



## Cholinergic modulation of food and drug satiety and withdrawal

Nicole M. Avena <sup>a,b,\*</sup>, Pedro V. Rada <sup>c</sup>

<sup>a</sup> University of Florida, College of Medicine, Department of Psychiatry, McKnight Brain Institute, Gainesville FL 32610, United States

<sup>b</sup> Princeton University, Department of Psychology, Princeton, NJ 08540, United States

<sup>c</sup> Universidad de Los Andes, School of Medicine, Laboratory of Behavioral Physiology, Merida 5101-A, Venezuela

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### ABSTRACT

Although they comprise only a small portion of the neurons in the region, cholinergic interneurons in the dorsal striatum appear to play an important role in the regulation of various appetitive behaviors, in part, through their interactions with mesolimbic dopamine (DA) systems. In this review, we describe studies that suggest that the activity of cholinergic interneurons in the nucleus accumbens (NAc) and cholinergic projections to the ventral tegmental area (VTA) affect feeding behavior. *In vivo* microdialysis studies in rats have revealed that the cessation of a meal is associated with a rise in acetylcholine (ACh) levels in the NAc. ACh activation will suppress feeding, and this is also associated with an increase in synaptic accumulation of ACh. Further, we discuss how, in addition to their role in the ending of a meal, cholinergic interneurons in the NAc play an integral role in the cessation of drug use. Another cholinergic system involved in different aspects of appetitive behavior is the projection from the pedunculopontine nuclei directly to the VTA. Activation of this system enhances behaviors through activation of the mesolimbic DA system, and antagonism of ACh receptors in the VTA can reduce drug self-administration. Finally, we discuss the role of accumbens ACh in both drug and palatable food withdrawal. Studies reveal that accumbens ACh is increased during withdrawal from several different drugs of abuse (including cocaine, nicotine and morphine). This rise in extracellular levels of ACh, coupled with a decrease in extracellular levels of DA, is believed to contribute to an aversive state, which can manifest as behaviors associated with drug withdrawal. This theory has also been applied to studies of overeating and/or "food addiction," and the findings suggest a similar imbalance in DA/ACh levels, which is associated with behavioral indications of drug-like withdrawal. In summary, cholinergic neurons play an important role in the modulation of both food and drug intake, as well as the aversive aspects of food- and drug-related addictive behaviors.

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### 1. Introduction

Food intake and drug use have been shown to activate common brain systems, which underlie the reinforcing aspects of these behaviors. The mesolimbic dopamine (DA) system has received a lot of attention with regard to studies of the common reinforcing nature of food and drugs of abuse [1–3]. While DA clearly has an important role, other neurotransmitters have recently begun to receive more attention as primary contributors to the regulation of food and drug intake. In this paper, we will focus on the distinct role that cholinergic neurons have in food and drug ingestion, particularly with regard to their unique contributions to the cessation of food and drug intake, as well as their role in aversive aspects that can ensue following overeating or drug use. Moreover, there is a relationship between DA and cholinergic functions in reward-related brain regions that has been reviewed

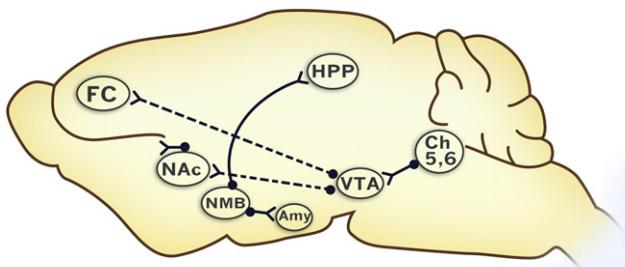
elsewhere [4–6], and a theory has been proposed that the balance of these neurotransmitter levels in the ventral striatum plays a role in motivated behaviors [5,6], much like the theory that exists regarding the role of the balance of DA and ACh in the dorsal striatum in the control of locomotor activity [7].

### 2. Mesolimbic ACh projections and inputs

Cholinergic neurons exist in multiple brain regions and activation of their receptors has important roles in many different brain processes and behaviors. In particular, ACh pathways have become interesting to study within the context of reward. As shown in Fig. 1, two major ACh projections innervate key components of the reward system. There is a forebrain projection from the nucleus basalis magnocellularis that provides input to the hippocampus and amygdala. While this pathway is generally implicated in degenerative aspects associated with Parkinson's and Alzheimer's diseases [8], it can also be associated with the learning and memory components of drug addiction [9]. There is also a hindbrain projection of ACh neurons from mesopontine cell groups (Ch 5, 6, pedunculopontine tegmental and laterodorsal

\* Corresponding author at: University of Florida, College of Medicine, Department of Psychiatry, McKnight Brain Institute, Gainesville FL 32610 United States. Tel.: +1 352 294 4935; fax: +1 609 259 3787.

E-mail address: [navena@ufl.edu](mailto:navena@ufl.edu) (N.M. Avena).



**Fig. 1.** Schematic depicting regions of the brain with cholinergic influence on feeding and drug reward and withdrawal. Solid lines represent ACh projection, and broke lines represent DA projections. FC = frontal cortex; HPP = hippocampus; NAC = nucleus accumbens, NMB = nucleus basalis magnocellularis; Amy = amygdala; VTA = ventral tegmental area; Ch 5,6 = pedunculopontine tegmental and laterodorsal tegmental nuclei.

tegmental nuclei) directly to the VTA, where they modulate the activity of DA neurons that innervate the NAc [10–13]. Finally, cholinergic interneurons exist in the NAc, where they comprise less than 1% of the neurons in this area, but are the sole direct cholinergic input to this region [14]. As a result, the NAc receives cholinergic input via activation of DA neurons in the VTA, as well as local influence by these cholinergic interneurons.

Of particular note is the fact that these cholinergic interneurons have an important role in the output projections from the NAc to multiple brain regions. Based on the literature and research described below, we propose that these output pathways may have distinct roles in promoting either satiety or appetite, depending on their specific co-transmitters [5]. The opioid peptide dynorphin is a co-transmitter in one GABA-output pathway and enkephalin is a co-transmitter on the other main GABA output pathway [15]. It is proposed that DA promotes appetite or satiety through activation of a select GABA output pathway and cholinergic activation of these pathways via muscarinic receptors.

## 2.1. Accumbens cholinergic activity modulates the cessation of feeding

The cessation of food intake is often considered in terms of gut-brain communications [16,17]. Indeed, vagal inputs to the brain and hormones that are released by gastric distension have powerful control over whether an animal will eat a meal or whether it will refrain from feeding [18,19]. Orexigenic and anorexigenic neurotransmitters have important roles in multiple brain regions and their specific roles can often depend on their location in the brain. In this section, we focus on the specific effect that ACh neurons and receptors, primarily in the NAc, have on food intake and satiety.

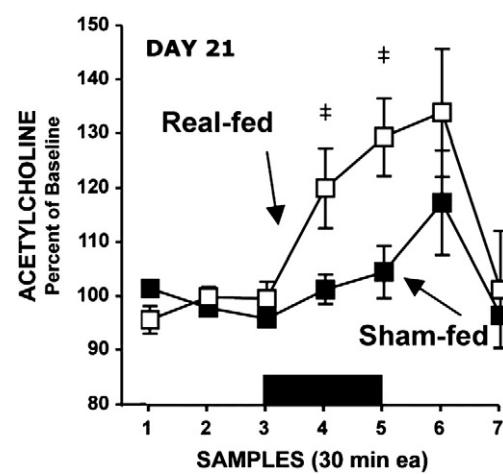
A lot of the information that has been ascertained regarding cholinergic regulation of feeding behavior has come from *in vivo* microdialysis studies. For example, there is survival value in refraining from eating certain foods, such as in the case of conditioned taste aversion. It has been shown that a conditioned taste aversion can increase extracellular ACh levels in the NAc [20], and conversely, infusion or local administration of the cholinergic agonist neostigmine can induce a conditioned taste aversion [21]. This suggests that inhibition of feeding behavior is associated with a rise in extracellular levels of ACh in the NAc. Further, microdialysis studies also reveal that there is an increase in extracellular levels of ACh in the NAc at the end of a meal [22]. When a meal is prolonged, such as in the case of a binge meal, the rise in extracellular levels of ACh is delayed, and mimics the time course of an exaggerated meal [23]. This delay in the rise of ACh may be related to a delay in satiety that could occur as a result of binge eating. Further support for the theory that increased extracellular levels of accumbens ACh are associated with the cessation of feeding comes from data showing that when rats binge eat sugar while at a reduced body weight, or when they

are sham fed sucrose using a gastric cannula, accumbens ACh is blunted [24,25] (Fig. 2). Thus, in situations in which it would be physiologically advantageous for the animal to continue to eat, such as when they are underweight or not retaining the food that is consumed, ACh levels in the NAc are not increased. Perhaps ACh levels serve as a signal to regulate intake of food.

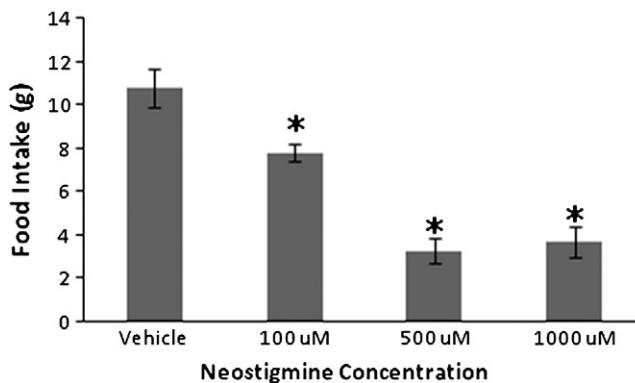
Behavioral studies support the theory that increasing levels of accumbens ACh can promote satiety. When rats are perfused with the indirect cholinergic agonist neostigmine into the NAc, they stop feeding (but continue to drink water normally) [4]. We have also found this effect, as shown in Fig. 3. Sprague-Dawley rats that were food deprived for 20 h were bilaterally microinjected in the NAc with neostigmine. Following the injection, rats were offered chow during the dark cycle. Food intake in the next 3 h decreased dose-dependently in neostigmine-injected rats compared with Ringer-injected control rats (100 mM, n=10; 500 μM, n=5; 1000 μM, n=5 and Ringer's solution, n=5; p<0.01). This finding was cross-validated by infusing neostigmine (1 mM) using reverse dialysis in non-food deprived rats during the dark cycle. In these rats, neostigmine inhibited food intake, while the control animals infused with Ringer's solution ate steadily over 4 h (1 mM, n=8; Ringer's solution, n=6; p<0.03). Together, these results suggest that increased extracellular ACh in the NAc can inhibit feeding. Thus, by promoting ACh levels in the synapse, food intake is attenuated.

It is important to consider that whenever feeding behavior decreases there is always the possibility that this is the result of malaise rather than satiety. In fact, as described above, we know that neostigmine injected in the NAc can induce a conditioned taste aversion [21]. However, the above-mentioned effects with neostigmine appear to be specific to reducing food intake that is not a result of malaise, as shown by water intake not being affected by neostigmine [4]. Further, additional studies support the idea that the promotion of ACh produces a food-specific effect. For example, systemic injection of appetite-suppressing drugs (*D*-fenfluramine + phentramine) also increases ACh in the accumbens [26].

Other studies suggest that food intake can be promoted by depleting ACh via local injection of the selective cholinergic neurotoxin ethylcholine aziridinium mustard (AF64A) into the NAc. In an acute (1 wk) feeding test, rats that were given this lesion showed a 2-fold increase in food intake [4]. Interestingly, despite this increase in food intake, rats with AF64A lesions in the NAc showed a significant and lasting lag in body weight gain in comparison to the sham-



**Fig. 2.** Rats with gastric fistulas were either real-fed (drain-valve sealed) or sham-fed (drain-valve open) 10% sucrose (marked with black bars) for 1 h. ACh rises during the meals in real-fed animals (open squares), but fails to rise during sham meals (filled squares). ‡ p<0.05. Adapted from [25].



**Fig. 3.** The cholinergic agonist neostigmine injected bilaterally in the NAc shell causes a dose-related decrease in intake of standard rodent chow. \* p<0.05.

operated controls [27]. Thus, there may be some compensatory mechanisms that occurs when ACh in the accumbens is ablated, which results in rats maintaining a less-than-normal body weight in the long term.

Work by Ann Kelly and her colleagues suggests that ACh receptor antagonism (not agonism) can promote satiety [28]. They find that scopolamine, a pan-antagonist for postsynaptic and presynaptic muscarinic receptors, reduces intake of high-fat food as well as lever pressing for food [29]. However, it should be noted that since scopolamine also blocks the presynaptic M2 autoreceptors on ACh neurons, blocking them increases the extracellular levels of ACh [30]. Thus, the antagonism of the muscarinic receptors with scopolamine might be inducing satiety by increasing extracellular levels of ACh, which could be acting on available muscarinic receptors or through an unknown mechanism to promote satiety. Thus, the exact role of muscarinic receptor mediation in feeding behavior is debatable, and further studies are needed in order to clarify the mechanism of action for the behaviors that have been observed.

In addition to the activity of cholinergic interneurons in the NAc, cholinergic influence in the hypothalamus also appears to participate in the regulation of food intake. This has been shown indirectly by the orexigenic peptide galanin in the hypothalamus lowering extracellular levels of ACh in the NAc [31]. Further, norepinephrine, which in the paraventricular nucleus of the hypothalamus can stimulate food intake, also reduces extracellular levels of ACh in the NAc [32]. More recent studies suggest that cholinergic nicotinic receptors in the hypothalamus activate pro-opiomelanocortin neurons, which subsequently activate melanocortin 4 receptors that are critical for nicotine-induced decreases in food intake in mice [33].

## 2.2. Cholinergic activity can influence drug intake

As discussed above, increased levels of ACh in the NAc are associated with food satiety, and the activation of specific receptors seems to be important in facilitating this effect, although more research is needed to fully understand the exact mechanisms through which this occurs. The literature suggests that there are overlaps in brain mechanisms that are associated with various appetitive behaviors, including those seen in some types of excessive feeding behaviors (such as overeating or binge eating), and drug use. In order to discuss the overlaps that may exist between overeating and drug addiction as they relate to ACh, in this section, we will very briefly discuss the effects that cholinergic neurons have on the intake of drugs of abuse. For more comprehensive reviews on this topic, see Williams and Adinoff [34] and Sofuoglu and Mooney [35].

Much like the topic of feeding, data are emerging to help disentangle the complicated neurocircuitry and receptor subtype roles in aspects of drug addiction. Different lines of research suggest a fundamental role for accumbens cholinergic interneurons in drug reward.

Systemic injection of acetylcholinesterase inhibitors, which serve as indirect ACh agonists by inhibiting ACh enzymatic degradation, can decrease cocaine self-administration in monkeys [36], block heroin seeking [37], and prevent cocaine and heroin conditioned place preference in rats [38], as well as preference for cocaine in mice [39]. Other studies have assessed the specific role of cholinergic interneurons in the NAc in the development of cocaine conditioning. Not only are these neurons activated by cocaine, but silencing of these neurons during cocaine exposure blocks cocaine conditioning in rats [40].

Perhaps the most well-known example of cholinergic regulation of drug intake comes from studies of nicotine. Smoking decreases appetite and many smokers report that they smoke to control their body weight [41]. Nicotine is an agonist of nicotinic ACh receptors [42]. Activation of nicotinic receptors on both NAc interneurons and/or on cell bodies that exist in the VTA increases DA in the NAc [43,44], and this release of DA is associated with the potent reinforcing value of nicotinic agonists. Blockade of the nicotinic cholinergic receptors in the VTA (using the antagonist mecamylamine) prevents DA release in response to systemic cocaine [4], which normally increases extracellular levels of ACh in the VTA. This suggests that psychostimulants may require cholinergic input on DA neurons in the VTA. Thus, nicotinic receptors expressed in the VTA are necessary for the effects of systemic nicotine on DA neuron activity and DA-dependent behaviors, such as locomotion, reinforcement, and behavioral sensitization [45,46]. Activation of muscarinic receptors can also influence drug self-administration. The mixed muscarinic agonist oxotremorine inhibits self-administration and breakpoint for cocaine [4,47]. Further, local injection of the muscarinic M2 autoreceptor antagonist oxotremorine-sesquifumarate into the lateral dorsal tegmental nucleus reduces motivation for food as well as cocaine self-administration, suggesting that inactivation of cholinergic input to the VTA is needed for these behaviors [4]. However, recent studies suggest that M4 receptors also may have a critical role in the facilitation of drug intake; M4 receptor knockout mice show increased intake of cocaine [48].

Thus, several studies highlight the important role of cholinergic input in the development of drug addiction [49]. Based on this work, it has been suggested that the cholinergic system be targeted in treating nicotine and other drug addiction [34,35,45]. Preclinical experiments support this idea. For example, when the nicotinic antagonist mecamylamine is added to the solution of cocaine, rats still consume it, but do not progressively escalate their intake of it [4,50]. Since escalation of intake is associated with the development of dependence, antagonism of nicotinic receptors might attenuate the development of dependence on cocaine. Furthermore, cholinesterase inhibitors have been used to attenuate the subjective effects of methylphenidate [51] and amphetamine [52].

## 2.3. ACh activity is modulated by food and drug withdrawal

In light of the recent publicity surrounding the obesity epidemic, the concept of “food addiction” has been popularized. In particular, clinical accounts of “food addiction” have been the topic of many books and popular diet programs [53–57]. In these accounts, people describe symptoms of withdrawal when they deprive themselves of highly-palatable foods, and these feelings are combined with food craving, particularly for carbohydrates, chocolate, and sugar, which can trigger impulsive eating. This leads to a vicious cycle of self-medication with foods that, for some people, may result in obesity or an eating disorder. Although food addiction has been popular in the media and proposed to be based on brain neurochemistry [58,59], this phenomenon has only recently been systematically studied in the laboratory.

The concept of addiction in animals and the means by which it can be studied are rooted in the classical drug addiction literature. There

are known overlaps that exist in brain reward regions that are activated by food and drugs of abuse [1,3,60,61]. We have used models that were developed with rats for studying drug dependence and adapted them to test for signs of food dependence. In our animal model, rats are food deprived daily for 12 h, then are given food and a sugar solution (25% glucose or 10% sucrose) after a delay of 4 h into their normal circadian-driven active period to stimulate a large meal (for review, see [62]). As a result, rats drink the sugar solution copiously (i.e., they binge), especially when it first becomes available each day, and they ultimately enter a state that resembles drug dependence on several dimensions [1]. Clinical studies have also been conducted using scales and brain imaging, lending support to the findings in animal models that suggest that some foods can produce behaviors and brain changes that resemble drug addiction (for review, see [60,63]).

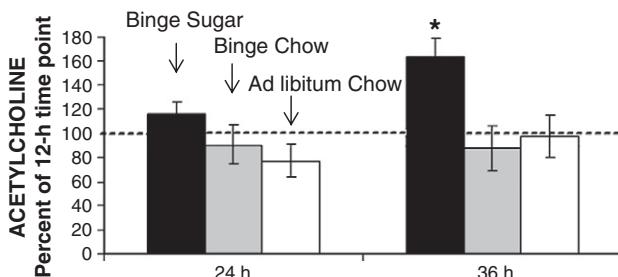
Together, this clinical and preclinical work has led to the suggestion that excessive intake of palatable food, which can sometimes result in obesity, can lead to a dependent-like state [1,63,64]. While in terms of neurochemistry, the majority of the work in this region has focused on the mesolimbic DA system [23,65–68], here we will review data that has come from our group, which shows similarities that exist between drug use and binge intake of palatable food with regard to accumbens ACh.

As mentioned above, the balance between DA and ACh in the NAc has been suggested to have a role in aspects of reinforcement, with drugs of abuse increasing extracellular levels of DA while ACh is relatively low [5]. However, in cases of withdrawal, the opposite balance is seen. Morphine dependent rats that are given an opioid antagonist to precipitate withdrawal show a decrease in extracellular levels of DA that is coupled with an increase in ACh [69–71]. This same imbalance of DA/ACh has been shown during withdrawal from other drugs, including alcohol and nicotine [72,73].

Food addiction studies using animal models show that rats that repeatedly overeat palatable foods enter a state in which they show behavioral indications of withdrawal [62,66]. In addition to these behaviors, they show alterations in extracellular levels of ACh in the NAc that are consistent with the findings described above for drugs of abuse. When withdrawal is precipitated with the opioid antagonist naloxone or it emerges spontaneously in response to fasting (Fig. 4) rats show an increase in the levels of ACh in the NAc that is coupled with an increase in NAC DA. Thus, rats in withdrawal from palatable food appear to show the profile of ACh in the NAc that has been seen in withdrawal from drugs of abuse.

### 3. Conclusions

Cholinergic influence on mesolimbic systems clearly has a role in the ingestion of both food and drugs of abuse. In this review, we highlight studies that have been conducted to uncover the contribution that ACh makes toward feeding behavior, and we conclude that



**Fig. 4.** Extracellular ACh in the NAc following 24 and 36 h of fasting. Extracellular ACh was significantly increased in the 12-h binge sugar + chow group (which also shows behavioral signs of opiate-like withdrawal and other signs of addiction to the sugar) at the 36 h fasting point compared with both control groups. \*p<0.05 compared with both binge (12-h) chow and ad libitum chow.  
Reproduced with permission from [62].

increased levels of ACh in the NAc act to promote satiety. Cholinergic input, via nicotinic receptor activation, facilitates the intake and perhaps promotes dependence on many different drugs of abuse. Finally, we discuss how both excessive intake of palatable foods and drugs of abuse can result in a state of behavioral withdrawal, which is characterized by relatively lower levels of DA in the NAc, coupled with elevated ACh.

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