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Accumbens dopamine-acetylcholine balance in approach and avoidance

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Summary

Understanding systems for approach and avoidance is basic for behavioral neuroscience. Research on the neural organization and functions of the dorsal striatum in movement disorders, such as Huntington's and Parkinson's Disease, can inform the study of the nucleus accumbens (NAc) in motivational disorders, such as addiction and depression. We propose opposing roles for dopamine (DA) and acetylcholine (ACh) in the NAc in the control of GABA output systems for approach and avoidance. Contrary to DA, which fosters approach, ACh release is a correlate or cause of meal satiation, conditioned taste aversion and aversive brain stimulation. ACh may also counteract excessive DA-mediated approach behavior as revealed during withdrawal from drugs of abuse or sugar, when the animal enters an ACh-mediated state of anxiety and behavioral depression. This review summarizes evidence that ACh is important in the inhibition of behavior when extracellular DA is high and the generation of an anxious or depressed state when DA is relatively low.

Introduction

The balance of DA/ACh in the dorsal striatum has a role in the ability of a Parkinson's disease patient to move [1]. Therefore, effective treatments aim to increase DA levels and concurrently reduce the relative overabundance of ACh. It is as if DA enables the person to start moving in response to signals from the cortex [2], and ACh acts as a governor to prevent over-responding and facilitate stopping and the selection of alternative action patterns [3,7]. We suggest the same may be true in the NAc for motivation and motivational disorders.

Many questions remain concerning the opposing neurochemical factors that counteract DA. Recent results suggest that dynorphin, which is a co-transmitter in one of the GABA output pathways, inhibits DA neurons and, when in excess, can cause depression [4] and may have an important role in drug addiction [5]. Enkephalin is a co-transmitter in the other main GABA output. It has been suggested that ACh controls enkephalin expression as part of a hedonic system for overfeeding [6]. Studies from our laboratory find that the ACh interneurons are responsive to a constellation of inputs that inhibit behavior output or redirect it so as to escape or avoid an aversive condition [8]. Several animal models of satiation or avoidance will be reviewed, each with particular attention to DA and ACh in the NAc. Each of the animal models of human behavior reviewed below is interesting from a clinical, as a well as basic neuroscience, point of view. These models represent meal satiation, taste aversion, escape from brain stimulation, depression, drug withdrawal and sugar withdrawal [8].

Opposing functions of DA and ACh in the basal ganglia

Recent reviews emphasize a fascinating feature of the basal ganglia, movement system. It is now believed to be comprised of not just the one classic “loop” from the dorsal striatum to the substantia nigra and back, but rather a linked set of loops, or a “spiral” [9]. Three main loops have recently been characterized. Starting along the midline, one loop carries information

between the medial accumbens and the medial ventral tegmental area (VTA), another connects the lateral accumbens and the lateral VTA, and the final, far lateral loop is travels between the dorsal striatum and the substantia nigra (SN) [10]. Each of the three loops has different functions that may be activated independently or sequentially.

Each loop has two major descending components: a direct path and an indirect path to the midbrain VTA or SN (and to the globus pallidus-internal). In the NAc, the GABA neuron direct path contains dynorphin as one of its co-transmitters, along with the peptides substance P (SP) and cocaine-and-amphetamine-related transcript (CART) [11]. The indirect pathway also has GABA output neurons, but this is the one with enkephalin as a co-transmitter.

DA in the striatum has at least two types of effects. It excites the GABA/dynorphin output via a predominance of D1-type receptors and inhibits the GABA/enkephalin output cells via D2-type receptors [12,13]; although other mechanisms could be involved [14]. ACh interneurons in the striatum are thought to do the opposite of DA. ACh inhibits output cells where D1 receptors excite, and ACh excites where D2 receptors inhibit [13].

We hypothesize that this striatal arrangement may be the anatomical basis for a similar DA/ACh reciprocal opposition in the accumbens loops that control motivation and some aspects of learning. We tested this in two ways: (1) by injecting neurotransmitter agonists and antagonists into the NAc to determine their effects on DA/ACh balance, while measuring the resultant behavior, and (2) by having the animal engage in avoidance behaviors to determine if ACh is released in the NAc. The evidence suggests that ACh inhibits the approach system via muscarinic M1 receptors, and thereby counteracts the effects of DA at the D1 receptors. What then controls ACh release? ACh is inhibited, in part, by opioids acting at the mu-type receptors and serotonin acting at 5HT1A receptors. This helps to account for the mood enhancing and motivational enhancing effects of opiates and antidepressants; they both can decrease extracellular ACh.

We assume that changes in extracellular neurotransmitter level modulate the NAc output cells and that this is what is reflected in behavior. It is a good assumption given the overwhelming evidence for “volume transmission” as a basis for neuromodulator function. It is clear that both DA and ACh can act at a distance from the release sites by diffusion to extra-synaptic receptors that serve to modulate membrane potential [15]. Thus the microdialysis technique provides a measure of changes in the extracellular levels of the endogenous DA and ACh that work by volume transmission. Likewise, local micro-injection or reverse dialysis to infuse dopaminergic and cholinergic drugs can be behaviorally effective by volume diffusion.

Accumbens DA/ACh balance and behavior

Six opposing behavior patterns are described below. In each one, behavior activation for approach involves an increase in extracellular DA in the NAc; whereas ACh is correlated with, or causes, the shift from approach to avoidance. The results are summarized in Table 1.

Feeding and satiety

Dopamine—DA in the NAc can increase appetite. Early microdialysis studies found that instrumental feeding responses or appetitive hypothalamic stimulation releases DA in the NAc, and it can stay high for some time afterward [16]. DA release can carry information as to sucrose concentration and thus palatability [17]. Measures of release on a subsecond time scale show that DA is relatively high during food-seeking [18]. DA depletion with 6-hydroxy-dopamine suggests that DA is needed for instrumental work output [19]. DA antagonists briefly increase operant responding for food, which then gradually declines, suggesting a loss of reward and not simply loss of motivation or motor impairment [20,21]. Ahn & Phillips [22] use a random

interval schedule of food reinforcement and suggest that reinforcement uncertainty maintains high DA levels in the medial NAc over many days of training. They interpret this microdialysis data as compatible with an incentive motivation view of DA function, as opposed to a reward-value function or response-reinforcement function. The computational approach has led to a proposal for two ventral striatal systems, one for the primary value of a stimulus (US) via the lateral hypothalamus and another that responds to the learned value (CS) as determined in the amygdala.[23]. Di Chiara [24] recently summarized what DA does and does not do. For example, a novel palatable food stimulus releases DA in the medial NAc shell during the first meal experience, and this effect depends on mu-opioid receptor stimulation in the VTA. This DA response habituates with additional free-feeding exposures, unless the animal is food deprived. As confirmation, we find that ingestion of a sucrose solution releases DA in the medial NAc during the first exposure, and less the second time it is administered. However, under conditions of predictable daily availability, in mildly food deprived, sweet taste releases DA in the NAc, time after time [25].

Acetylcholine—ACh in the NAc has a role in the onset of satiation. As feeding slows down towards the end of a meal, we observe an increase in extracellular ACh in the NAc [26,27]. Its overall satiety effect appears to depend largely on muscarinic receptors. Although ACh can release DA by an action at nicotinic receptors, local injection of the mixed muscarinic agonist arecoline will inhibit feeding, and feeding can be reduced with the relatively specific muscarinic M1 receptor antagonist pirenzepine (P. Rada et al., unpublished data). The mixed, muscarinic agonist oxotremorine fails to inhibit bar pressing for food, but can inhibit self-administration of cocaine [28]

Seemingly contradictory findings by Kelly's group [29] suggest that ACh may have a role in promoting feeding. They find that the muscarinic antagonist scopolamine reduced lever pressing for food. Scopolamine blocks most types of muscarinic receptors, including the M-2 receptor that is both postsynaptic and presynaptic. As a presynaptic autoreceptor on the cholinergic neurons, the M-2 type receptors provide local negative feedback, and blocking them releases ACh [30], which might then suppress eating. Thus it is possible that rats stop eating with scopolamine because of the release of ACh, but more work is needed to understand the mechanisms underlying this issue, as muscarinic receptors of various types have numerous functions within NAc circuitry.

We find that appetite-suppressant drugs release ACh in the NAc, and these therapies may be applicable to drug abuse as well as feeding [31,32]. d-Fenfluramine combined with phentermine, given systemically, increases extracellular ACh in the NAc at a dose that inhibits both eating and cocaine self-administration [31,33,34]. ACh enhancement by acetylcholinesterase inhibitors blocks cue-induced heroin seeking [35] and blocks cocaine and heroin conditioned place preference, which is reversed by selective ablation of ACh neurons [36]. Endogenous appetite suppressants such as hypothalamic DA, serotonin and cholecystokinin (CCK) also act via the NAc by releasing ACh [37].

To further test the ACh-satiety theory, rats were surgically equipped with a gastric fistula so that food could be drained from the stomach. As shown in Figure 1, when they drank 10% sucrose for an hour in the normal fashion (fistula closed), DA was released, followed by ACh. When the sucrose was allowed to drain out of the stomach (fistula open), they drank more sucrose, DA was released as usual, but ACh did not rise until the fistula was closed again [27]. Thus, sham feeding greatly attenuates ACh release. To summarize, we suggest that ACh can act at M1 receptors that oppose dopamine's D2 receptor effects on the indirect GABA output pathway for behavior inhibition, and in this way ACh may contribute to satiation.

Conditioned taste preference and aversion

Dopamine—The decision to eat, or not to eat, is clearly based on prior experience with tastes that signal nutrition or poison. Foods for which animals have a conditioned taste preference release DA. Rats were trained to drink a novel, mildly bitter-tasting solution that automatically triggered the injection of nutritious polycose into the stomach. Compared with a control flavor paired with just water, the animals soon develop a preference for the novel flavor in a two-bottle test [38]. When that flavor was squirted into the mouth, it resulted in the release of DA in the NAc. DA was presumably involved in eliciting the approach behavior seen in the preference test [39].

Taste aversion has the opposite effect of taste preference. When the taste of saccharin is made aversive by pairing it with lithium chloride-induced nausea, animals avoid drinking saccharin, the taste signal in the NTS changes to resemble that of quinine [40], and microdialysis reveals a shift from saccharin-induced DA release to a decrease below baseline [41]. This conditioned decrease in DA release could be a major factor in conditioned taste aversion.

Acetylcholine—As seen in Figure 2, when rats have a conditioned aversion to saccharin, because of pairing the taste with nausea, the taste significantly increases ACh release in the NAc [42]. Thus a sweet taste can release DA or ACh depending on the learned physiological consequences. Elevated ACh is, by itself, sufficient to cause a taste aversion. This was shown by micro-injecting neostigmine into the NAc to block degradation of ACh and thereby elevate extracellular levels in association with the taste of saccharin. A conditioned taste aversion to saccharin is generated by the local rise in ACh [43]. In summary, there is a decrease in extracellular DA and increased release of ACh in response to a taste that had been associated with nausea. From an evolutionary standpoint, this is sufficient to produce survival-necessitated avoidance behavior such that the animal stops, and then goes to find something else to eat.

Hypothalamic self-stimulation (ICSS) and stimulation-escape

Dopamine—Intracranial self-stimulation (ICSS) with lateral hypothalamic electrodes releases DA in the NAc. The hypothalamus contains motivational systems for several behaviors, including feeding [44] and mating [45]. Lateral hypothalamic outputs such as orexin cell groups may be coded for feeding, with leptin receptors [46] on some orexin cells and others for mating with inputs that are sensitive to estrogen or androgen [45]. This suggests the possibility of behaviorally-coded outputs. An electrode site that elicits feeding can, depending on stimuli available in the environment, be made to elicit other behaviors, or it may even elicit oral signs of aversion [47]. Indeed, some electrodes support both ICSS and stimulation-escape, with the animal's choice of two levers shifting from approach to escape as a function of increased satiety, increasing body weight, insulin-induced satiety, or appetite-suppressant drugs [48,49]. Similarly, ICSS at a mating site loses its effectiveness after castration, and ICSS is restored by androgen-replacement therapy [50]. After a male ejaculates, the preponderance of behavior shifts from ICSS to stimulation-escape [49]. The next question is what happens in the NAc when stimulation becomes aversive.

Acetylcholine—Aversive hypothalamic stimulation increases the level of extracellular ACh in the NAc. Figure 3 shows ACh levels in the NAc in rats pretested using one lever and for ICSS and another for responding to escape from recurrent stimulation for 5 s. In the animals with electrode sites where stimulation released ACh, ICSS was relatively slow. If the recurrent stimulation was then turned on automatically, causing a relatively high extracellular level, this increased the animal's lever pressing to escape the ACh-mediated state [51]. As a result, escape behavior effectively lowered ACh (Figure 3). This implies that high ACh is a negative reinforcer (Table 1).

Motivation and depression

Dopamine—Given the role of DA in motivation, one might expect a depressed animal to display decreased DA. In the forced-swim test, a rat is tested for escape efforts in a water tank two days in a row. They readily give up trying to escape on the second day, as shown by less active swimming behavior and more passive floating. Extracellular DA in the NAc decreases during the swim test when animals become behaviorally depressed [52].

Acetylcholine—We were surprised to find that ACh does not change during passive floating. Instead, it decreases briefly after the animal is removed from the water the first day and then increases, with the interesting discovery that basal ACh is still high before going back in the water the second day when behavior is depressed [53]. Thus, ACh levels reflect a lasting state correlated with behavioral depression.

We tested the cholinergic receptor types, nicotinic and muscarinic, that might be responsible for this depression-related effect. Nicotinic receptors are unlikely to be involved, because we have shown that local nicotine releases DA [54]. Turning to the muscarinic receptors, local bilateral injection of a muscarinic agonist arecoline depresses swimming behavior, and the relatively specific M-1 antagonist pirenzepine increases escape efforts (Figure 4) [30]. This is not a locomotor effect because there was no hyperactivity in an open field. Thus the M-1 type receptor is a candidate for accumbens-induced depression.

Antidepressants are well known to restore escape swimming [55]. We find that fluoxetine infused directly into the NAc by reverse dialysis causes an immediate increase in escape efforts [56]. To achieve the same effect with systemic administration requires two weeks of treatment. If the accumbens ACh-depression hypothesis is correct, then an antidepressant drug should lower ACh. It does. When fluoxetine is infused by reverse-microdialysis into the NAc, it lowers extracellular ACh [56]. A serotonin-1A receptor agonist 8-OH-DPAT, given locally has the same effect [57]; thus identifying the type and location of one of the relevant receptors for antidepressant therapy.

In summary, we suggest that behavioral depression, as modeled by the forced swim test, is associated with low DA and a protracted rise in ACh. The rapid onset of immobility on the second day of the test is mediated in part by ACh acting at postsynaptic M1 receptors. Local fluoxetine raises extracellular serotonin, which then acts at serotonin-1A receptors to lower ACh, thereby reducing M1 stimulation and alleviating behavioral depression.

Drug self-administration and drug withdrawal

Dopamine—Morphine, phencyclidine, amphetamine and nicotine are examples of drugs that can increase extracellular DA, even when infused locally in the NAc [58–61]. Numerous explanations for addiction to opioid and DA receptor stimulation have been offered. Examples include intracellular changes involving gene expression in the NAc [62], habit learning [63], loss of cortical executive control [64], abstinence-induced incubation of the reinstatement of responding for drug-related cues [65], and a cycle of unpleasant withdrawal effects, including conditioned withdrawal, that leads to self-medication with the drug in an effort to regain normalcy [66]. These processes are not mutually exclusive, and several may involve DA in one site or another.

Acetylcholine—Withdrawal signs can be elicited in rats by administering the appropriate receptor antagonist after prolonged drug use. For example, rats received injections of morphine daily for a week, causing DA release each time [60,61]. Then they received naloxone to block opioid receptors, which caused DA to decrease and ACh to be released instead. Koob and colleagues [66,67] have argued that withdrawal is an aversive state. They show that the

threshold for brain self-stimulation reward rises during withdrawal from addictive drugs. If this state is due in part to accumbens ACh, then naloxone given systemically, or methyl-naloxonium infused locally in the accumbens, should cause the release of ACh in morphine-dependent rats. This is in fact the case. An opioid antagonist injected into the NAc causes a conditioned place aversion [68] and lowers extracellular DA while releasing ACh [60,69]. It is unexpected that rats will self-inject the cholinergic agonist carbachol into the NAc [70]. However, we find that carbachol decreases ACh release by stimulating M2-muscarinic autoreceptors, and it also releases DA, which may help explain self-injection [71].

In summary, most addictive drugs activate accumbens dopaminergic functions that foster approach. In cases of pharmacologically induced withdrawal, DA decreases and ACh is released. It is as if ACh were disinhibited, revealing its function as an opponent process. Based on the results cited above with conditioned taste aversion, behavioral depression and brain stimulation-escape behavior, we conclude that high ACh during drug withdrawal, especially when DA is low, generates an aversive state. This DA/ACh imbalance may be an important aspect of drug addiction. Theoretically, any type of behavior could be addictive if it repeatedly releases surges of DA and leads to withdrawal-induced loss of dopaminergic tone and increased extracellular ACh.

Sugar bingeing and its opiate-like withdrawal state

Dopamine—Our data show, in essence, that bingeing on sugar can be, in many ways, like taking a low dose of an addictive drug. Feeding behavior and cocaine both increase extracellular DA in the NAc [72]. The effects of cocaine and heroin on extracellular DA are more potent than those of food. Cocaine acts everywhere there are DA reuptake sites and does so every time the drug is administered. Heroin acts in many sites, from the brain to the gut. Psychostimulants and opiates cause local homeostatic compensations in terms of receptor trafficking and synthesis of neurotransmitters and receptors. Food would not be expected to produce addictive effects of the magnitude caused by drugs. Perhaps this is one reason the DA system that projects to the NAc evolved to stop firing when the food taste is no longer novel or salient. Recordings from DA cells in the VTA of monkeys, suggests that even the conditioned response to DA wanes with repetition [73,74]. Moreover eating has postingestional satiation effects that gradually raise ACh levels to counteract DA [26,27]. Thus under most mealtime circumstances we are well protected from developing an “addictive” state with regard to food. However, alternating feasting with famine is another story.

A surge of DA can be released in the NAc every time the animal binges if trained with alternate food deprivation and access to chow and sugar [25]. A control group with *ad libitum* access to 10% sucrose solution does not show the effect, nor does a group that has sugar to drink only twice, on Day 1 and again on Day 21. However daily 12-h food deprivation followed by excessive sucrose intake causes a rise in DA, even on Day 21. This effect in the NAc is analogous to receiving a low dose of an addictive drug every day for 21 days. Signs of dependency also appear. In brief, they fall into three behavioral categories, First “excessive intake”, which refers to an unusually large meal in the form of a “binge,” that is larger than an animal would take when feeding *ad libitum* [25], second, “withdrawal,” which occurs in response to fasting, or when naloxone is administered, [75], and third, “craving,” which, for lack of a better word, is defined as long-lasting signs of enhanced motivation seen during abstinence. These protracted effects seen after more than a week of sugar abstinence include: first, “cross-sensitization,” in which the animals are hyperactive in their exploration of an open-field when given a low dose of amphetamine or cocaine [75,77], second, the “deprivation effect,” in which the animals engage in more lever pressing for sugar than ever before [78], third the “gateway effect”, shown as an increased intake of alcohol compared with control rats

[79], and (d) the “incubation effect,” which refers to the growing motivation to lever press for sugar-associated cues during abstinence [80].

There are concomitant neurochemical changes in sugar-bingeing rats. An enkephalin system in the NAc shows decreases in enkephalin mRNA [81] as Kelley's group observed using intermittent access to a palatable sweet-fat drink (Ensure) [82]. With sugar bingeing, we find that there is also an increase in mu-opioid receptor binding [83]. The DA system adapts with increased D1 and decreased D2 receptor binding in the striatum relative to chow-fed controls [82]. Drug-dependent rats show many of these same effects, and in human drug addicts and people who are obese, brain imaging reveals a decrease in D2 receptor binding, which is interpreted as dopaminergic involvement in compulsive drug or food intake [84].

Acetylcholine—Naloxone or 36-h food deprivation can cause opiate-like withdrawal signs in rats trained to binge on sugar. These signs include first, teeth-chattering and anxiety as measured by avoidance of the open arms of an elevated plus-maze [75], second, behavioral depression in the swim test (MN Avena et al., data unpublished), and in terms of neurochemistry, (c) the predicted decrease in DA and increase in extracellular ACh in the NAc [75]. This is much like naloxone-precipitated withdrawal from morphine.

In summary, repeated daily bingeing on a sugar solution can cause “surges” of DA in the NAc that causes adaptations in both DA and opioid systems.[85] These changes contribute to opiate-like withdrawal signs, which include behavioral manifestations of increased ACh release combined with relatively low extracellular DA. As explained above, we assume that this causes an aversive state involving anxiety and a tendency to behavioral depression. Thus, sugar, when it is taken in a feast- and-famine fashion, may promote a feedback cycle similar to an addiction, with repetitions of high extracellular DA followed by low DA and relatively high ACh. This opioid-related high DA, followed by a deprivation-induced, cholinergic-mediated avoidance state, may be advantageous when food is scarce. It can be troublesome in times of plenty.

It is an interesting question whether social and scientific norms will be promulgated such that the term “addiction” is applied to natural behaviors. The popular press already has many books and articles about “natural addiction” to a variety of excessive behaviors. The difference between strong motivation and well-defined addiction has yet to be determined. The evidence outlined above suggests that, under certain circumstances, bingeing on a sugar solution can produce effects that are at least analogous, perhaps homologous, to the changes caused by addictive drugs.

Conclusions

One of the opponent processes that counteracts the effects of DA in the NAc may be the release of ACh. It could act in part at muscarinic receptors of the M1-type to inhibit dopamine's D1-receptor effects on the GABA/dynorphin output neurons that control approach. Hypothetically, ACh may also act on other receptors to counter dopamine's D2-receptor effects on the GABA/enkephalin output, which may mediate aspects of avoidance. In the accumbens shell, where inputs from the hypothalamus and elsewhere influence feeding, DA fosters foraging for food or drugs. ACh, on the contrary, is released during the satiation process or a conditioned taste aversion. Animals will lever press to escape from brain stimulation that releases ACh, thus lowering their ACh levels in the NAc. After an animal binges on sugar repeatedly or receives drugs that create surges of DA, the brain adapts with the alterations in mRNA expression and receptor binding, such as those that have been described. Then during withdrawal, ACh is released in relative excess, with pathological effects on behavior. We conclude that ACh is important in the inhibition of behavior when extracellular DA is high, such after a palatable meal, but ACh is also involved in generating an anxious or depressed state when DA is

relatively low, such as during withdrawal from a diet of sugar bingeing. The implication is that people would work to alleviate this ACh-based condition, assuming something releases DA to get them started (reinstatement). This sequence of neurochemical changes could perpetuate the addictive behavior pattern.

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Figure 1.

A. The upper graph shows that DA is released in the NAc on each day of microdialysis, in rats that have 12 hours of deprivation followed by 2 hours of 10% sugar access daily (black bar), regardless whether the animal sham feeds (gastric fistula open) or real feeds (fistula closed).

B. The lower graph shows ACh is released when real feeding, but not when sham feeding. From [27].

Figure 2.

When the animals with a conditioned taste aversion (CTA) tasted saccharin (the CS) that had been paired with nausea on two prior days, ACh increased significantly and remained elevated for the next 2 hours (* $p < 0.05$). Control groups received saline paired with nausea (unconditioned) or saccharin and nausea that were unpaired (pseudo-conditioned). From [42].

Figure 3.

Extracellular ACh in the NAc is shown before, during and after 60 min of lateral hypothalamic stimulation in five situations. Animals were grouped according to whether they were “pure self-stimulators” that only pressed the self-stimulation lever, those that would do both, indicating a mixed reward-aversion site, and those that did not self-stimulate, but assertively pressed the escape lever, i.e. “escapers”. In the top curve (filled diamonds), extracellular ACh more than doubles in ‘escapers’ when they received automatic stimulation that was inescapable at the time. In the next curve (open circles) the same animals reduced their ACh release significantly by stimulation-escape responding. In the middle curve (filled circles) the escapers pressed a different lever for self-stimulation on a different day. Self-stimulation increased ACh

half as much as automatic inescapable stimulation. The bottom two curves are for different rats that were pure self-stimulators that failed to learn stimulation-escape (open squares and filled squares). They showed the smallest rise in ACh. From [51].

Figure 4.

Swimming time following injections of cholinergic drugs in NAc (black bars), compared with vehicle (white bars). Local injection of arecoline, a muscarinic agonist, decreased swim time (left graph); the animals gave up more quickly. Conversely, pirenzepine, an M1 receptor antagonist, increased swimming escape attempts in the manner of an antidepressant (right graph), but note this is a local injection; so this is a locally-induced antidepressant effect. Swimming time following a drug injection on a different day is expressed as a percentage of control. Significant changes in the within-subject response to drug injections are indicated with asterisks (** $p < 0.01$, *** $p < 0.001$). From [30]

Table 1

Changes in extracellular levels of dopamine and acetylcholine in the NAc during six animal models of avoidance behavior

Behavioral test	DA	Ach	Outcome
Satiation	↑	↑	Slow feeding
Conditioned Taste Aversion	↓	↑	Stop feeding
Brain Stimulation Escape	↑	↑↑	Work to escape
Swim Depression	↓	↑	Swim immobility
Morphine Withdrawal	↓	↑	Anxiety and swim immobility
Sugar-Binge Withdrawal	↓	↑	Anxiety and swim immobility