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Review

# A threshold model for opposing actions of acetylcholine on reward behavior: Molecular mechanisms and implications for treatment of substance abuse disorders

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## HIGHLIGHTS

- Different classes of cholinergic agents produce biphasic effects on appetitive responding.
- Phasic activation of cholinergic tone in the accumbens-VTA above a low-level threshold appears to increase the likelihood of rewarded behaviors.
- Greater and more prolonged activation above a second higher-level threshold is associated with a decreased likelihood of reward.
- Effects on nicotinic receptors, dopamine release, and medium spiny neuron activity are potential mediators of thresholds that shape behavior.
- High-affinity β2* nicotinic receptors play a greater role in reward enhancement, and low-affinity homomeric α7 receptors underlying inhibition.

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## ABSTRACT

The cholinergic system plays important roles in both learning and addiction. Medications that modify cholinergic tone can have pronounced effects on behaviors reinforced by natural and drug reinforcers. Importantly, enhancing the action of acetylcholine (ACh) in the nucleus accumbens and ventral tegmental area (VTA) dopamine system can either augment or diminish these behaviors. A threshold model is presented that can explain these seemingly contradictory results. Relatively low levels of ACh rise above a lower threshold, facilitating behaviors supported by drugs or natural reinforcers. Further increases in cholinergic tone that rise above a second upper threshold oppose the same behaviors. Accordingly, cholinesterase inhibitors, or agonists for nicotinic or muscarinic receptors, each have the potential to produce biphasic effects on reward behaviors. Pretreatment with either nicotinic or muscarinic antagonists can block drug- or food- reinforced behavior by maintaining cholinergic tone below its lower threshold. Potential threshold mediators include desensitization of nicotinic receptors and biphasic effects of ACh on the firing of medium spiny neurons. Nicotinic receptors with high- and low- affinity appear to play greater roles in reward enhancement and inhibition, respectively. Cholinergic inhibition of natural and drug rewards may serve as mediators of previously described opponent processes. Future studies should evaluate cholinergic agents across a broader range of doses, and include a variety of reinforced behaviors.
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## 1. Introduction

ACh is widely distributed in the central nervous system, where it functions as a signal for local circuits and projection neurons. Both types of cholinergic neuron are involved in brain learning and reward functions. Synaptic levels of ACh are regulated by choline acetyltransferase, the rate-limiting enzyme for formation of ACh, and cholinesterases that inactivate it. ACh activates two categories of receptor: nicotinic and muscarinic. Neuronal nicotinic ACh receptors (nAChRs) are a family of ligand-gated ion channels that are made of combinations of type 2 through 9 alpha subunits, and type 2 through 4 beta subunits, arranged to form a pentameric pattern. Different subunit combinations give rise to various types of nAChRs, which differ in sensitivity to nicotine, calcium conductance, and propensity to desensitize [1], discussed in greater detail below. In contrast, muscarinic receptors are members of the superfamily of G protein-coupled receptors. Five muscarinic subtypes have been cloned which function through either activation of phospholipase (types 1, 3, and 5) or inhibition of adenylate cyclase to decrease the concentration of intracellular cAMP (types 2 and 4) [2]. Dopamine neurons express multiple types of muscarinic and nicotinic ACh receptors, and a dense mingling of dopaminergic and cholinergic neurons in limbic areas of the brain allows coordinated functioning of these neurotransmitter systems [3,4].

The cholinergic system is well known for its role in learning, memory, and attention. In general, cholinergic activation modifies these functions with an inverted-U dose-effect relationship [5,6]. Accordingly, nicotinic or muscarinic cholinergic antagonists can disrupt learning and memory in human or animal experiments, with this effect reversed by restoring ACh function [7,8]. Either cholinesterase inhibitors or cholinergic agonists with nicotinic or muscarinic selectivity can enhance learning under conditions in which cholinergic function is diminished, but disrupt the same behaviors when administered at higher doses [9,10], which can be associated with signs of yawning, tremor, involuntary jaw movements, and diarrhea in animals [11]. Overall, these findings are consistent with an optimal level of central cholinergic activity for learning and memory, with deviations in either direction capable of impairing learning and memory. Parallel to this, interaction of the ACh and dopamine systems to modulate drug-reinforced and drug-seeking behaviors can also be interpreted using an inverted-U dose-effect relationship.

## 2. Behavioral significance of striatal acetylcholine elevations

Augmented release of ACh in the striatum and nucleus accumbens has been observed under a number of qualitatively different conditions [12]. Locomotor activity in rats is correlated with dialysate levels of ACh in the striatum, hippocampus, frontal cortex [13,14]. Handling of rats increases extracellular ACh in both the nucleus accumbens core and shell, with repeated exposure to an open field further increasing values in the shell but not the core region [15]. Importantly, disruption of an established contingency that requires learning of a new pattern of responding appears to increase extracellular ACh. In the dorsal striatum, reversal of maze requirements for food reward caused pronounced increases in ACh which resolve as rats learn to maximize correct responding [16].

Activation of cholinergic neurons has also been implicated in the rewarding effects of both natural and drug reinforcers [17]. Repeated exposure to different classes of abused substances can produce persistent increases in the activity of cholinergic neurons in the nucleus accumbens [18]. Psychostimulant-reinforced behavior can cause long-lasting decreases in levels of choline acetyltransferase in the nucleus accumbens [19]. During cocaine self-administration, greater increases in ACh occur in dialysate from the nucleus accumbens shell [20] or VTA [21], relative to neurotransmitter increases that occur in animals that receive drug noncontingently. This early-session accentuation also occurs in cocaine-trained animals evaluated during extinction (substitution of inert injections) [21]. As rats acquire reinforcement in a runway model, psychostimulant, opiate, or food induced elevations in ACh in the nucleus accumbens core increase over consecutive trials, while levels of dopamine do not change [22,23]. In these experiments, drug-induced increases in ACh also did not vary in magnitude for rats that received noncontingent injections.

ACh elevations have also been linked to satiety caused by feeding and aversive states [24]. In deprived rats, both ACh and dopamine in the nucleus accumbens increased in response to food or water [25]. For freely feeding rats, extracellular ACh in the nucleus accumbens increases and reaches a maximum as satiety occurs. In drug-dependent animals, withdrawal produced by blockade of opiate, nicotinic, or benzodiazepine receptors increases ACh concentration in the nucleus accumbens [26]. Exposure to a flavor that has been paired with lithium-induced illness increases ACh concentration in dialysate from the nucleus accumbens, and infusion of a cholinesterase inhibitor into the nucleus accumbens can produce conditioned taste aversions [27]. Aversive hypothalamic stimulation (AHS) releases ACh in the nucleus accumbens, and rats that lever press to terminate AHS decrease their concentration of ACh in accumbal dialysate [28]. Apparently, elevated levels of ACh in the nucleus accumbens can serve as a neural indicator of aversiveness, or as a signal that inhibits appetitive behaviors. In many instances, accumbal levels of dopamine change in an opposite direction to that of ACh in response to an aversive stimulus. For example, exposure to an aversively-conditioned flavor [27] or precipitated withdrawal [26] can cause decreases in dopamine that accompany increases in accumbal ACh. Taken together, these findings show that elevations