tends to decrease breakpoint somewhat at the high end of the dose–effect function where large hyperphagic effects are obtained (Zhang et al. 2003, also see Fig. 2e). Moreover, intra-Acb infusions (into sites bordering the core and ventral shell) of a behaviorally active dose of the AMPA receptor antagonist, 6-cyano-7-nitroquinoxaline-2,3-dione, fail to alter responding for food-associated conditioned reinforcement (Burns et al. 1994).

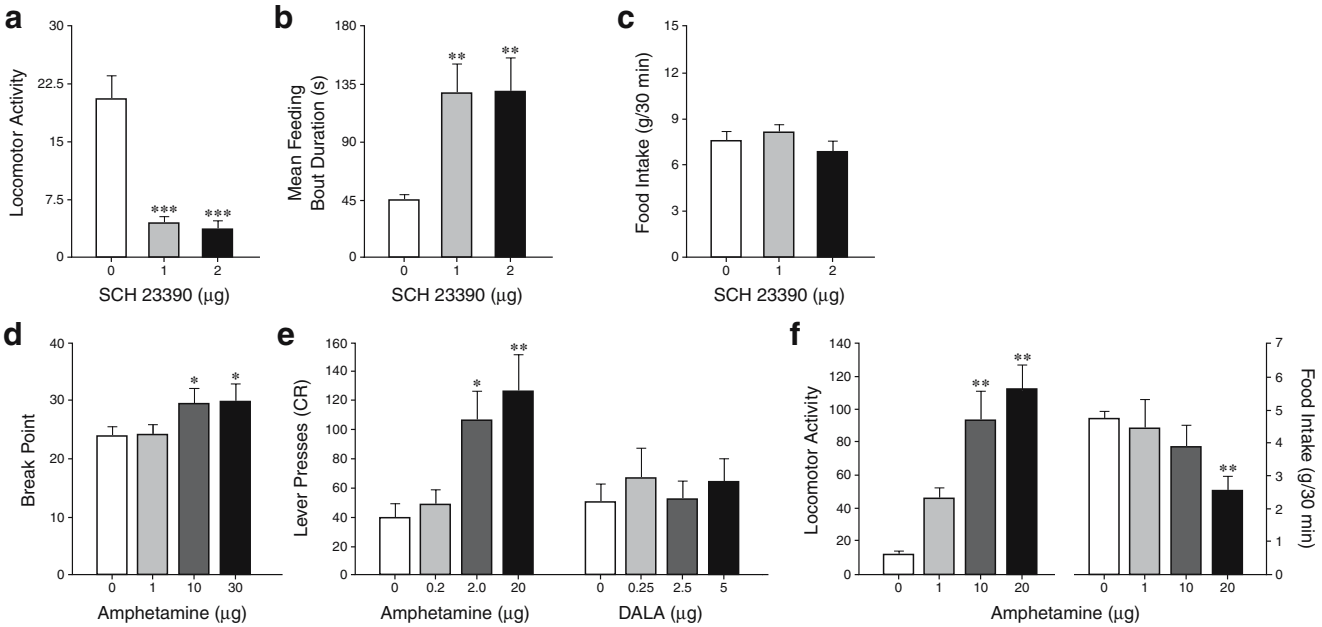

Fig. 1 Intra-Acb dopaminergic manipulations influence general locomotor activity and food-seeking behaviors, but do not appear to mediate actual ingestion. **a**–**c** Intra-Acb infusions of the dopamine D1 receptor antagonist, 7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (*SCH 23390*), markedly reduce locomotor activity (**a**), while significantly lengthening feeding bout duration (**b**). Actual food intake was unaltered (**c**) due to a diminution in the number of feeding bouts initiated (not shown). Similar results were obtained with D2-selective antagonists. **d**–**e** Intra-Acb amphetamine increases breakpoint for responding for food reward (**d**) and food-associated conditioned reinforcement (*CR*; **e**), consistent with an enhancement of the incentive motivational properties of food, but in the same dose range decreases actual food intake (**f**). An opioid receptor agonist, DALA, does not augment food-related CR responding (**e**). (Reprinted from Kelley et al. 2005b, with permission from Elsevier)

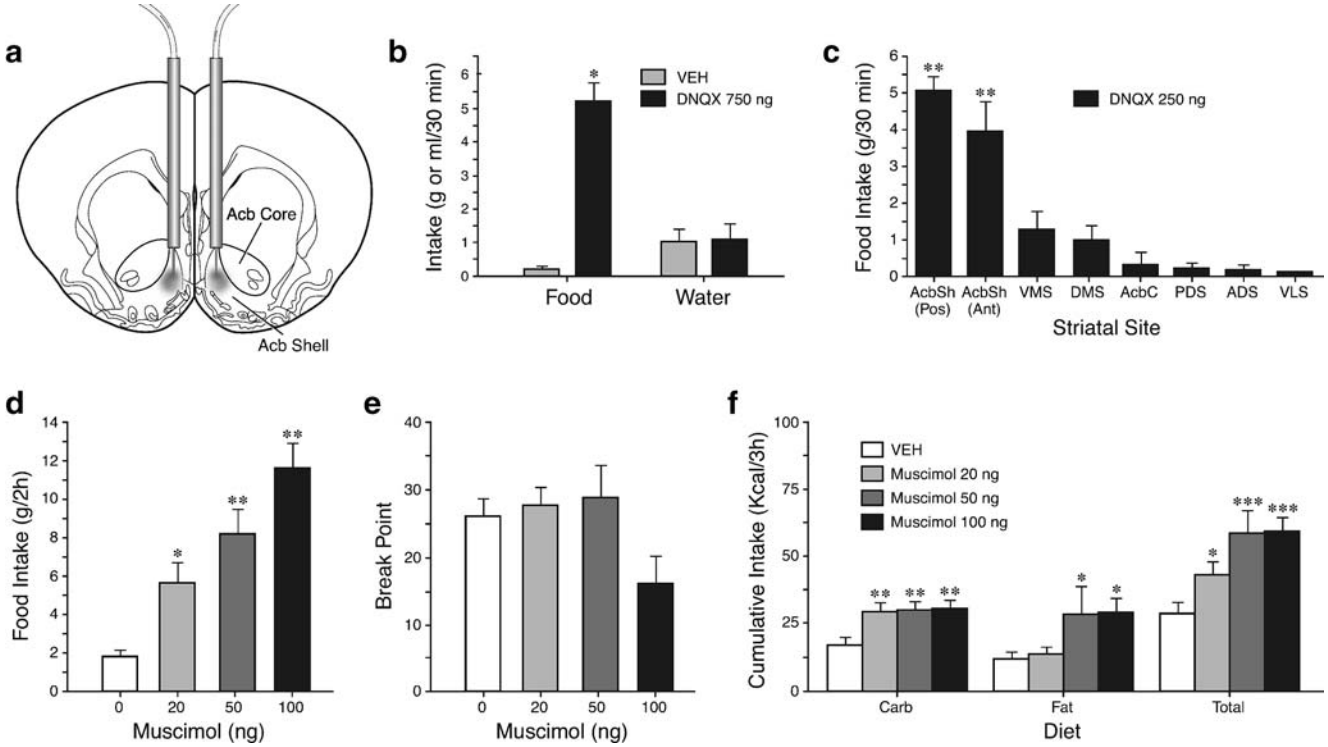

Fig. 2 Functional inhibition of Acb shell output via glutamate receptor blockade or stimulation of GABA receptors augments food intake, but not operant responding for food reward. **a** Diagram of intra-Acb cannula placements in core and shell. **b**, **c** Intra-Acb shell blockade of AMPA-type glutamate receptors with 6,7-dinitroquinoxaline-2,3-dione (*DNQX*) augments feeding but not prandial drinking (**b**), this effect is obtained specifically in the Acb shell (**c**). **d**–**f** Stimulation of $GABA_A$ receptors in the Acb shell with muscimol markedly increases food intake (**d**) regardless of macronutrient content (**f**), but does not significantly increase food-reinforced progressive ratio breakpoint (**e**). (Reprinted from Kelley et al. 2005b, with permission from Elsevier)

Opioid peptide manipulations Infusions of mu receptor or delta receptor, but not kappa receptor, agonists into the striatum increase food intake (Bakshi and Kelley 1993a,b; Bodnar et al. 2005; Evans and Vaccarino 1990; Mucha and Iversen 1986; Zhang and Kelley 2000); these effects are seen in widespread areas of the striatum, although there is an anatomical gradient whereby larger effects are obtained with more ventrally placed infusions, including the Acb shell (Bakshi and Kelley 1993b; Zhang and Kelley 2000). Unlike the effects seen with intra-Acb shell GABA receptor stimulation, the hyperphagia associated with mu receptor agonists is influenced by the macronutrient content and taste characteristics of the food; when presented with a concurrent choice between equally preferred carbohydrate- or fat-enriched foods, intra-Acb mu receptor stimulation augments fat intake selectively (Zhang et al. 1998, see Fig. 3a). Also in contrast to GABA-agonist effects, intake of palatable but noncaloric tastant solutions (saccharin, saline) is increased, and ingestion of palatable foods is reduced by intra-Acb opioid receptor blockade (Kelley et al. 1996; Zhang and Kelley 2002, see Fig. 3b,d). With regard to operant responding, intra-Acb infusions of mu receptor agonists increase breakpoint (Zhang et al. 2003, see Fig. 3c), but fail to enhance responding for conditioned reinforcement (Cunningham and Kelley 1992, see Fig. 1e).

Finally, none of these neuropharmacological manipulations enhances the acquisition of food-reinforced fixed-ratio responding in ad libitum-fed rats (Hanlon et al. 2004).

This pattern of dissociations lends support to the idea that three distinct, yet interacting processes are instantiated at the level of the Acb: the invigoration of food-seeking behaviors in a manner that is *independent* of actual commerce with the goal object (as mediated by dopamine), the enhancement of food-seeking behaviors in a fashion *dependent* upon the interaction of the food with the gustatory apparatus (as mediated by striatal opioids), and the selective augmentation of consummatory responses in the absence of increased instrumental responding for food reinforcement (as governed by the functional inhibition of Acb shell output by GABA stimulation or glutamate receptor antagonism). When describing effects as 'independent of' or 'dependent upon' commerce with food, we mean to highlight the distinction between the effects of dopaminergic stimulation, which enhances progressive ratio breakpoint as well as responding for conditioned reinforcement (in which food is not encountered during conditioned responding) and opioid receptor agonism, which fails to augment instrumental responding in the absence of actual interaction with the food (i.e., breakpoint is enhanced, but conditioned reinforcement is not). Effects seen with amino

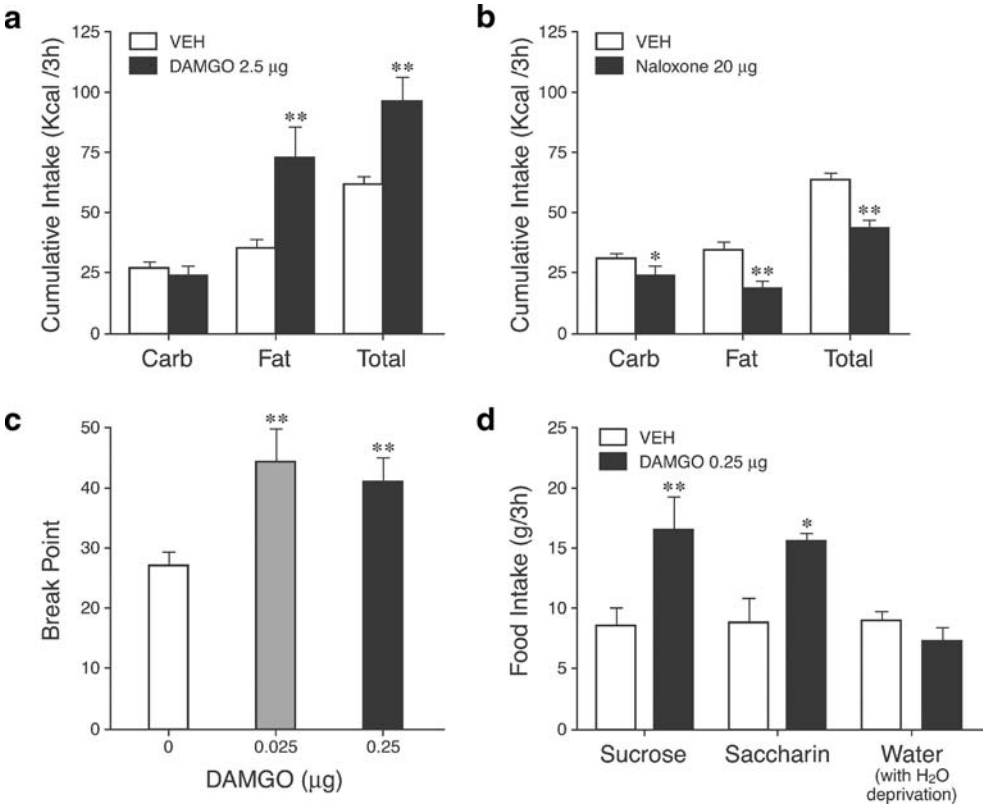

Fig. 3 Stimulation of mu-opioid receptors in the Acb preferentially increases the intake of calorie-dense and palatable foodstuffs. **a**, **b** Stimulation of Acb mu-opioid receptors with the peptide agonist, D-Ala(2), Nme(4),Gly-ol(5)-enkephalin (*DAMGO*), increases fat intake (**a**), while intra-Acb opioid receptor blockade with naloxone diminishes both fat and carbohydrate intake (**b**). Intra-Acb DAMGO also increases intake of palatable saline and saccharin solutions (**c**). In a similar dose range, intra-Acb DAMGO augments food-reinforced progressive ratio responding; contrast this with the lack of mu-opioid agonist effects on food-associated conditioned reinforcement see in Fig. 1e. (Reprinted from Kelley et al. 2005b, with permission from Elsevier)

acid manipulations are also dependent upon interaction with the food but in a fashion whereby the effects of this interaction fail to influence instrumental responding. Taken as a whole, the dissociable effects of dopaminergic, amino acid, and opioid manipulations provide strong support for the idea that the definition of reinforcement or incentive processes as related to learned instrumental behaviors does not apply in the same way to the topography of individual responses within a feeding bout. Perhaps most striking in this regard is the dissociation between the dramatic effects of intra-Acb shell GABA receptor agonism, which produces a hyperphagia so intense that rats are sometimes seen attempting to ingest food faster than it can be swallowed (Stratford and Kelley 1997) and the failure of the same manipulation to enhance breakpoint (Zhang et al. 2003). If the bites of food during GABA-mediated hyperphagia are dependent upon either increased incentive salience of the food, or the augmented rewarding aspects of ingestion, why are these processes not manifested as enhanced progressive ratio responding? A similar question could be asked regarding the failure of intra-Acb shell GABA stimulation to enable the acquisition of food-reinforced instrumental responding for sugar pellets, although the same manipulation increases the intake of the pellets, when freely available in the food hoppers, by 400% above baseline levels (Hanlon et al. 2004). In some ways, intra-Acb dopamine and amino acid manipulations produce opposite effects; with the former, instrumental responding is strongly affected and consummatory behaviors are spared, with the latter, food-reinforced instrumental responses are unchanged by the same manipulations that dramatically increase free-feeding behaviors. Along the same lines, the dissociations between intra-Acb dopaminergic and opioid manipulations suggest that the control over behavior by the acute, presumably rewarding or hedonic, aspects of commerce with palatable foods can be pharmacologically 'pulled apart' from the ability of food-associated second-order stimuli to control goal-seeking behavior. We suggest that these pharmacologically induced dissociations reflect distinct modes of forebrain control over subcomponents of appetitively motivated behavior sequences. This idea is not new, but what is surprising is that these discrete processes appear to be mediated by highly intermingled, yet distinguishable, substrates within overlapping territories of the same brain region.

These interpretations find strong support in an important series of studies on the Acb mediation of taste reactivity. First, as previously mentioned, severe forebrain dopamine depletions fail to alter the hedonic-like reactions associated with intra-oral administration of a palatable liquid (Berridge and Robinson 1998; Berridge et al. 1989). Conversely, intra-Acb amphetamine administration failed to augment

hedonic taste reaction patterns at doses that augmented lever pressing induced by presentation of a Pavlovian conditioned stimulus for food delivery (Wyvell and Berridge 2000). In contrast, stimulation of mu opioid receptors, particularly in the medial Acb shell, markedly enhanced hedonic taste reactivity patterns (Pecina and Berridge 2000, 2005). These dissociations between dopamine- and mu-opioid-mediated effects on taste reactivity are in excellent agreement with our findings that the augmentation of food-reinforced instrumental responding depends upon actual commerce with the food in the case of opioid-mediated, but not dopamine-mediated, effects. Intra-Acb GABA receptor stimulation, however, produces more complex effects on taste reactions. Infusions of the GABA receptor agonist, muscimol, placed far rostrally, enhance hedonic reactions, while placements at the mid-rostral level yield aversive responses. Nevertheless, muscimol infusions into both sites augment food intake (Reynolds and Berridge 2002). This dissociation provides further evidence for a disconnection between the factors sustaining the consummatory act and the processes of reinforcement and incentive control that govern the ability of taste or other food-related stimuli to influence goal-directed behavior. But how to interpret the effects of a neural manipulation that dramatically increases the consummatory act of feeding in the absence of corresponding effects on either food-reinforced instrumental responding or the hedonic perception of taste?

To address this question, we have recently developed a working hypothesis stating that that during normal feeding, GABA- and glutamate-dependent substrates in the Acb shell, via direct connections to downstream nodes in feeding-related hypothalamic circuitry, act as a neural 'circuit breaker' for the simple, patterned oromotor behaviors associated with ingestion (Kelley et al. 2005b). Thus, we posit that hypothalamic and/or midbrain circuits that serve as motor controllers for the consummatory act are under tonic inhibitory modulation by forebrain *gating centers* such as the Acb shell, an idea that is consistent with the model of forebrain control over diencephalic 'behavioral control columns' proposed by Swanson (2000). The presence of a physiological drive for feeding may be associated with the development of a GABA signal in the Acb shell, which diminishes Acb output, thereby disinhibiting downstream feeding substrates and reducing the threshold for entering a neural state favorable for the consummatory act. This arrangement also allows for the sudden termination of feeding via a phasic glutamate signal to the Acb shell when necessitated, for example, by the appearance of a threat or sudden change in the sensory characteristics of the food (e.g., like encountering a worm in an apple). Note that this hypothesis implies that the presence of a strong GABA signal in the Acb shell would attenuate the effects upon behavior of higher-order computations arriving via hippocampal, amygdalar, or prefrontal cortical afferents; conversely, strong glutamate signals reaching the Acb shell from these regions would interrupt feeding or elevate the threshold for switching into the consummatory act. In other sectors of the Acb and striatum, glutamate-coded corticolimbic input may convey information relevant to feeding initiation or the expected reward value of food; in accordance with current theories of striatal function, we posit that the impact of this glutamate-coded information would be enhanced by dopamine transmission (O'Donnell 2003; West et al. 2003). Such an anatomical segregation of 'feeding interruption' and 'feeding promotion' inputs to striatum could represent a neural substrate for the previously discussed trade-offs between the drive to feed and the environmental suitability of feeding (as dictated, for example, by ambiguous or potentially threatening stimuli). Key to this working hypothesis is the proposition that glutamate-coded feeding interruption signals are targeted specifically to the Acb shell; even within the shell, it would appear that there is greater involvement of more anterior and medial subterritories. In this regard, it is interesting that the Acb hot spot for mu-opioid enhancement of hedonic taste reactivity appears to be exclusively localized to the medial shell, corresponding very well with the zone yielding the strongest hyperphagic responses to GABA receptor stimulation (Pecina and Berridge 2005). It is tempting to speculate that this overlap could represent a mechanism by which the rewarding experience of taste, as instantiated in augmented striatal opioid tone, prolongs the feeding consummatory act by elevating the threshold for competing motivational states to interrupt feeding. Finally, this model would predict that the disinhibition of downstream feeding motor controllers by an artificial, pharmacological GABA signal in the shell would recapitulate the more basic motoric aspects of the feeding consummatory act in the absence of more complex response strategies (i.e., instrumental acts such as lever pressing) that are likely mediated by higher-order distributed forebrain networks.

Although this model is speculative, data are emerging to support its physiological plausibility. We have found, for example, that intra-Acb shell administration of a drug that elevates endogenous GABA levels, gamma-vinyl GABA, produces a strong feeding response (Stratford and Kelley 1997); conversely, a recent study showed that intra-Acb administration of GABA receptor antagonists strongly attenuates the feeding response induced by food deprivation or a lipoprivic manipulation (Kandov et al. 2006). In compelling agreement with our model, a recent electrophysiology study showed that a subset of Acb neurons is inhibited in a manner time-locked to the onset and duration of consummatory licking behavior (Taha and Fields 2005). Moreover, in support of the idea that the inhibition of Acb

shell output results in the disinhibition of feeding-related hypothalamic centers, it has been shown that intra-Acb GABA receptor stimulation activates Fos expression in hypothalamic substrates normally activated under conditions of negative energy balance (Baldo et al. 2004; Zheng et al. 2003); in addition, pharmacological inhibition of the lateral hypothalamus eliminates the hyperphagia elicited by intra-Acb shell amino acid manipulations (Maldonado-Irizarry et al. 1995; Stratford and Kelley 1999).

When Acb control over feeding-related consummatory behaviors is viewed not as governing each bite or lick via the attribution of incentive salience or the computation of 'reward' but rather as gating, a process of switching back and forth between a neural state favoring appetitive reactions (heightened activity, incentive control of behavior by higher-order learned representations, elevated arousal levels) vs consummatory reactions (ambulatory immobility, control over behavior by internal homeostatic and gustatory cues, repetitive simple motor acts, and diminished vigilance and arousal), many of the complexities presented by the relative sparing of ingestion by moderate levels of intra-Acb dopamine-compromising manipulations vanish. For example, when one considers measures relevant to switching into feeding bouts, rather than individual consummatory behaviors or total food intake, then the commonly observed results of dopamine receptor blockade, such as increased latency to initiate the first bout, decreased number of bouts, and increased mean bout duration (e.g., Bakshi and Kelley 1991a; Baldo et al. 2002; Tombaugh et al. 1979), are quite easy to reconcile with the results from operant-based methods of assaying food reward. Thus, dopamine-dependent mechanisms may energize approach responses toward food, and modulate the expenditure of motor effort in acquiring food, but once the food is contacted and ingestion begins, forebrain control over maintenance of the feeding bout may be governed more selectively by Acb opioid and amino acid transmission. Importantly, this analysis can resolve the difficulties posed by the aforementioned pharmacologically induced dissociations between instrumental responding for food and actual eating, if one posits a mutually antagonistic relationship between Acb dopamine mediation of appetitive/approach responses and the process by which the forebrain 'switches modes' into the more automatic, patterned activity of ingestion. The present analysis is also compatible with models ascribing a specialized role for Acb dopamine in energizing arousal and motor output associated with the phase leading up to the switch into the consummatory act (Blackburn et al. 1987; Kelley and Stinus 1985; Salamone and Correa 2002), and is particularly in good agreement with Ikemoto and Panksepp's reward-seeking model, which posits distinct and reciprocally inhibitory interactions between those substrates that generate seeking-like appetitive behaviors, and those that govern consummatory responses (Ikemoto and Panksepp 1999).

How then to characterize dopamine's role in reward? It would appear that evidence is lacking to support a role for this monoamine in the hedonic aspects of the feeding consummatory act. Moreover, although the appetitive phase certainly possesses positive affective properties (we have all felt the 'joy of anticipation'), it should be noted that Acb dopamine levels also rise in response to aversive stimuli (Bassareo et al. 2002; Imperato et al. 1992; Tidey and Miczek 1996). Hence, dopamine transmission does not appear to be linked in an exclusive way to the generation of positive affective states, and yet is crucial for the process of positive reinforcement (i.e., the ability of interactions with a goal object to influence future responses directed toward the same goal), implying that some other function must be involved. One candidate may be the modulation of plasticity-related mechanisms responsible for 'stamping in' associations relevant to rewarding outcomes. The literature on dopamine and learning is beyond the scope of the present discussion, and there are many excellent reviews on this topic, as well as some controversy (Beninger and Miller 1998; Berke and Hyman 2000; Berridge 2005; Horvitz 2002; Kelley 2004; Robinson et al. 2005; Wickens et al. 2003). Briefly, however, the concept that dopamine is involved in some function related to the formation or maintenance of internal representations of motivationally relevant stimuli is a key part of several theoretical perspectives. For example, dopamine has variously been proposed to mediate the reboosting of incentive salience attributions when a previously "liked" stimulus is reencountered (Berridge and Robinson 1998), to provide a training signal to the forebrain related to the reliability of stimuli in predicting reward (Schultz 2002), to help stamp in associations between motor acts and their outcomes (Kelley 2004), or to modulate the formation of stimulus–reward associations that influence instrumental behaviors (Beninger and Miller 1998). Note that many of these constructs are conceptually related. The mechanisms by which such processes are accomplished are presently unknown, although there is some evidence that dopamine D1 receptor activation can modulate glutamate-mediated transduction events related to cellular plasticity (Arbuthnott et al. 1998; Kerr and Wickens 2001; Nicola et al. 2000). Although the relevance of these molecular processes to dopaminergic mechanisms of reinforcement has yet to be definitively established, there is compelling evidence from pharmacological antagonist studies indicating that blocking D1 and *N*-methyl-D-aspartate receptors in striatal and other corticolimbic regions prevents the establishment of action–outcome associations in the context of food-reinforced operant responding (Baldwin et al. 2000; Hernandez et al. 2005; Kelley et al. 1997; Smith-Roe and Kelley 2000). The

interruption of dopamine-dependent plasticity events related to reward learning in the absence of an actual decrement in the hedonic aspects of feeding could account for dopamine antagonist-induced reinforcement impairments in the absence of changes in food intake.

Conclusions and future directions

To function adaptively, animals must perform computations relevant to choosing the best response to an extraordinarily complex set of stimuli and contingencies. These computations often involve selections among several potentially adaptive yet incompatible behaviors. Imagine, for example, a hungry rat searching for food in a new and potentially threatening location; calculations are made regarding the amount of effort to expend in foraging, how often to stop and scan for predators, etc. Suddenly, food is encountered, and additional evaluations are made: Does it taste good? Has it made me sick in the past? Should I eat it here or carry it back to my nest? Obviously, we do not mean to imply that these evaluations and 'choices' reflect conscious decisions. Rather, they are an emergent property of neural mechanisms that integrate internal homeostatic signals, representations of the motivational valence of stimuli encountered in the environment, information from the sensorium, and so on. Such a view is central to incentive motivation theories of behavior (Bindra 1974; Toates 1986). For many years, the dominant paradigm held that the activation of a unitary central reward substrate could account for both the production of goal-seeking behaviors and the rewarding aspects of interaction with the goal, with the process of response selection inextricably linked to the functions of this presumably dopaminergic substrate. While in its broad strokes this idea retains validity, the evidence outlined in the present review suggests that, at least at the level of the Acb, the processes that control goal-seeking behavior, mediate the hedonic aspects of interaction with the goal, and flexibly switch the animal in or out of the patterned activity and altered vigilance of the consummatory act depend upon the distinguishable contributions of dopaminergic, opiatergic, and Acb shell amino acid signaling. We suggest that the distinct neurochemical mediation of these processes accounts for the resistance of consummatory measures of food intake to dopamine-compromising manipulations that significantly diminish goal-seeking behavior and reinforcement.

Throughout this paper, we have used the terms 'appetitive' and 'consummatory' as convenient semantic labels with which to group distinct feeding-related behaviors that appear to be influenced in common by a given neural manipulation. For example, anticipatory activity, food carrying, nosepoking, and vigorous lever pressing, all of which occur before actual interaction with the goal, are sensitive to the interruption of dopamine transmission in the Acb. There are, unfortunately, fewer behavioral or physiological windows into the neural processes that take place during commerce with the goal object. The two discussed in this paper, actual chewing or licking and taste reactions, share the important feature of resistance to dopamine-compromising manipulations, and sensitivity to striatal mu-opioid stimulation. Additional insight might arise from the analysis of transient changes in vigilance or sensory responsiveness during consummatory activities. For example, as mentioned previously, there is a literature on EEG rhythms and evoked potentials suggesting that the act of ingestion is accompanied by patterns indicative of diminished arousal. It is interesting to review some of these findings in greater detail. Several studies showed that the onset of consummatory behavior (often milk drinking in cats occurring immediately after an operant response resulting in milk delivery) is characterized by a time-locked, temporary shift from typical alert waking desynchronized cortical EEG activity into a synchronous slow wave sleep-like pattern (Buchwald et al. 1964; Clemente et al. 1964; Hackett and Marczynski 1969; Sterman and Wyrwicka 1967). Analogous changes have been observed with regard to hippocampal theta rhythms, i.e., hippocampal activation is seen during 'voluntary' behaviors such as ambulation, but not during 'automatic' behaviors such as consummatory licking or chewing (Vanderwolf 1975). Cortical synchronization associated with the consummatory act does not appear to be an artifact of repetitive muscle movements because one study showed that the synchronous pattern was seen in cats with milk or broth intake, but not during prandial water drinking (Sterman and Wyrwicka 1967). This latter observation raises the possibility that taste-related hedonic processes contribute to transient changes in cortical responsiveness. Strikingly, administration of the dopamine antagonist, chlorpromazine, at a dose that greatly reduced locomotor activity, failed to reduce milk intake and actually increased the cortical EEG synchronization seen during milk drinking (Cervantes et al. 1975). In humans, changes in scalp-recorded direct current potentials indicative of widespread cortical inhibition have been detected during the oral administration of sucrose (Schmitt et al. 2000), and several studies have documented diminished startle reactivity in association with pleasant affective states (Brody et al. 1994; Schupp et al. 1994; Bradley et al. 2006).

These findings support the idea that the sensorimotor aspects of the consummatory act (and possibly their attendant affective properties) are associated with a state in which forebrain control of instrumental goal-seeking behaviors is temporarily kept 'off line'. In this context, it is interesting to consider the evidence that fluctuations in

phasic monoamine activity during feeding map onto these purported transient state changes accompanying the switch into consummatory activity. For example, as discussed previously, recent voltammetry results indicate that Acb dopamine levels decrease to baseline levels (or below baseline levels) during actual ingestion (Richardson and Gratton 1996; Roitman et al. 2004). It has also been shown that locus coeruleus unit discharge rates decrease during automatic behaviors such as grooming or ingesting sweetened water (Aston-Jones and Bloom 1981) and, conversely, that subpopulations of neurons in medullary serotonergic nuclei show increased activity in a manner time-locked to the duration of feeding behavior or other automatic activities (Jacobs et al. 2002). The phasic changes in serotonergic activity have been proposed to represent a mechanism to "...obviate the need for continuous repetitive excitatory inputs to maintain a continuous output in motor systems," and to "...suppress inputs that might disrupt motor output" (Jacobs et al. 2002, p 51); both of these purported functions are consistent with the view of feeding bouts elaborated herein. It may, therefore, be interesting to explore relationships between the limbic forebrain substrates governing taste evaluations and descending modulation of hypothalamic motor control modules and the pathways mediating the transiently diminished responsiveness to external sensory inputs during automatic consummatory activities. Could opioid- and amino acid-coded signals in the Acb shell also reach the brainstem monoamine systems and, thereby, indirectly modulate responsiveness to external sensory events in the context of feeding behavior? If so, this could represent a mechanism whereby forebrain computations relevant to gustatory cues and taste hedonics could promote a switch into patterned feeding activity (via activation of hypothalamic control modules) while at the same time enabling a temporary neural state permissive of automatic motor behaviors like the feeding consummatory act (via modulation of the monoamine systems). Of course, many other routes of control (e.g., modulation of thalamic inputs to cortex and striatum, see Kelley et al. 2005a) are also possible. The insights on Acb control of feeding reviewed herein provide a potential framework for systems-level inquiries into such issues. While it is overly simplistic to draw a line separating appetitive and consummatory behaviors, the evaluation of multiple behavioral/physiological indices of feeding behavior may yield novel neuroethological terminology and concepts. Such information would be of great relevance to a richer understanding of the neural mechanisms underlying reward.

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