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CHAPTER 4.3

Microdialysis in the study of behavior reinforcement and inhibition

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Abstract: Brain microdialysis has been a valuable technique in the neuroscience field for more than 20 years. In vivo microdialysis in freely moving rats allows measurement of neurotransmitter release in response to ongoing behaviors. In this chapter we review findings using microdialysis in the study of behavior reinforcement and inhibition. This literature leads to the development of the dopamine hypothesis of reward and the cholinergic hypothesis of aversion and their underlying neural circuitry. Within the context of natural rewards, we discuss many of the key findings using microdialysis in the nucleus accumbens, ventral tegmental area and hypothalamus to study feeding, water intake, and mating. Artificial rewards, such as intracranial self-stimulation and drug reward, are also reviewed. Finally, data are summarized that suggest a natural reward, sugar, may take on behavioral and neurochemical properties of an artificial reward, such as a drug of abuse, under certain conditions

I. Introduction

I.A. Brain microdialysis

The microdialysis technique is a valuable tool in basic and clinical research. It has been extensively and successfully used, particularly in the neuroscience field, for almost three decades (Mark et al., 1991; Ungerstedt, 1991; Westerink, 1995; Muller, 2002; Bourne, 2003; Plock and Kloft, 2005). The popularity of this technique is due to its advantages with respect to other in vivo sampling techniques. It permits recovery of endogenous and exogenous substances from the brain or body, or infusion of drugs through the microdialysis probe (i.e., reverse microdialysis). Dialysis occurs by solute exchange through the porous membrane of the probe following chemical gradients. The collected amount of the analytes in the dialysate is proportional to what is released near the probe (Segovia et al., 1986; Schwartz et al., 1990). Since the dialysates are pure protein-free ultrafiltrates, they do not suffer enzymatic degradation and can be chemically analyzed without pretreatments. Thus, it is possible to continuously sample from the extracellular environment in virtually all living tissues and organs of sufficient size. The analytes are typically analyzed by high-performance liquid chromatography (HPLC). Coupling microdialysis with improved analytical techniques such as capillary electrophoresis or mass spectrometry allows for the study of chemical changes in very short periods and in very small sample volumes (see Chapter 3.4).

The main application of microdialysis has traditionally been the study of chemicals in the brain. Before the invention of microdialysis,

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neurotransmission studies were based on techniques such as push–pull perfusion and tissue homogenates (Korf, 1986; Myers et al., 1998; Kottegoda et al., 2002; Rui and Lebaron, 2005). Microdialysis initially studied chemical changes in discrete brain areas of anesthetized rats (Hernandez et al., 1983; Segovia et al., 1986), but rapid improvements in the technique soon made it possible to sample from freely behaving animals (Zetterstrom and Ungerstedt, 1984; Hernandez et al., 1986; Carboni et al., 1989; Westerink, 1995; Fillenz, 2005). Microdialysis in freely behaving animals is ideal for studying the relationship between particular chemical messengers and changes in ongoing behaviors, such as feeding (Hoebel et al., 1989; Hernandez et al., 1991; Meguid et al., 1996; Bassareo and Di Chiara, 1999a, b; Rouch et al., 1999; Smith, 2004; Rada et al., 2005), drinking (Yoshida et al., 1992; Tanaka et al., 2004; Molander et al., 2005), mating (Pfaus et al., 1990; Dominguez and Hull, 2005), exercising (Meeusen et al., 2001), cognitive processes (Pepeu and Giovannini, 2004), pain (Stiller et al., 2003), intracranial self-stimulation (ICSS) (Hernandez and Hoebel, 1988a; You et al., 2001), drug self-administration (Hurd et al., 1999; Ranaldi et al., 1999), and in neuropsychiatric animal models (Hernandez et al., 1990, 1991; Hoebel et al., 1992; Joseph et al., 2003; Invernizzi and Garattini, 2004; Wilcox et al., 2005).

A Medline search indicates there have been more than 10,000 *microdialysis* publications in the last 25 years, with no indication of a decline in its use. So far, 71% of microdialysis studies are in *rats,* and of those 74% are in the *brain*. Behavioral studies represent 18% of all microdialysis studies, and reward studies correspond to about 10% of those, almost all of which have been conducted in rats.

I.B. The concept of neural reward and aversion processes

This chapter will review some of the findings that the microdialysis technique has offered in the field of behavior reinforcement and its inhibition. Pavlov (1927) used the term ''reinforcement'' to refer to the strengthening of the association between an unconditioned stimulus and a conditioned stimulus that results when the two are paired. Skinner (1938) defined a ''reinforcer'' as a stimulus administered following a correct, arbitrarily chosen, response that increases the probability of occurrence of the response. The terms reinforcement and reward will be used interchangeably in this chapter and will include both positive and negative reinforcement (i.e., behavior to get, or get rid of, the reinforcer). Primary reinforcers, such as food, water, and sex, have an inherited role in proliferating the survival of the animal or the species, while secondary reinforcers, such as associated environmental stimuli, are learned.

Aversion, or behavior inhibition, will be considered as the opposite of reward in that it is a process that suppresses, instead of increasing, a behavior. This type of response can also be a lifesaver. For example, a conditioned taste aversion prevents an animal from eating a food that has previously been associated with sickness. Normally, once the consummatory phase of a natural behavior has been satisfied an inhibition of the behavior occurs. This behavior inhibition, with regard to feeding, is defined as the satiation process leading to satiety, and although the animal is averse to further eating, the state is generally described as pleasant.

In this chapter, we will review results that suggest the dopamine (DA) system in the nucleus accumbens (NAc) is part of a reinforcement system. DA release can activate an animal and contribute to a desired state. Cholinergic interneurons may counteract DA and play a role in behavior inhibition. Thus depending on the balance of neurotransmitter functions and the circuits in which they are embedded, an animal will either increase or decrease its response rate or response force. We hypothesize that high extracellular DA reinforces behavior, be it approach or escape behavior. If acetylcholine (ACh) also rises the approach behavior becomes inhibited and satiation ensues. Escape behavior lowers ACh. Low extracellular DA coupled with chronically increased ACh release depresses an animal and may lead to a condition

variously described as immobility, helplessness, or despair.

I.C. Anatomical substrates of reward

The neural circuitry involved in reward and aversion is part of brain systems engaged in emotions. The limbic system was originally conceived as a series of interconnected brain areas that played an important role in the acquisition, storage, and expression of emotion, and was described as a circuit between hypothalamus and the cerebral cortex (Papez, 1995), and later expanded to include other structures such as the amygdala (AMYG), hippocampus (HIPP), and NAc. From early studies by Mogenson and collaborators, it was concluded that the NAc was a structure that linked "emotions to action" (Mogenson et al., 1980). In the 1950s, Olds and Milner (1954) serendipitously discovered that rats would self-administer electrical pulses directly into many of the sites that coincided with areas of the limbic system, suggesting that the brain had specialized "centers" for reward. Many researchers contributed to the effort of tracing the "reward pathway" starting with the circuit from the lateral hypothalamus (LH) to the ventral tegmental area (VTA) and the NAc as proposed by Wise and Hoffman (1992). As can be seen in Fig. 1, the neural circuitry of reward comprised at least two loops. The first loop includes the LH and connects to structures in the hindbrain, returning to the NAc and then back to the hypothalamus directly and indirectly through the ventral pallidum (VP) (Leibowitz and Hoebel, 2004; Kelley et al., 2005). Others have described links from midbrain cholinergic cells to the VTA (Yeomans et al., 2001), and a glutamatergic/orexin path directly from the LH to the VTA and to the NAc (Harris et al., 2005). A second "loop" is composed of cortical glutamatergic inputs to the NAc with connections from the NAc to the VP, then to the mediodorsal thalamus projecting back to the prefrontal cortex (PFC). This second loop, which is actually a series of concentric loops or a spiral, receives important afferents from the AMYG and HIPP (McGinty, 1999; Napier and Mitrovic, 1999; McFarland et al., 2004). This cortical–subcortical loop involving the basal ganglia motor system also branches off in the thalamus to connect with the primary motor system. It is evident from the perspective of Fig. 1, following Mogenson's "reward circuitry," theory that the NAc is at one of the intersections between limbic and motor systems. Another classic view has received renewed attention with modern evidence that the LH connects reciprocally with the cortex (Rolls, 1984; Oomura, 1988). Neuroanatomists later described the extended amygdala as interconnecting structures that shared strong histological homologies, including the AMYG, stria terminalis, substantia innominata, and the NAc (de Olmos and Heimer, 1999). This designation clearly differentiated the NAc shell, as part of the extended AMYG, from the NAc core and dorsal striatum (STR) (Zahm et al., 1996; Cadoni and Di Chiara, 1999; Weiner, 2003). Efforts to differentiate the specific functions of the NAc shell vs. core have led to very interesting hypotheses of Pavlovian-instrumental transfer, learning, motivation, and habit formation, which are reviewed elsewhere (Robbins et al., 1989; Kalivas and Nakamura, 1999; Di Chiara, 2002).

I.D. Dopamine hypothesis of reward

Initial studies in the early 1970s showed that specific lesions of the DA projections from the midbrain to the STR produced deficits in feeding and drinking, resembling the "lateral hypothalamic syndrome" characterized by aphagia and adipsia (Teitelbaum and Epstein, 1962; Ungerstedt, 1970, 1971). The deficit in feeding and drinking occurred without somatosensory impairment but rather as a form of sensory neglect (Zigmond and Stricker, 1972; Marshall and Teitelbaum, 1974; Lindholm et al., 1975). It was suggested that the dopaminergic system in the medial forebrain bundle was probably damaged as the ascending fibers ran through the far-lateral LH. Studies by Wise and colleagues and others have demonstrated that neuroleptics (DA receptor antagonists) attenuate the expression of various behaviors such as feeding, drinking, ICSS, and drug self-administration (Wise, 1978; Xenakis and Sclafani, 1981; Bailey et al., 1986; Ettenberg and Camp, 1986; Ettenberg, 1989;

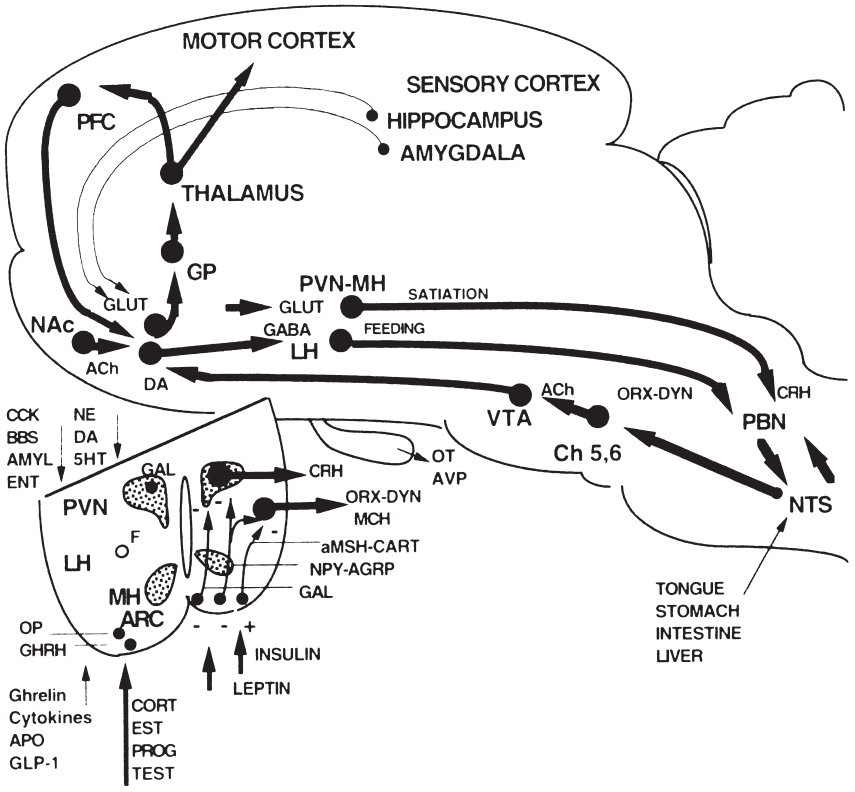

Fig. 1. Diagram of the reward circuitry showing the convergence in the NAc of the cortical and subcortical loops.

Wise and Rompre, 1989; Horvitz et al., 1993; Samson and Chappell, 2004; Xi et al., 2005a, b). Microdialysis studies have given further support to these behavioral findings by showing that natural reinforcers, as well as artificial reinforcers such as ICSS and drugs of abuse increase extracellular DA in the NAc (Hernandez and Hoebel, 1988b; Nakahara et al., 1989a, b; Wise et al., 1995a; Ranaldi et al., 1999). Electrophysiological studies in monkeys have emphasized the role of dopaminergic neurons in the animal's capacity to predict the occurrence of a novel event and reward learning (Schultz, 1997, 1998a, b; Tobler et al., 2005). Berridge and Robinson (1998) also suggest that DA may be involved in "incentive salience" and emphasize this role in motivation. Their conclusions are based on several experiments using "taste reactivity" to measure affective reactions suggesting that DA-depleted rats have normal hedonic reactions and associative learning (Berridge and Robinson, 1998). Moreover, DA blockers do not seem to block oral approach reflexes, nor do specific DA agonists potentiate such measures, but they do alter the incentive value of the reward (Pecina et al., 1997, 2003; Berridge and Robinson, 1998). Recently, in DA-deficient mice, it was demonstrated that DA was not necessary for learning or liking, but it was necessary for seeking of the reward (Robinson et al., 2005), which could be reinstated by localized restoration of DA function with viral vectors (Szczypka et al., 2001). Most recently, brain imaging studies have been used to detect the active parts of the brain during various aspects of reinforcement, with attention drawn to changes in DA receptor function during the cognitive aspects of reinforcement (Kalivas and Volkow, 2005).

Stressful events and aversive stimuli can also increase DA levels in the NAc (Abercrombie et al., 1989; Keefe et al., 1993; Salamone, 1994;

Salamone et al., 1997; Rada et al., 1998b). On the surface this seems to argue against any theory that DA mediates reward, but on reflection, there is more to reward than simple pleasure. DA could also be involved in the relief from stress and pain, both in the motivation to achieve relief and the reward of achieving it. This fits with the theory that DA has a role in salience and in negative reinforcement as well as positive reinforcement.

None of these discoveries rule out the possibility that DA activates a pleasure response at some point in the circuit, including mu-opioid receptor "hot spots" in the NAc for "liking" a taste (Pecina and Berridge, 2005). The opioid peptide enkephalin in the NAc has been related to reward and can activate both mu and delta receptors to increase the release of DA (Di Chiara and Imperato, 1988; Bals-Kubik et al., 1989). Opiates are involved in eliciting feeding in the NAc (Kelley et al., 2000) as well as in many other limbic system sites (Levine and Billington, 2004). Moreover, it was shown in 1980, in one of the first local self-administration studies, that rats will self-administer morphine directly into the NAc (Olds, 1982).

Microdialysis experiments have encountered all of these interesting dimensions to the study of DA's role in reward. DA increases in the NAc shell during an animal's first exposure to a novel food, and this response disappears at a second meal even though the animal consumes as much as the first time (Bassareo and Di Chiara, 1999b; Bassareo et al., 2002; Rada et al., 2005). The DA response can be reinstated by food deprivation (Bassareo and Di Chiara, 1999b) or an animal can learn to restore it, and obtain a DA surge every day, by binge eating (Rada et al., 2005).

I.E. Cholinergic hypothesis of aversion

Microdialysis has also contributed to a theory of "aversion" or behavior inhibition. The details are given in later sections of this review under the topics of feeding satiation, mating satiation, ICSS escape and drug withdrawal. In brief, we find that ACh is released in the NAc in a variety of situations that all have behavior inhibition as a common feature. Extracellular ACh rises toward the end of a meal (Mark et al., 1992; Rada et al., 2005) and is also elevated after experiencing the forced swim test and thus may contribute to behavioral depression (Chau et al., 2001). Acetylcholine also increases in the NAc during aversive hypothalamic stimulation, and most telling, extracellular ACh levels decrease when the animal performs stimulation–escape responses (Rada and Hoebel, 2001). Evidence will be presented for the general principle that accumbens ACh is relatively high compared with DA during withdrawal from addictive substances (Rada et al., 1996, 2004; Colantuoni et al., 2002; Rada and Hoebel, 2005). Since withdrawal is an aversive condition that results in many behavioral signs of distress, including anxiety and depression, one can surmise that relatively high levels of ACh in the NAc can enhance a circuit that can cause either behavior inhibition or aversion or both.

II. Natural rewards

Rewards can be classified as nondrug rewards or drug rewards (Di Chiara, 2002), or as natural and artificial rewards. We will classify natural rewards as those reinforcers studied in natural behaviors (feeding, thirst, and mating) and artificial rewards as drug reward and ICSS. Artificial rewards act via natural pathways but have magnified responses. We will focus first on natural rewards and later show how they too can become magnified, thereby blurring the distinction between nondrug and drug rewards.

II.A. Feeding

Of all the natural rewards under investigation, feeding behavior is the most studied using the microdialysis technique. The study of ingestive behavior has progressed substantially during the last decade with the discovery of new peptides involved in feeding regulation and the development of new animal models of feeding disorders (see comprehensive reviews by Berthoud, 2004; Leibowitz and Hoebel, 2004). In the present chapter, we will focus specifically on findings using brain

microdialysis that have impacted the ingestive behavior field.

Most research on feeding behavior using brain microdialysis has concentrated on the hypothalamus and NAc. Fig. 1 shows a way in which these areas are linked (also see Rolls, 1994; Berthoud, 2000). The hypothalamus has maintained its early start in feeding research as an area clearly involved in feeding initiation and satiation, and a place where most feeding neuropeptides act (Leibowitz and Wortley, 2004). Circuits in the hypothalamus can foster foraging for one macronutrient or another (Leibowitz and Wortley, 2004) and are under the control of hormones that signal nutrient stores in the body (Leibowitz and Hoebel, 2004; Strader and Woods, 2005). The NAc is a terminal field of the mesolimbic dopaminergic system involved in hedonic and motivational aspects of feeding as discussed above. Many other limbic areas are also involved, but these two sites capture the basic subcortical functions of sensory input, physiological modulation and motor output. Higher structures project to limbic sites with information from learning and memory stores (Rolls, 2000). One can start anywhere in these wonderful circuits. Given the topic of this chapter, we start with the NAc.

II.A.1. NAc microdialysis during feeding

II.A.1.a. Dopamine in the NAc. Dopamine is the most studied neurotransmitter in relation to natural rewards. As mentioned briefly in the Introduction, lesion of the LH is characterized by aphagia and adipsia (Anand and Brobeck, 1951a, b; Teitelbaum and Epstein, 1962), and this syndrome was due in part to damage incurred by dopaminergic projections to the STR (Ungerstedt, 1970, 1971). This spurred the study of a possible role for DA in an animal's reaction to natural rewards. DA antagonists injected locally into the accumbens increase operant responding for food, which then gradually declines suggesting a loss of reward and not simply motor impairment (Wise, 1978). There is also a loss of reaction to the taste of sugar (Schneider et al., 1986). Microdialysis studies have shown that feeding releases DA in the NAc (Hernandez and Hoebel, 1988a, b; Radhakishun et al., 1988; Hoebel et al., 1989; Westerink et al., 1994). An initial use of microdialysis to understand if DA in the NAc is involved in conditioning was carried out by Mark et al. (1991), showing that oral infusion of a palatable food, saccharin, increased DA release in the NAc, and the opposite response was observed if the saccharin had been associated with sickness in a conditioned taste aversion paradigm.

Di Chiara and colleagues (Bassareo and Di Chiara, 1997, 1999b; Tanda and Di Chiara, 1998) find that a novel, unconditioned, palatable food stimuli (Fonzies) releases DA only during the first experience, and this effect habituates on the second exposure, suggesting that DA in the NAc is involved in acquisition rather than maintenance of incentive motivation (Bassareo and Di Chiara, 1997). The first experience with a novel food raises DA selectively in the shell and not the core of the NAc (Tanda and Di Chiara, 1998; Bassareo and Di Chiara, 1999a), and this increase is dependent on stimulation of mu-opioid receptors located in the VTA (Tanda and Di Chiara, 1998). Similar results have been found using sucrose. Ingestion of a 10% sucrose solution releases DA in the NAc shell during the first exposure, but less on a second exposure 24 h or 21 days later, again suggesting that DA release in the NAc shell depends on the novelty of the stimulus (Rada et al., 2005). DA release is proportional to sucrose concentration (Hajnal et al., 2004), and under certain feeding conditions DA can be released with a palatable food time after time, as discussed in Section III of this chapter (Rada et al., 2005).

Postingestional factors can influence DA release in the NAc. In a conditioned taste preference paradigm, a neutral taste that was previously associated with infusion of a highly caloric solution into the stomach can increase DA levels in the NAc (Mark et al., 1994), suggesting that the DA increase observed when rats drink sucrose could be due, in part, to prior experience with its caloric content (Hajnal and Norgren, 2001; Rada et al., 2005). An alternative explanation could be that DA increases in the NAc shell as a consequence of the orosensory stimulation. In order to bypass most postingestional factors a gastric fistula can be implanted so that a liquid diet (e.g., sucrose) can

be drained out (Mook et al., 1988; Smith, 1998). Sham-feeding confirms that the taste of sucrose can release DA in the NAc (Hajnal et al., 2004; Avena et al., in press(b)), thereby corroborating the effect of saccharin (Mark et al., 1991). Together, these results demonstrate that DA release in the NAc can vary with orosensory stimulation, postingestive factors, and the presence of a novel palatable food.

II.A.1.b. Acetylcholine in the nucleus accumbens (behavior inhibition). Acetylcholine in the STR and accumbens is released from interneurons that represent 5% of the cellular population (Bolam et al., 1984; Meredith et al., 1989). Some clues as to the effects of cholinergic interneurons on reward mechanisms can be deduced from Parkinson's disease. These patients have destruction of DA neurons in the basal ganglia and present symptoms such as bradikinesia, rigidity, and abnormal movements (dorsal STR), and also an anhedonic state (ventral STR) (Fibiger, 1984; Isella et al., 2003; Lemke et al., 2005) including weight loss (Chen et al., 2003; Palhagen et al., 2005; Tuite et al., 2005). A general hypothesis suggests that normal functioning of the basal ganglia depends on a balance between DA/ACh in the STR (Grewaald et al., 1974). When the DA neurons degenerate, an imbalance occurs, with a relative increase in ACh release (Spehlmann and Stahl, 1976; Rodriguez-Puertas et al., 1994). This led us to the theory that ACh in the NAc could counteract DA's rewarding signal and thus produce behavioral inhibition.

Few studies have investigated the role of ACh in the NAc during feeding. Acetylcholine increases in the accumbens at the end of the meal and probably signals satiety (Mark et al., 1992). When neostigmine, an acetylcholinesterase inhibitor and indirect cholinergic agonist, was infused through a dialysis probe bilaterally in the NAc, a decrease in food intake was observed (Mark et al., 1992). Moreover, bilateral infusion of a muscarinic (M1) receptor agonist (arecoline) shortens the time interval to reach satiety (Rada et al., unpublished data). Lesion of the cholinergic interneurons with a specific neurotoxin makes rats eat more, although they lose body weight (Galosi et al., 1997; Hajnal et al., 2000). Further evidence that ACh could be involved in behavioral inhibition comes from conditioned taste aversion experiments, in which an aversive taste increases ACh levels in the NAc (Mark et al., 1995) and local injection of a cholinergic agonist into the accumbens induces a conditioned taste aversion (Taylor et al., 1992). Finally, the hypothesis that ACh signals satiety was tested using the sham-feeding paradigm. If ACh signals satiety, then sham-fed rats should consume large amounts of food without any change in accumbens ACh. Indeed, rats that are sham-fed drink large amounts of a liquid diet (10% sucrose) and show no significant change in ACh levels in the NAc during the meal. Evidently postingestional signals are needed to activate ACh interneurons during feeding behavior as can be seen in Fig. 2 (Avena et al., in press).

Several anomalous behavioral results question the idea that ACh serves as a behavior-inhibition signal in the NAc, but there are alternative explanations for these results. Carbachol, a nonspecific cholinergic agonist, is self-administered directly into the accumbens (Ikemoto et al., 1998). In a feeding paradigm, local injection of the nonspecific muscarinic antagonist, scopolamine, reduces lever pressing for food and sucrose consumption and increases locomotor activity (Pratt and Kelley, 2004; Kelley et al., 2005; Pratt and Kelley, 2005). In these experiments a nonspecific agonist and antagonist, were used, making the interpretation difficult. For instance, brain microdialysis has shown that local infusion of scopolamine into the accumbens increases ACh release, probably by antagonizing M2 presynaptic autoreceptors (Chau et al., 1999, 2001), and local infusion of carbachol not only decreases ACh release but also increases DA release, possibly explaining why rats would self-administer this drug (Fig. 3).

II.A.1.c. Glutamate and GABA in the nucleus accumbens. Evidence has been accumulating for roles of accumbens glutamate (GLU) in reward, motivation and novelty (Saulskaya and Mikhailova, 2004; Kalivas and Volkow, 2005). Local injection in the NAc of an AMPA/kainate antagonist is sufficient to stimulate feeding in satiated rats (Maldonado-Irizarry et al., 1995). This was later corroborated by microdialysis, showing

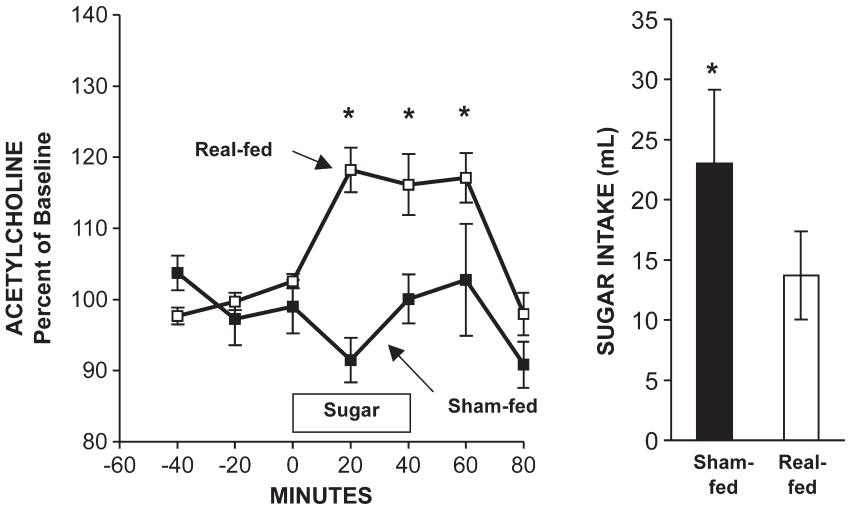

Fig. 2. Changes in extracellular levels of ACh in the NAc of sham-feeding and real-feeding rats. Acetylcholine only increased in real-feeding rats during sugar intake. Bar graphs indicate the amount of sugar consumed in the sham-feeding rats (black bars) compared with real-feeding rats (open bars). Asterisks indicate $p<0.05$.

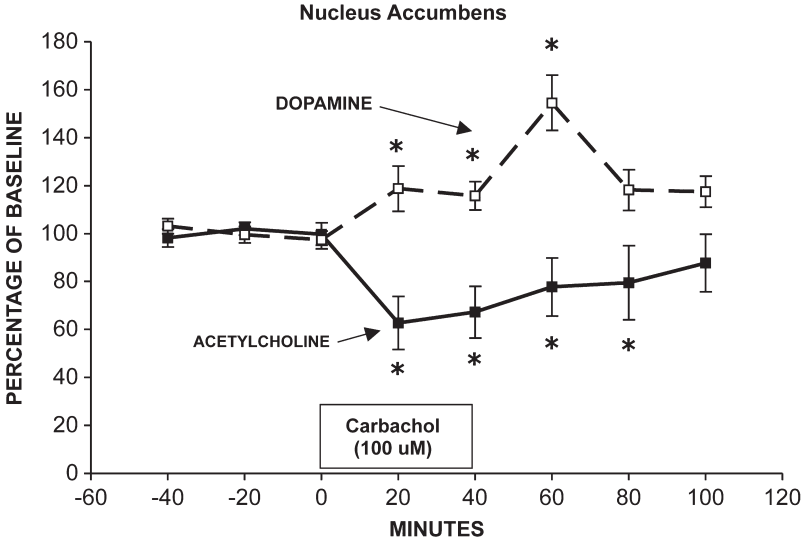

Fig. 3. A 40 min infusion of carbachol (100 μM) in the accumbens by reverse microdialysis simultaneously decreased extracellular ACh and increased DA levels in the NAc. Asterisks indicate $p<0.05$.

that free feeding in food-deprived rats significantly decreased GLU release in the NAc (Rada et al., 1997). Intraaccumbal injection of raclopride, a D2 antagonist, prevents the GLU decrease (Saulskaya and Mikhailova, 2002). Glutamate is released in the NAc following the presentation of an inedible object when the rat expects food (Saulskaya and Mikhailova, 2002) and also during the presentation of a conditioned aversive stimuli (Saulskaya and Mikhailova, 2004), suggesting that GLU is released in the NAc when the motivational value of the reward is changed or aversive.

Several pharmacological studies show that local injections of GABA agonists into the NAc increase food intake (Reynolds and Berridge, 2002; Hanlon et al., 2004); however, presently there are no known microdialysis studies that have measured the effect of feeding on GABA release.

II.A.2. Ventral tegmental area microdialysis during feeding

This brain area is of utmost importance since DA neurons, forming the mesolimbic system, originate in the VTA (Fallon and Moore, 1978). These DA neurons are known to be under the influence of other neurotransmitter systems including GLU (Taber and Fibiger, 1997; Westerink et al., 1997; Floresco et al., 2001; Harris and Aston-Jones, 2003), GABA (Cruz et al., 2004; Ye et al., 2004), and the opioids (Cowen and Lawrence, 1999).

II.A.2.a. Dopamine in the ventral tegmental area. Dopamine is not only released in its terminal region, the NAc, but also in its dendritic area. While the majority of research has focused on the NAc, studies have shown that extracellular DA increases in the VTA in response to opioids (Klitenick et al., 1992; Yoshida et al., 1993). With regard to feeding, extracellular DA increases in the VTA while an animal eats (Yoshida et al., 1992).

II.A.2.b. Acetylcholine in the ventral tegmental area. The VTA receives cholinergic inputs from the pedunculopontine nuclei (Woolf, 1991). Infusion of nicotine directly into the VTA by reverse microdialysis stimulates DA release in the NAc (Nisell et al., 1994). Muscarinic receptors in the VTA have also been shown to modulate feeding and drinking behavior. For instance, local injection of a muscarinic antagonist suppresses feeding and ICSS (Rada et al., 2000; Sharf and Ranaldi, 2006). Conversely, ICSS stimulates ACh release in the VTA (Rada et al., 2000). In this brain area, ACh seems to facilitate behavior by directly stimulating DA neurons that release DA in the NAc (Forster and Blaha, 2000; Yeomans et al., 2001).

II.A.3. Hypothalamic microdialysis during feeding

In the following paragraphs we will discuss some of the neurochemical findings using brain microdialysis to measure amines and amino acids in the hypothalamic region that have important links to the reward circuitry.

II.A.3.a. Dopamine in the hypothalamus. Dopamine in the hypothalamus is thought to play a very different role in feeding than in the NAc. Early studies suggested that DA in the LH might be involved in the anorectic effect of amphetamine (Leibowitz, 1975). This was later confirmed when a local LH injection of sulpiride, a relatively specific D2 antagonist, was sufficient to induce feeding and drinking (Parada et al., 1988) and, with repeated injections, obesity (Baptista, 1999). DA in the LH may be essential in locomotion related to food and water seeking (Parada et al., 1990). Microdialysis studies have found that eating induces a significant increase in DA levels in the LH, with no change observed in rats fed intragastrically, suggesting that oropharyngeal stimulation is important (Yang et al., 1996). However, in this report samples were taken every 20 min, so it is difficult to know whether the DA increase was signaling satiety. DA increase is directly correlated with the meal size and it has been suggested that obese Zucker rats may have an inherently higher DA "threshold" level for satiety in the LH (Yang and Meguid, 1995). It is difficult to know if DA signals satiety and obese rats have a higher threshold or whether obese rats eat more because they release more DA in the LH. Behavioral experiments support the DA satiety explanation since DA agonists act as anorectics when injected into the LH (Leibowitz, 1975). Moreover, rats self-administer a DA antagonist directly into the LH and this releases DA in the NAc, thus linking LH DA to the inhibition of NAc DA reinforcement (Parada et al., 1995).

The ventromedial hypothalamus (VMH) usually has an opposing response to that observed in the LH. The VMH sends GABAergic projections to the LH that may inhibit feeding (Beverly and Martin, 1989). The VMH also receives dopaminergic inputs, which respond in the opposite manner to the LH, with a decrease in extracellular

DA concentrations during a meal (Yang et al., 1997), which depends directly on the size of the meal (Meguid et al., 1997). The DA decrease in the VMH depends in part on oropharyngeal stimulation (Yang et al., 1997). In summary, DA release in the hypothalamus is involved in feeding behavior and the LH and VMH probably have opposing dopaminergic functions. The source of DA in the hypothalamus could be local DA cell clusters as well as the mesolimbic system (Fuxe and Ungerstedt, 1968).

II.A.3.b. Norepinephrine in the hypothalamus. Extracellular norepinephrine (NE) in the hypothalamus follows a circadian rhythm, suggesting that it plays an important role in the animal's overall state of arousal (Margules et al., 1972; Jacobs and Chan, 1987; Stanley et al., 1989). The earliest studies, and more precisely in the paraventricular nucleus (PVN), can enhance food intake (Grossman, 1960; Leibowitz, 1970, 1972). Microdialysis studies found that NE is released in the PVN at the beginning of the active feeding period coinciding with the onset of the active cycle of the rat (dark onset) (Hoebel et al., 1989; Stanley et al., 1989; Mitome, 1994; Morien et al., 1995; Tachibana et al., 2000, 2001). It was later found that PVN NE increases in satiated rats during a large meal at dark onset, and it also increases at the start of the dark cycle in food-deprived rats given a carbohydrate meal (Paez et al., 1993). In rats maintained on a restricted schedule, NE levels rise just before the meal (Mitome et al., 1994).

Further studies have looked at the effect of various drugs or peptides, which can modify ingestive behavior, on hypothalamic NE. For instance, galanin (GAL) and neuropeptide-Y (NPY) are both peptides that, if injected in the PVN, can induce feeding (Kyrkouli et al., 1990), and also increase NE levels in the PVN in rats if food is present (Kyrkouli et al., 1992). If food is not present, GAL still increases NE levels, but NPY decreases it (Kyrkouli et al., 1992). Intraventricular injection of NPY increases both food intake and NE in the PVN (Matos et al., 1996). Alpha-adrenergic antagonists are capable of blocking the GAL- but not the NPY feeding response (Kyrkouli et al., 1990). These results are consistent with previous behavioral studies showing that GAL-induced eating is probably mediated through the NE system.

Anorectic drugs modify NE release in the hypothalamus. For instance, systemic injection of phenylpropanolamine, an alpha-1 adrenoceptor agonist, suppresses food intake in rats and simultaneously decreases extracellular levels of NE in the PVN (Davies et al., 1993). In contrast, the alpha-2 blocker, idazoxan, also suppresses food intake in the rat, but instead of the expected decrease in NE levels in the PVN an increase occurs, which may be mediated through a presynaptic autoreceptor (Paez and Leibowitz, 1993). These results illustrate the importance of microdialysis in recognizing possible pre- and postsynaptic mechanisms of action for various peptides and drugs that modulate ingestive behavior.

Few studies have looked at the effect of obesity on NE levels in the hypothalamus, although it is known that chronic infusions of NE into the VMH or the PVN induce hyperphagia and obesity (Leibowitz et al., 1984; Cincotta et al., 2000). One model of obesity uses male offsprings of female rats that were undernourished during the first two trimesters of pregnancy or had been injected with insulin during the third trimester (Jones and Friedman, 1982; Jones and Dayries, 1990). Microdialysis of the medial hypothalamus in the obese offspring showed a significant elevation in extracellular NE levels compared with control rats (Jones et al., 1995). Thus, NE may play a role in feeding or body weight regulation in this model of gestation-linked obesity.

II.A.3.c. Histamine in the hypothalamus. Pharmacological studies have demonstrated that local hypothalamic histamine modulates food intake (Ookuma et al., 1989). This was confirmed by locally manipulating histamine levels in the PVN and VMH using an inhibitor of the synthetic enzyme histidine decarboxylase. Experimentally decreasing histamine levels induces feeding, but only at the start of the light cycle and only in the PVN or VMH, not in the LH or dorsomedial hypothalamus (Ookuma et al., 1993). Histamine may modulate ingestive behavior in the hypothalamus by interacting with the noradrenergic system. Local injection of a histamine H1 receptor antagonist

increases feeding and extracellular NE, and this effect is blocked by a specific alpha-2 adrenoceptor antagonist (Kurose and Terashima, 1999).

II.A.3.d. Serotonin in the hypothalamus. Medial hypothalamic (MH) injection of serotonin (5-HT) or its agonists inhibit feeding behavior (Leibowitz, 1986; Leibowitz et al., 1987, 1988). Initial microdialysis studies of 5-HT during a meal demonstrated that 5-HT increased in the LH and also in the medial hypothalamus in anticipation of a meal when smelling food, as well as during the meal (Schwartz et al., 1990), suggesting that 5-HT may play a role in the response to food-related appetitive stimuli and then contribute to satiety when postingestional factors release CCK or related satiety signals. Later studies demonstrated that 5-HT increases if the rat is given a carbohydrate meal, and this increase is detected 15 min after the start of the meal, possibly contributing to satiety. In this same report, it was found that a protein or fat meal could decrease 5-HT levels (Rouch et al., 1999). This may relate in part to tryptophan uptake for 5-HT synthesis after a carbohydrate meal (Fernstrom and Wurtman, 1974). Other researchers have found changes in hypothalamic 5-HT levels in normal and obese rats consistent with the theory that 5-HT can act as a satiety signal (Mori et al., 1999; Fetissov et al., 2000; De Fanti et al., 2001). Several groups have investigated the effect of satiety peptides on hypothalamic 5-HT release. Enterostatin or leptin can increase extracellular 5-HT in the LH (Koizumi and Kimura, 2002; Telles et al., 2003). Conversely, Orosco and collaborators suggest that 5-HT causes the release of insulin in the PVN-VMH region (Orosco et al., 2000). These microdialysis studies point to a role for 5-HT in modulating circuits that control food intake, including a strong synergistic effect with postingestional satiety factors.

II.A.3.e. Acetylcholine in the hypothalamus. In the LH several studies have demonstrated the potentiation of eating and drinking water following local injection of a muscarinic agonist (Grossman, 1960; De Parada et al., 2000). However, so far there seems to be no published microdialysis studies of ACh release in the LH during feeding behavior.

II.A.3.f. Glutamate and GABA in the hypothalamus. Retrograde labeling shows that GLU inputs to the LH originate in the frontal cortex, AMYG, NAc, preoptic area, SN, VTA, parabraquial nuclei, and the nucleus of the solitary tract (Duva et al., 2005). Glutamate has been shown to induce feeding when injected locally in the LH (Stanley et al., 1993a, b; Khan et al., 1999; Duva et al., 2002). Moreover, injection of NMDA into the LH induces eating without affecting locomotion (Duva et al., 2001, 2002). Extracellular levels of GLU in the LH increase at the beginning of a meal and then decrease by the end of the meal (Rada et al., 2003). It would seem that GLU initiates eating as a fast-acting neurotransmitter, and the maintenance of the behavior probably depends on other neurotransmitters.

It has been suggested that there exists reciprocal connections between the medial and LH. In the medial hypothalamus GABA can induce eating (Beverly and Martin, 1989, 1990). Furthermore, following acute glucoprivation that would increase appetite, extracellular GABA increases in the VMH while an opposite response occurs in the LH (Beverly et al., 1995). Early studies injecting a GABA agonist into the LH showed an increase in feeding, while antagonists did the opposite (Kelly et al., 1977; Kelly and Grossman, 1979; Tsujii and Bray, 1991). However, later studies suggest a decrease in feeding when a GABA agonist is locally injected into the LH (Maldonado-Irizarry et al., 1995), but an antagonist does not initiate feeding (Stratford and Kelley, 1999). Monitoring GABA in the LH every 30 s during a meal it was found that it increased at the end of the meal, possibly signaling satiety (Rada et al., 2003). This could also explain the absence of response using antagonists in the LH to induce feeding, since GABA levels might be too low before the meal for an antagonist to show any effect at that time.

II.A.4. Hypothalamic accumbens connections

There are both direct and indirect connections between the hypothalamus and the NAc (Kelley et

al., 2005). Microdialysis has provided evidence that these sites may interact. Most, but not all, neurotransmitters or peptides that promote feeding when injected into the hypothalamus also stimulate DA and decrease ACh release in the NAc, while satiating peptides do the opposite (Leibowitz and Hoebel, 2004). Injection of the cholinergic agonist, carbachol or the DA antagonist, sulpiride, into the LH both increases food intake and simultaneously increases DA release in the NAc (De Parada et al., 2000). Similarly, injection of NE or GAL into the PVN of the hypothalamus increases food consumption, which is correlated with a significant increase in DA and decrease in ACh in the NAc (Hajnal et al., 1997; Rada et al., 1998). Conversely, cholecystokinin (CCK) injected into the PVN decreases food ingestion while decreasing DA in the NAc (Helm et al., 2003). Cholecystokinin does not increase ACh unless it is injected simultaneously with 5-HT, which then produces a profound decrease in food intake along with increased ACh release (Helm et al., 2003). This suggests that under normal circumstances, postingestional factors would provide CCK release for interaction with 5-HT contributing to the decrease in DA and increase in ACh release in the NAc. In summary, as a general rule, the hypothalamus controls feeding behavior, in part, by modulating DA and ACh in the NAc (Hoebel et al., 1999).

An exception to the hypothalamic accumbens rule is NPY. Injection of this peptide into the PVN induces eating in the rat, however, no changes in extracellular DA or ACh were detected (Rada et al., 1998a), suggesting that NPY can induce feeding by some other mechanism, or requires other cofactors that were not present.

II.B. Water intake

Compared with the abundant data on food intake, there are relatively few brain microdialysis studies on water intake. It has been reported that drinking releases DA in the NAc and VTA (Yoshida et al., 1992; Young et al., 1992). Injection of a D2 receptor antagonist in perifornical LH can induce drinking and increase DA in the NAc (Parada et al., 1988, 1990). This activation of the DA mesolimbic system could mediate some of the rewarding aspects of drinking behavior.

Similar to the effect seen with food intake, ACh increases in the VTA during drinking, and blockade with muscarinic receptors in the same area inhibits water intake (Rada et al., 2000). In the LH, extracellular ACh also increases during drinking, and the exogenous administration of cholinergic drugs or D2 receptor blockers increases water intake (Puig de Parada et al., 1997). These microdialysis studies are in agreement with behavioral studies that show an increase in water intake following pharmacological manipulation of the cholinergic system with carbachol (Grossman, 1960).

Angiotensin II injections into the subfornical organ induce drinking (McKinley et al., 2001) and release NE in the PVN and LH, even when water is not available (Gerstberger et al., 1992). However, this NE increase is attenuated if rats are allowed to drink (Ushigome et al., 2002; Tanaka et al., 2003). These studies indicate that a hypothalamic component of the noradrenergic system participates in drinking behavior. Angiotensin injection in the lateral ventricle releases DA in the NAc (Jones, 1986). This effect is enhanced if the rat is allowed to drink in response to the injection (Hoebel et al., 1994).

II.C. Mating

The NAc participates in the control of sexual behavior in the same way that it does with other natural reinforcers. Microdialysis in the NAc of male and female rats shows an elevation of extracellular DA levels during sexual behavior (Damsma et al., 1992; Mas et al., 1995; Becker et al., 2001). In the NAc of sexually active male rats DA levels increase when a receptive female rat is presented, and increase even more during copulation (Pfaus et al., 1990; Pleim et al., 1990). Damsma and colleagues have examined the effects of locomotion, exposure to a novel chamber, sex odors, and sexual activity on DA transmission in the NAc and STR (Damsma et al., 1992). The DA increase seen during copulation is greater following active

locomotion (wheel running) or exposure to novel stimuli (mating chamber, fresh bedding, or soiled bedding). This increase was more intense in the NAc than the STR. Thus, neither novelty nor locomotion can account for the increase of DA in either area, suggesting that the anticipatory and consummatory aspects of sexual behavior are naturally occurring events in which reinforcement is likely mediated by DA release in the NAc.

Dopamine in the NAc and STR is also increased during sexual behavior in females, but only when the female controls the time of intromissions (Becker et al., 2001). The timing of copulatory stimuli is critical for the magnitude of the increase in accumbens DA. When intromissions are spaced 1–2 min apart and insemination would most likely result in pregnancy, DA significantly increases in the NAc. This increase is not a passive response to coital stimuli or copulation-related motor activity, and possibly reflects other qualitative information about the copulatory stimuli.

The medial preoptic area (MPOA) is located at the rostral end of the hypothalamus and is a critical integrative site for male sexual behavior in most vertebrate species. DA agonists in MPOA facilitate sexual behavior, while antagonists impair copulation, genital reflexes and sexual motivation (Mas et al., 1987; Bitran et al., 1988; Warner et al., 1991; Dominguez and Hull, 2005). Microdialysis in the MPOA has shown a DA increase during appetitive (noncontact exposure to sexual stimuli such as exposure to a receptive female) and consummatory (copulation) phases (Fumero et al., 1994; Dominguez et al., 2001; Triemstra et al., 2005). Recently, it was shown that GLU, by stimulating nitric oxide, is responsible for this increase in MPOA DA during copulation (Dominguez et al., 2004).

Bilateral olfactory bulbectomy completely prevents mating in male rodents; however, unilateral bulbectomy does not. Microdialysis performed in the MPOA of animals with unilateral bulbectomy during mating shows that DA increases only in the contralateral and not in the ipsilateral side, suggesting that somatosensory cues alone are not sufficient to release DA in the MPOA during sexual behavior in the absence of chemosensory input (Triemstra et al., 2005). Sexually excitatory olfactory stimuli activate the medial AMYG (MeA), which in turn projects to the bed nucleus of the stria terminalis and the MPOA leading to DA release and facilitation of copulation (Kostarczyk, 1986; Gomez and Newman, 1992; Dominguez et al., 2001).

Microdialysis in the anterior LH area suggests that 5-HT inhibits behaviors during the postcopulatory phase of male sexual behavior (Lorrain et al., 1999). Serotonin injection in the LH also inhibits basal and female-induced DA release in the NAc. This suggests that the neural circuit promoting sexual quiescence during the postejaculatory interval include serotonergic input to the LH, which in turn inhibits DA release in the NAc. This fact may have relevance for understanding the sexual side effects common to antidepressants medications (Rudkin et al., 2004).

III. Artificial rewards

III.A. Intracranial self-stimulation

Olds and Milner (1954) discovered ICSS in the mid 1950s to produce positive reinforcement. Research, using intracerebral microdialysis, has focused mainly on how ICSS modulates DA release in the NAc. Most studies show that LH or VTA ICSS releases DA in the NAc (Hernandez and Hoebel, 1988a; Nakahara et al., 1989a, b; Phillips et al., 1992; Fiorino et al., 1993; You et al., 1998, 2001). Similarly, electrical brain stimulation of the PFC significantly increases DA release in the NAc (Taber and Fibiger, 1995; You et al., 1998, 2001). This rise in NAc DA is intensity dependent and can be blocked with the excitatory amino acid antagonist kynurenic acid injected either into the VTA or directly into NAc, suggesting that the neural signal engages the VTA (You et al., 1998). In addition, like food reward, self-stimulation of the LH also increases ACh release in the VTA and an infusion of atropine, through reverse dialysis, completely blocks self-stimulation confirming that this cholinergic system in the hindbrain is involved in activating the DA neurons in the VTA (Rada et al., 2000; Sharf and Ranaldi, 2006).

As discussed in previous paragraphs, an electrolytic lesion of the LH produces aphagia and adipsia. Conversely, electrical stimulation of the LH induces feeding in satiated animals (Anand and Brobeck, 1951a, b; Hoebel and Teitelbaum, 1962; Valenstein et al., 1968; Hoebel, 1976). Using microdialysis to monitor DA levels in the NAc, an increase in DA levels was demonstrated following electrical stimulation of the perifornical LH or eating (Hernandez and Hoebel, 1988a; Rada et al., 1998b). This suggests that ICSS and feeding share common circuitry and that DA in the NAc could be part of the signal.

Using hypothalamic sites where electrical stimulation was either positively or negatively reinforcing, or both, DA was released in the NAc by automatic stimulation, self-stimulation or stimulation–escape responding. DA increases even during stimulation escape using a MH site that was purely aversive (Rada et al., 1998b). These results confirm that DA in the NAc is not only involved in positive reinforcement, but in negative reinforcement as well.

As cited in the prior section on ACh in the NAc, the aversive LH stimulation causes release of accumbens ACh. Stimulation–escape responding significantly decreases extracellular ACh levels (Rada and Hoebel, 2001). This supports the theory that elevated ACh in the accumbens is aversive, and reducing it is part of the reward earned by stimulation–escape responses.

III.B. Drug reward

Almost all drugs abused by humans increase DA in the NAc (Di Chiara and Imperato, 1988; Hernandez and Hoebel, 1988b; Pothos et al., 1991; Rada et al., 1991a, 2001; Tanda et al., 1997; Di Chiara, 1998; Koob et al., 1998; Hoebel et al., 1999) with the exception of benzodiazepines and barbiturates (Masuzawa et al., 2003; Rada and Hoebel, 2005). Withdrawal in contrast decreases DA release in the NAc (Parsons et al., 1991; Pothos et al., 1991; Weiss et al., 1992; Diana et al., 1993, Hildebrand et al., 1998; Rada et al., 2004) and, in several cases, increases ACh release (Rada et al., 1991b, 1996, 2001, 2004). Although the benzodiazepine, diazepam (Valium), does not release DA, its withdrawal does release ACh. On the theory that relatively high extracellular ACh is aversive, this could contribute to the use of diazepam for self-medication (Rada and Hoebel, 2005).

Note that with natural satiety, ACh increases, but DA is "normal" or elevated. However, during drug withdrawal DA and ACh often respond in opposite directions, with a decrease in DA and increase in ACh. It was hypothesized that this imbalance probably gives rise to an aversive state.

IV. Natural and artificial rewards: do they share common reward mechanisms and circuitry?

IV.A. Sugar addiction

Natural reward mechanisms presumably were selected in the wild to promote behaviors that are necessary for the survival of the species. In normal animals these reinforcers have opposing mechanisms that inhibit the behavior once the specific need has been satisfied. However, drugs of abuse activate the reward circuits without necessarily activating the inhibitory components of the regulatory system. A large body of evidence suggests that natural reinforcers and drugs of abuse share common reward circuitry. For example, both food and drug reinforcers increase extracellular DA in the NAc (Di Chiara and Imperato, 1988; Hernandez and Hoebel, 1988b; Radhakishun et al., 1988; Pothos et al., 1991; Rada et al., 1991a; Salamone, 1994; Wise et al., 1995a, b; Tanda and Di Chiara, 1998; Cappendijk et al., 1999; Acquas et al., 2002). These reinforcers seem to also share behavioral responses. For instance, sweet taste or morphine prolongs a meal. This can be blocked with naloxone, an opiate antagonist (Sclafani et al., 1982; Nader et al., 1994; Gosnell et al., 1996). Consumption of sugar can act as an analgesic by releasing endogenous opioids (Kanarek et al., 1991). Weight loss increases opiate-induced eating and also drug self-administration (Hagan and Moss, 1991; Specker et al., 1994; Cabeza de Vaca and Carr, 1998).

An animal model of binge eating has been developed by the Hoebel laboratory to systematically study whether excessive sugar intake can elicit behavioral and neurochemical changes similar to those of drugs of abuse (Avena et al., in press(a)). Several diagnostic criteria used to study drug abuse reveal that binge eating of palatable foods, a major behavioral component of obesity, may have some addictive-like properties. For example, rats maintained on a diet of intermittent access to a sugar solution and chow gradually escalate their intake of sugar over the course of one month and "binge" on the sugar when it becomes available each day (Colantuoni et al., 2001). These animals also have increased D1 and mu-opioid receptor bingeing, and D3 receptor mRNA in the NAc (Bassareo and Di Chiara, 1997; Colantuoni et al., 2001; Spangler et al., 2004). Drugs of abuse are known to repeatedly increase DA release in the NAc without habituation of the response as seen with palatable food (Bassareo and Di Chiara, 1997). Sugar bingeing also repeatedly releases DA in the NAc (Rada et al., 2005), similar to addictive drugs (Fig. 4). A similar result is obtained when sugar-bingeing rats sham-feed during the binge, suggesting that the taste of sugar is sufficient to release DA repeatedly in the NAc (Avena et al., in press(b)). Signs of withdrawal such as teeth chattering, grooming, anxiety, depression, and distress vocalization are found in sugar-bingeing rats. This is most noticeable when withdrawal is precipitated by an opioid antagonist, suggesting that the endogenous opioid system is altered by the excessive bingeing. During both naloxone precipitated and even during simple withdrawal of the sugar (spontaneous withdrawal, unpublished observations) microdialysis reveals decreases in DA and increases ACh in the NAc (Colantuoni et al., 2002), indicative of a drug-like withdrawal state (Pothos et al., 1991; Rada et al., 1991, 1996). Craving-like behavior is seen in sugar-binge animals as they manifest increased intake after 2 weeks of abstinence, known as a "deprivation effect" (Avena et al., 2005). After a month of abstinence the animals respond more than before for cues previously associated with sugar (Grimm et al., 2005).

Evidence of cross-sensitization between sugar bingeing and withdrawal-induced locomotion (Avena and Hoebel, 2003), withdrawal-induced locomotion (Gosnell, 2005), or enhanced alcohol intake (Avena et al., 2004) has been shown, suggesting that a common neural pathway, presumably DA, mediates these behaviors. Thus, each of these similarities suggest that binge eating on sugar results in a state qualitatively similar to drug abuse, and that this state persists and can foster future intake of sugar or drugs of abuse and suggests that a natural reinforcer such as sugar can

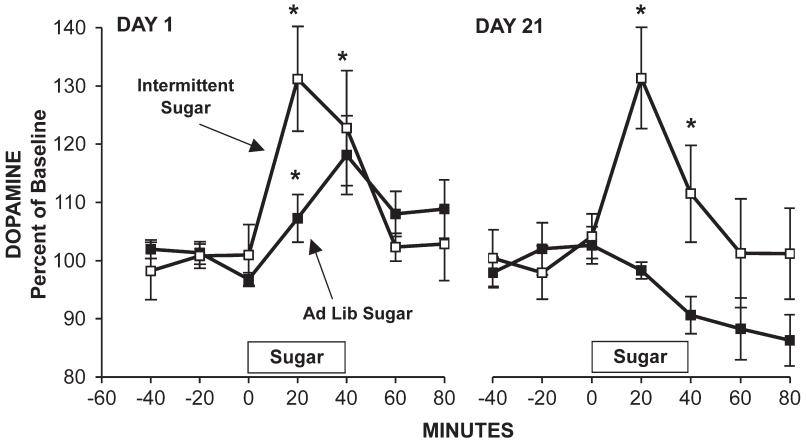

Fig. 4. Dopamine increases the first time rats have access to sugar; however, this response habituates and disappears in following trials if rats have *ad libitum* access to the sugar. In contrast, rats receiving intermittent sugar show the same DA response every time, similar to drugs of addiction.

change from a substance of use to a substance of abuse. All of these results point to a natural function for addiction that is usurped by the more powerful drugs of abuse.

V. Conclusions

Brain microdialysis was invented by Ungerstedt (1984) and continues to be an immensely valuable technique for monitoring biochemicals and their metabolites in vivo. The measurement of release is one of the criteria for proving that a substance is a neurotransmitter. Moreover, measurement of release during behavior provides a critical piece of information in determining when and where the neurotransmitter-coded system is active. As faster time-sampling techniques are invented to match the rate of nerve impulse flow, microdialysis will continue to have a place for verifying measurement of the actual neurotransmitter in relation to behavior and underlying neural processes that depend on volume conduction through the extracellular and ventricular fluids of the brain.

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