Nicotinic Acetylcholine Receptors and Nicotinic Cholinergic Mechanisms of the Central Nervous System

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Abstract

Subtypes of neuronal nicotinic acetylcholine receptors (nAChRs) are constructed from numerous subunit combinations that compose channel-receptor complexes with varied functional and pharmacological characteristics. Structural and functional diversity and the broad presynaptic, postsynaptic, and nonsynaptic locations of nAChRs underlie their mainly modulatory roles throughout the mammalian brain. Presynaptic and preterminal nicotinic receptors enhance neurotransmitter release, postsynaptic nAChRs contribute a small minority of fast excitatory transmission, and nonsynaptic nAChRs modulate many neurotransmitter systems by influencing neuronal excitability. Nicotinic receptors have roles in development and synaptic plasticity, and nicotinic mechanisms participate in learning, memory, and attention. Decline, disruption, or alterations of nicotinic cholinergic mechanisms contribute to dysfunctions such as epilepsy, schizophrenia, Parkinson's disease, autism, dementia with Lewy bodies, Alzheimer's disease, and addiction.

INTRODUCTION

nAChRs: Nicotinic acetylcholine receptors

ACh: acetylcholine

AD: Alzheimer's disease

Nicotinic acetylcholine receptors (nAChRs) belong to the superfamily of ligand-gated ion channels that includes $GABA_A$, glycine, and $5\text{-}HT_3$ serotonin receptors (1–7). A wide variety of subtypes of nAChRs arise from combinations of subunits that compose the channel-receptor complex. Although these subtypes display a range of different functional and pharmacological properties, they share basic features. They occupy three main functional states in response to agonist: closed at rest, open pore, and closed desensitized. Brief exposure to high concentrations of the neurotransmitter, acetylcholine (ACh), causes opening of the water-filled, cation-selective pore. After a couple of milliseconds, the receptor closes to a nonconducting state. Prolonged exposure to low concentrations of nicotine, as obtained from tobacco use, produces significant desensitization, which stabilizes the receptor in a closed state that is unresponsive to agonist (8–11).

The diversity of nAChR subtypes and their dendritic, somal, axonal, presynaptic, and postsynaptic locations contribute to the varied roles these receptors play in the central nervous system (CNS). Presynaptic and preterminal nicotinic receptors enhance neurotransmitter release, and postsynaptic and nonsynaptic nAChRs mediate excitation as well as activity-dependent modulation of circuits and intracellular enzymatic processes. By modulating activity-dependent events, nAChRs participate in fundamental aspects of synaptic plasticity that are involved in attention, learning, memory, and development (3, 12–16). Decline, disruption, or alterations of nicotinic cholinergic mechanisms have been implicated in various dysfunctions, such as schizophrenia, epilepsy, autism, Alzheimer's disease (AD), and addiction (17–23).

NEURONAL NICOTINIC RECEPTOR STRUCTURE

Neuronal nAChRs are assembled from five transmembrane subunits that are arranged around a central water-filled pore (1, 5, 24). Neuronal subunits that form nAChRs in $\alpha\beta$ combinations include $\alpha2$–$\alpha6$ and $\beta2$–$\beta4$. Subunits capable of forming homomeric nAChRs are $\alpha7$–$\alpha9$, and $\alpha10$ forms a heteromer with $\alpha9$. The $\alpha8$ subunit has been found in avian tissue but has not been detected in mammals. Of the subunits capable of forming homomers, only the $\alpha7$ subunit is widely distributed in the mammalian brain. Subunits forming heteromers or homomers are not completely distinct because the subunits from these separate classes also are capable of combining to form nAChRs.

The basic structure of neuronal nicotinic receptors is homologous to the muscle nAChR (24). The pseudo crystalline form of the muscle-type nAChRs isolated from the *Torpedo californica* electric organ revealed the structure at 3.6 Å resolution (25, 26). A lateral cross section of the nAChR displays an extracellular water-filled vestibule that is approximately 20 Å in diameter and extends 60 Å from the membrane surface into the synaptic cleft. The pore narrows at the level of the surface membrane, and permeant ions pass along this ionic pore for approximately 40 Å. Permeation studies and structural data indicate that the narrowest cross section near the inner surface of the membrane is short (3–6 Å) and approximately 7 Å in diameter (24, 26, 27).

A schematic linear representation of a subunit reveals a long extracellular N-terminal domain, four transmembrane segments, an intracellular loop delimited by

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the third and fourth transmembrane domain, and a short C-terminal end. Both the N-terminal and C-terminal face the extracellular space, and the second transmembrane segment (TM2) aligns along the pore at the center of the structure. TM2 provides the main lining along the ionic pore with a minor contribution from TM1 where the pore widens toward the extracellular membrane surface (24, 28–30).

TM1–4: transmembrane domain 1 through 4 of a folded nAChR subunit

AChBP: ACh binding protein

N-Terminal Domain, Agonist Binding, and Channel Gating

Early electrophysiology studies indicated that that there are two ACh binding sites per receptor, and the amino acids contributing to the ligand-binding pocket were initially identified by photoaffinity labeling (31). The binding sites reside at the interface between two adjacent subunits (24, 32). In the case of the muscle receptors, the two ACh molecules bind at the interface between the α-γ subunits (or α-ε in the adult form) and between the α-δ subunits.

Although these studies provided a preliminary description of the agonist binding site, little was learned about its three-dimensional structure. Crystals obtained from an ACh binding protein (AChBP) secreted by glial cells in the mollusk (Lymnaea) nervous system provided a major breakthrough (33). This small, water-soluble protein binds ACh with high affinity. Moreover, it forms crystals that provide structure down to 2.6 Å resolution, which revealed the atomic organization of the protein. As with the nAChR, five subunits form the AChBP, and their structure and organization remarkably resemble the extracellular N-terminal domain of the nAChR. The AChBP serves as a template for the three-dimensional organization of the extracellular ACh binding domains of nAChRs. Crystallization of the AChBP in the presence of a ligand, such as nicotine or carbamylcholine, provided insights into the agonist and protein interactions, confirming that nicotine binds at the interface between two adjacent subunits and interacts with defined amino acid residues (24, 34). In the case of heteromeric receptors, such as the α4β2 nAChRs, it was shown that ACh binds in a small pocket formed between the α4 and its adjacent β2 subunit. Therefore, both α and β subunits contribute to the pharmacology of the heteromeric binding site. In the case of homomeric receptors, such as α7 nAChRs, the ligand binding site is defined by the sidedness of adjacent α7 subunits.

Despite the progress made by these observations, the following important questions remain: How does the nAChR change conformation, and what states are stabilized by the presence of an agonist or competitive antagonist (24, 32, 35, 36)? Although the AChBP is a very valuable tool, this protein does not provide a channel that undergoes the same conformational changes as a functional nAChR. To capitalize on the structural resolution provided by the AChBP, however, competitive inhibitors (such as α-conotoxin derivatives) have been crystallized with the AChBP to probe the binding conformations (34, 37). Unique amino acids within the vicinity of the ACh binding pocket participate in the binding of these polypeptide ligands, and α-conotoxin ImI, for example, may inhibit the nAChR by stabilizing the desensitized conformation.

A series of interacting residues participates to transmit the agonist binding conformational changes to channel gating (35, 36). Structural models in conjunction with

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single-channel current measurements of the muscle-like nAChR revealed invariant charged amino acids that electrostatically couple α-subunit binding domains, ultimately linking them to the channel-forming α-helix. Movement of these structures underlies nAChR channel gating.

Cationic Permeability of the Pore

Mammalian nAChRs are cation selective, being permeable to small monovalent and divalent cations. Sequence alignment of homologous cationic nAChR and anionic channel domains reveals a proline residue in the anionic channel is missing from the short intracellular segment between TM1 and TM2 of the nAChRs. A negatively charged glutamate residue at the inner mouth of the nAChR channel is missing from anionic channels, and a valine in TM2 is replaced by a threonine in the channel lining of the nAChR (38). Inserting the absent proline, removing the negatively charged glutamate, and replacing the polar threonine by valine converts the homomeric α7 nAChR from cationic to anionic selectivity (38).

Nicotinic receptor activity causes depolarization, and the divalent cation permeability plays an important physiological role by supplying ionic signals, including calcium (39–41). The relative permeability of calcium to sodium estimated from permeability ratios is ~0.1 for muscle, ~2.0 for heteromeric neuronal, and ≥10 for homomeric α7 or the heteromeric α9/α10 nAChRs (30, 42–46). The higher calcium permeability of the α7 nAChRs arises from the arrangement of charged residues at the inner mouth of the ionic pore and polar residues in the outer part of the channel. Substitution of the glutamate residue found at the inner mouth of the α7 nAChRs by the neutral alanine residue suppresses calcium permeability (30). Similarly, replacement of the α7 leucine at the synaptic, extracellular end (position 254 or 255) of the pore by threonine dramatically reduced the calcium permeability of the α7 receptors. However, substitution of the leucine by threonine at another polar ring of amino acids within the pore (position 247 in the chick α7) did not alter divalent ionic selectivity, but it did alter agonist/antagonist relationships and aspects of desensitization (29, 39). These data illustrate the importance of particular conserved amino acids and the complex relationship between the structure of the pore and the resulting function.

BROAD INNERVATION BY CHOLINERGIC PROJECTIONS

Cholinergic cell bodies are located in a loosely contiguous axis running from the cranial nerve nuclei of the brain stem to the medullary tegmentum and pontomesencephalic tegmentum, continuing rostrally through the diencephalon to the telencephalon (47). There are three major cholinergic subsystems above the brain stem that innervate nearly every neural area. One cholinergic system arises from neurons mainly in the pedunculopontine tegmentum and the laterodorsal pontine tegmentum, providing widespread innervation to the thalamus and midbrain dopaminergic areas and also descending innervation to the caudal pons and brain stem. The second major cholinergic system arises from various basal forebrain nuclei that make broad projections throughout the cortex and hippocampus. In general, these cholinergic

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projection systems provide broad, diffuse, and generally sparse innervation to wide areas of the brain. The third major cholinergic subsystem is an exception to this principle of broad innervation. This subsystem arises from a collection of cholinergic interneurons located in the striatum. Unlike many broadly projecting cholinergic neurons throughout the brain, these cholinergic interneurons make up approximately 2% of the striatal neurons, and they provide very rich local innervation throughout the striatum and the olfactory tubercle (48).

Nonsynaptic or Volume Cholinergic Transmission

Cholinergic projections do not always terminate at synaptic targets. Rather, it has been proposed that the majority of cortical and hippocampal cholinergic release sites are nonsynaptic and contribute to diffuse volume transmission (49, 50), which has been observed for other modulatory neurotransmitters, such as monoamines (51). It is not uncommon, however, to underestimate synaptic contacts from structural studies because not every potential angle of contact can be easily observed, and a higher proportion of synaptic connections has been reported (52). The extent of synaptic contacts is less important for volume transmission than determining whether ACh can "spill over" from the synapses or spread from nonsynaptic release sites into the extracellular space.

Spillover, which has been recognized at other neurotransmitter synapses, is likely to be an important contributor to cholinergic volume transmission. Unlike many neurotransmitter signals that are shaped by pumps that return the transmitter to the intracellular space, the spread of ACh from the release site is determined by diffusion and by acetylcholinesterase (AChE) hydrolysis of ACh. This enzyme, which rapidly cleaves ACh, is widely distributed in the CNS, but evidence indicates that the density and location of AChE does not always match the location of ACh release sites (53). For instance, in the main olfactory bulb of rats no AChE was found among granule cells that receive a large number of the cholinergic synapses, but enzyme activity was detected in areas where cholinergic synapses could not be detected. Cholinergic volume transmission enables ACh to diffuse and to act at lower concentrations some distance away from the release site. The amplitude, shape, and time course of the ACh signal depends on the local density and distribution of AChE relative to ACh release sites.

Another important aspect of this diffusive ACh signal is that its eventual hydrolysis creates choline, which also activates and desensitizes nAChRs in a subtype-selective manner (54, 55). At α7 nAChRs, it is estimated that choline exerts an agonist EC50 ≅ 1.6 mM and an IC50 ≅ 37 μM for desensitization (55). Extracellular choline has been estimated normally at 3–5 μM, but reaches near 20 μM or more under pathological conditions (55). Potentially more important, ACh reaches the millimolar range at the site of release. High-frequency ACh release and dense nearby AChE would likely produce choline signals that achieve relatively high concentrations in specialized microdomains. Therefore, ACh provides a diffuse, volume signal that continues as a longer-lived choline signal that acts both at an ongoing background level and at higher concentrations in specific microdomains.

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FUNDAMENTAL ASPECTS OF NICOTINIC RECEPTOR FUNCTION

The kinetics for nAChR activation, closure, and desensitization are influenced by the exact amino acid sequence of the subunits. Nicotinic receptor activation is best described by examining its dose-response profile, which portrays receptor activation as a function of agonist concentration. The α7 nAChR has a relatively low affinity for ACh activation, with an effective dose for half-activation at approximately 200 μM ACh. The α4β2 nAChR has a higher affinity, and its activation is best described by the sum of two activation curves (56). The high affinity is 1.6 μM, the low affinity is 62 μM, and the ratio of high to low is approximately 25% (56). Long-term exposure to agonist alters the ratio of high- to low-affinity nAChRs. For example, overnight nicotine exposure at concentrations comparable to those experienced by a smoker's brain increases the high- versus low-affinity ratio (56). In addition, the exposure slows down the response time course (57, 58). These kinds of modifications regulate homeostatic and regulatory responses of nAChRs in an activity-dependent manner as the exposure to ACh or nicotine varies.

Desensitization is a complex mechanism that is often described by multiple exponentials that reflect the conformational transition of the receptor to multiple inactive (desensitized) states (8, 9, 11). Usually at a cholinergic synapse, vesicular release produces a high ACh concentration in the synaptic cleft for only a few milliseconds before diffusion and acetylcholinesterase removes the neurotransmitter. In response to these high ACh concentrations, the high-affinity α4β2 nAChRs desensitize with slower kinetics than the rapidly desensitizing α7 nAChRs. However, successive synaptic activity and volume transmission of ACh may provide a sustained exposure to low agonist concentrations, and that process produces a slow form of desensitization. Because of their high affinity for agonist, the α4β2 nAChRs display significant slow desensitization for agonist concentrations below 0.1 μM. On the other hand, the α7 receptors are not effectively desensitized by agonist concentrations below roughly 1 μM (8–10). A comparable condition is observed if agonists, such as nicotine from tobacco or nicotinic drugs, are given systemically for a prolonged time period.

Another characteristic feature of neuronal nAChRs is that they display current rectification for transmembrane potentials above –40 mV. First reported for the α4β2 nAChRs, this functional feature has also been described at other receptor subtypes (45, 59). This receptor property allows current flow when the cell is hyperpolarized, but the current is progressively reduced when the transmembrane potential is more positive than –40 mV. Mutation of a single charged residue (glutamate to aspartate) at the inner mouth of the pore of the α7 receptor abolishes rectification (45, 60), which arises from a voltage-dependent progressive reduction of the channel mean open time.

Inward rectification of current by nAChRs creates a functional situation different from some other channels. For example, the NMDA subtype of glutamate receptors is blocked by external Mg^{2+} until the membrane is depolarized. Then, the Mg^{2+} is driven out of the channel by the depolarized voltage. Thus, NMDA channels provide a current with an accompanying Ca^{2+} influx at depolarized potentials, i.e.,

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at very active synapses. The nAChRs, on the other hand, pass current and provide Ca^{2+} influx at highly negative membrane potentials, which provide strong driving forces for inward current. At very active, depolarized postsynaptic membranes, the nAChRs make a progressively smaller contribution because of the voltage-dependent rectification. Similarly, nAChRs that are expressed presynaptically contribute best to signal transmission when the synaptic boutons are hyperpolarized or, in other words, in the interval between action potential firing. Unlike most voltage-dependent channels, extrasynaptic nAChRs (which may sense slowly rising but sustained agonist concentrations) contribute best to the modulation of neuron activity when the cell is close to its resting potential.

*: wildcard place holder indicating that other subunits may contribute to the composition of this nAChR

Aspects of Nicotinic Receptor Pharmacology and Modulation

As nicotinic receptors undergo conformational changes between functional states, the five subunits move relative to each other. Pharmacological properties of a given nAChR subtype are governed by the structural features of the ligand binding site and by the specific amino acid interactions that determine conformational transitions. Thus, different receptor compositions display distinct pharmacological profiles to agonists, antagonists, and modulators (61).

Certain ligands that bind to the subunits or to the interfaces between subunits at locations distinct from the agonist binding site modulate conformational transitions and modulate function. This process is called allosteric modulation (62). Allosteric effectors that potentiate nAChR function are positive effectors; those that inhibit are negative effectors.

Steroids and neurosteroids modulate the $\alpha4\beta2^*$ nAChR (63–65). Different steroids produce positive or negative modulation. A small number of amino acid residues at the C-terminal end of the $\alpha4$ subunit mediate 17-β-estradiol potentiation (64, 65). This example illustrates the importance of subunit-specific structural domains during allosteric modulation, which is produced at heteromeric nAChRs by a number of small ligands, such as zinc and galantamine (66, 67).

With its unique structural organization, low sensitivity to ACh, and fast kinetics, the $\alpha7$ nAChR is a good candidate for allosteric modulation. For example, ivermectin increases the apparent ACh affinity, the slope of the dose-response curve, and the amplitude of nAChR responses (68). Ivermectin is an example of a positive allosteric effector that modifies the pharmacological profile of the $\alpha7$ nAChR. Dimethylphenylpiperazidium (DMPP) normally is a partial agonist at this receptor subtype, but it becomes almost a full agonist following ivermectin exposure (68). 5-Hydroxy-indol (5-HI) allosterically increases the $\alpha7$ ACh-induced responses without modifying the response time course or sensitivity to the agonist (69). Another allosteric effector, 1-(5-chloro-2,4-dimethoxy-phenyl)-3-(5-methyl-isoxazol-3-yl)-urea (PNU-120596), dramatically modifies the response time course, amplitude of the current, and agonist sensitivity of the rat and human $\alpha7$ nAChRs (70). PNU-120596 stabilizes the receptor in the active open state and reduces desensitization without altering the single-channel conductance. In an amphetamine-induced

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DA: dopamine

rat model of the auditory gating deficit seen during schizophrenia, PNU-120596 improved gating as gauged by field potential recordings in the CA3 area of the hippocampus. Those data demonstrated a potentially valuable therapeutic influence of a positive allosteric modulator.

Phosphorylation of the intracellular domain between TM3 and TM4 provides another form of allosteric modulation. Dephosphorylation of the α7 receptor by genistein causes a significant increase of ACh-evoked responses without modifying the response time course or ACh sensitivity (71, 72). Results show that genistein does not alter the surface expression of nAChRs, but rather it modifies nAChRs in the cell membrane (71). Furthermore, Src-family kinases (SFKs) directly phosphorylate the cytoplasmic loop of α7 nAChRs in the plasma membrane. These regulatory mechanisms flexibility modify the influence of nAChRs over cell function, and must be taken into account when considering nAChR participation in neuronal circuits.

Modulation of nAChRs is a promising field of research that offers several therapeutic advantages over classical agonists or antagonists. First, modulation increases or decreases the response to endogenous ACh release without causing a permanent inhibition or activation of the receptors. Second, because allosteric modulators can bind at areas distinct from the agonist binding pocket, more subtle effects can be engendered by ligands that show very different structures as they bind to different sites on the various subunits or subunit interfaces. Possibly, allosteric effectors will provide safer therapeutic margins with fewer undesired side effects.

Presynaptic, Postsynaptic, and Nonsynaptic Nicotinic Receptors

Although fast, direct nicotinic synaptic transmission drives neuromuscular junctions and autonomic ganglion synaptic transmission, only rare cases of fast nicotinic transmission have been reported in the mammalian brain. In the rodent hippocampus, fast nicotinic transmission was detected as a small excitatory input onto GABAergic interneurons (73–75). In the developing visual cortex, nicotinic transmission was evoked onto glutamatergic pyramidal cells and GABAergic interneurons (76). Because cholinergic neurons in the brain are usually loosely distributed and often sparsely innervate broad areas, it is experimentally difficult to stimulate a large number of those neurons and to record from the precise location of their innervation. It is likely that fast nicotinic transmission is present at low densities in more neuronal areas than the few that have been presently reported. However, the accumulation of evidence suggests that direct, fast nicotinic transmission is not a major excitatory mechanism in the vast majority of the mammalian brain.

Modulation of neurotransmitter release by presynaptic nAChRs is the most prevalent and well-studied nicotinic role in the CNS. Activation of presynaptic nAChRs increases the release of many different neurotransmitters (1, 2, 4, 5, 40, 41, 77–83). Exogenously applied nicotinic agonists enhance and nicotinic antagonists often diminish the release of ACh, dopamine (DA), norepinephrine, and serotonin, as well as glutamate and GABA. The results of functional studies were confirmed by immunogold labeling for the α7 subunit, which was found at nearly every synapse in the CA1 stratum radiatum of the rat hippocampus (84). The α7 subunit was found

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in a perisynaptic annulus around dendritic postsynaptic spines, and the subunit was also located on both GABAergic and glutamatergic presynaptic terminals.

The activity of presynaptic nAChRs initiates a direct and indirect intracellular calcium signal that enhances neurotransmitter release (1, 2, 4, 41). Nicotinic receptors mediate a small direct calcium influx (42–44, 85). This calcium influx can trigger calcium-induced calcium release from intracellular stores (86). In addition, nAChR activity produces a depolarization that activates voltage-gated calcium channels in the presynaptic terminal (87). The overall effect is that presynaptic nAChR activity elevates intraterminal calcium and contributes to the increased neurotransmitter release.

Nicotinic stimulation enhances glutamate release on multiple timescales, extending from seconds to a few minutes (81), and contributes to the induction of synaptic plasticity (4, 13, 14, 16, 88). In some cases, the highly calcium-permeable α7-containing (α7*) nAChRs mediate the increased release of neurotransmitter, but in other cases different nAChR subtypes are involved. The forms of enhancement lasting several minutes or more require that the intraterminal calcium elevation acts as a second messenger to modify glutamatergic synaptic transmission indirectly. Properly localized calcium signals mediated by nAChRs initiate enzymatic activity (such as protein kinases and phosphatases) that is known to modify glutamatergic synapses (89, 90). Furthermore, properly timed presynaptic nAChR activity, arriving just before electrical stimulation of glutamatergic afferents, boosts the release of glutamate and enhances induction of long-term synaptic potentiation.

Nicotinic receptors also are distributed to preterminal, axonal, dendritic, and somatic locations (91, 92). Preterminal nAChRs located before the presynaptic terminal bouton indirectly affect neurotransmitter release by activating voltage-gated channels and, potentially, initiating action potentials (78, 91, 93). The evidence for preterminal nAChR influences is strongest at some GABAergic synapses. Preterminal nAChR activation depolarizes the membrane locally, thereby activating voltage-gated channels that directly mediate the presynaptic calcium influx underlying enhanced GABA release. This effect of preterminal nAChRs is inhibited by tetrodotoxin, which blocks sodium channels and, thus, prevents the regenerative voltage-dependent activation of calcium channels in the presynaptic bouton.

Axonal, dendritic, and somal nAChRs may also modulate transmitter release and local excitability in another way. Activation of nonsynaptic nAChRs alters the membrane impedance and, thereby, alters the space constant of the cellular membrane. These factors influence the spread and efficiency of synaptic inputs to activate action potential output in the target neuron. Furthermore, by directly exciting or by shunting the progress of an action potential at a bifurcation, axonal or dendritic nAChRs alter the spread of neuronal excitation. Strategically located nAChRs enable an action potential to invade only a portion of the axonal or dendritic arbor by inactivating some voltage-dependent channels owing to a local depolarization of the membrane. The wide nonsynaptic distribution of nAChRs also could enable them to influence the moment-to-moment membrane resting potential, which would consequently influence the ease of reaching the threshold for action potential output.

Overall synaptic and volume release of ACh activates and desensitizes nAChRs at synaptic and nonsynaptic positions. At nonsynaptic locations, nAChRs influence not

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only the excitability of a neuron but also its set point, which determines the overall electrical and chemical sensitivity and responsiveness. Ongoing cholinergic activity causes some depolarization of a neuron, moving it toward its threshold for firing action potentials. The nAChR activity contributes to calcium signals that regulate intracellular enzyme systems, influencing the subsequent responses of the cell. Signaling by nAChRs also is shaped by subtype-dependent desensitization that occurs as ACh spreads at lower concentrations that escape acetylcholinesterase, which is not always perfectly matched to ACh release sites. Diffusion of choline produced by ACh hydrolysis also helps shape the time and spatial dependence of nAChR signaling.

NICOTINIC CHOLINERGIC INFLUENCES OVER CORTICAL CIRCUITRY

Cholinergic innervation generally arises from projection systems that send broad, diffuse afferents into wide areas of the brain. Thus, nicotinic activity contributes a modulatory signal that influences many synaptic and nonsynaptic circuit components at any given moment in time. By subtly influencing various aspects of neuronal communication, nicotinic mechanisms contribute to the overall efficiency of circuits.

Nicotinic Cholinergic Influences within the Hippocampus

The hippocampus receives rich cholinergic innervation mainly from the medial septum-diagonal band complex (47, 94). A fine network of cholinergic fibers innervates throughout the hippocampus and dentate gyrus, and synaptic contacts are made onto pyramidal cells, granule cells, interneurons, and neurons of the hilus (95). In addition to those direct synaptic connections, there is highly significant cholinergic nonsynaptic, volume transmission into the hippocampus (49, 50).

Although $\alpha7$, $\alpha4$, and $\beta2$ predominate, the hippocampus expresses a wide variety of nAChR subunits. GABAergic interneurons more densely express nAChRs than the glutamatergic principle cells, which express low densities (14, 43, 84, 96). Presynaptic and preterminal nAChRs increase the release of neurotransmitters in the hippocampus, particularly the main neurotransmitters, GABA and glutamate (41, 78, 81, 97). Low-amplitude, fast nicotinic synaptic transmission indicates the presence of postsynaptic nAChRs (73–75), and currents activated by exogenously applied agonists have verified nonsynaptic nAChRs distributed at axonal, somatic, and dendritic locations (14, 46, 98–100). The diffuse extracellular ACh signal and the broad distribution of nAChRs at synaptic and nonsynaptic locations ensure multiple targets and a variety of nicotinic responses in the hippocampus.

The hippocampus contains various types of GABAergic interneurons that exert control over circuit activity. With muscarinic receptors inhibited, ACh exogenously applied to rodent GABAergic neurons of the CA1 stratum radiatum evoked nicotinic currents mainly mediated by $\alpha7^*$ nAChRs, but non-$\alpha7$ nAChRs also were minority contributors (78, 83, 100–102). The non-$\alpha7$ (usually $\alpha4\beta2^*$) nAChRs were commonly expressed in the same neuron with the predominant $\alpha7^*$ nAChRs. In most cases, the exogenously applied ACh caused action potential firing by the GABA

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neuron that consequently regulated the activity of nearby pyramidal neurons (100, 103). When the GABA interneurons directly innervated nearby pyramidal neurons, nicotinic activation of the interneuron inhibited the pyramidal neuron. In a small minority of cases, however, the nicotinic-induced GABAergic activity suppressed tonic GABAergic tone, causing disinhibition of the pyramidal neurons (100). These studies provide a proof of the principle that cholinergic afferents can influence GABAergic activity in the hippocampus via nAChRs, and that GABAergic activity regulates the efferent signaling of the principle cells. In vivo, the nicotinic regulation is likely to be subtle and dispersed over wide areas owing to the diffuse cholinergic innervation and synaptic and nonsynaptic distribution of various nAChR subtypes.

STP: short-term potentiation

LTP: long-term potentiation

LTD: long-term depression

Another nicotinic control over GABAergic signaling was demonstrated in neonatal hippocampal slices (104). In adults, GABAergic synaptic currents cause mainly hyperpolarization, but during early development $GABA_A$-mediated synaptic currents cause depolarization. In the rat CA3 region, spontaneous activation of $GABA_A$ receptors produces giant depolarizing potentials, whose frequency is controlled by $\alpha7^*$ and non-$\alpha7$ nAChRs. Because nAChRs (particularly the $\alpha7^*$ subtype) are elevated during development, they can be important for tuning the number and strength of developing synaptic connections in the hippocampus (22, 83, 105).

Nicotinic receptors also modulate glutamatergic synaptic plasticity. Indirect influences arise from the previously discussed GABAergic activity, which is capable of inhibiting pyramidal neurons and preventing the induction of short-term potentiation (STP) or long-term potentiation (LTP) (14, 100, 101). There also are direct nicotinic influences at glutamate presynaptic sites. When nAChR activity precedes or matches the arrival of an action potential at the presynaptic terminal, the intraterminal Ca^{2+} signal initiated by nAChR activity adds to that from voltage-gated Ca^{2+} channels to enhance the probability of glutamate release (41). This presynaptic nAChR activity increases the probability that a postsynaptic response will arise as a consequence of presynaptic activity (14, 16, 88). Not all hippocampal glutamatergic presynaptic terminals have nAChRs, and those that do mainly have the $\alpha7^*$ subtype (at least in rodents), but other subtypes also participate.

Postsynaptic or perisynaptic nAChRs also influence synaptic plasticity by causing a depolarization and initiating an intracellular Ca^{2+} increase. The timing of the nAChR activity is crucial for determining the influence over synaptic plasticity. A nicotinic postsynaptic depolarization and Ca^{2+} signal that is within a critical time window of presynaptic glutamate release boosts synaptic potentiation (14, 16). The depolarization contributed by nAChRs helps to relieve the Mg^{2+} block of postsynaptic NMDA receptors. In addition, the Ca^{2+} signal contributed by nAChRs supplements that of the NMDA receptor to enhance the probability of LTP induction. However, if that postsynaptic nAChR-initiated signal precedes presynaptic activity, a mismatch between nicotinic-induced activity and the postsynaptic response develops. In that case, synaptic long-term depression (LTD) can be observed (16). Activation and desensitization of nAChRs by bath-applied nicotine also increases LTD induced by a stimulus train, and it assists during the depotentiation of previously potentiated glutamatergic transmission in the hippocampus (106).

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Nicotinic modulation of hippocampal plasticity was studied mainly using exogenously applied nicotinic agonists and antagonists. The results provide a proof that nAChRs have the capacity to alter circuit communication and regulate hippocampal synaptic plasticity. When compared with the in vitro experiments, in vivo nicotinic mechanisms reach many synaptic and nonsynaptic locations, contributing a more subtle influence over the efficacy of hippocampal information processing.

Nicotinic Cholinergic Influences within the Neocortex

Cholinergic innervation to the cortex arises from neurons distributed within basal forebrain nuclei, including the medial septum, the vertical and horizontal diagonal band of Broca, the substantia innominata, and the nucleus basalis of Meynert (47, 95). The innervation sparsely reaches all cortical layers, but layer V is more heavily innervated, particularly in the motor and sensory areas. Cholinergic pathways often provide "en passant" innervation. A relatively large number of small varicosities containing synaptic vesicles do not make synaptic contacts with neighboring neurons. This situation produces volume transmission, with relatively low concentrations of ACh and choline reaching locations distant from the release site (50, 51). The diffuse volume concentrations of ACh may be comparable to those reached by nicotine from tobacco, which is 500 nM or lower in arterial blood (107). The major high-affinity nAChRs, $\alpha4\beta2^*$, are approximately equally sensitive to ACh or nicotine, and exogenous nicotine modifies measured electroencephalograms (EEGs). That influence of nicotine over broad circuit events (i.e., the EEG) suggests that diffusing low concentrations of ACh likewise activate and desensitize nAChRs at synaptic and nonsynaptic locations and alter the excitability of circuits. This influence is not restricted to pyramidal cells because cortical interneurons also express nAChRs (108, 109).

The details of nicotinic influences over cortical activity depend on the unique properties of pyramidal cells. Pyramidal cells extend their apical dendrite through the cortical layers and terminate in the outmost external layers. At their base, pyramidal cells extend additional dendrites that make connections laterally within the same layer. This geometry along with their electrophysiological characteristics enables pyramidal cells to have integrative properties and function as coincidence detectors. Pyramidal cells are able to initiate action potentials in two zones (110). The distal part of the apical dendrite is rich in calcium channels and can generate an action potential, allowing propagation of the synaptic signals coming from the apical tuft toward the cell soma. A second initiation zone at the cell soma fires sodium action potentials. In addition, back propagating action potentials from the cell soma to the apical dendrite inhibit or promote the calcium action potentials in the apical dendrite (111). Back propagation of the sodium action potential in layer V pyramidal neurons depends on the electrical characteristics of the apical dendrite as influenced by the high density of potassium channels that mediate I_h (112). Activation of I_h attenuates synaptic potentials, impairs their summation, attenuates back propagation of the action potential and, thereby, decreases the capability of generating the apical calcium action potential (113).

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The preceding brief summary illustrates that ion channels distributed along the surface of pyramidal cells modulate the neuronal integrative properties and change coincidence detection. Those integrative properties and coincidence detection are modified by ligand-gated $GABA_A$ channels (114), and nAChRs distributed at synaptic and nonsynaptic locations also likely contribute to these modulatory mechanisms in the cortex. Depending on the density and distribution of various subtypes, nAChRs can be expected to cause multiple modulatory influences over cortical activity. Activation of nAChRs on distal apical dendrites depolarizes the cell and promotes action potential firing. On the contrary, activation of nAChRs on the proximal apical dendrites nearer to the cell soma reduces membrane impedance and shunts signals incoming from the apical tuft. Activation of nAChRs on the axons (91) may either shunt the action potential triggered at the soma or initiate an ectopic action potential. Although there have been limited studies of ectopic action potential firing, it has been proposed that those action potentials are more prominent during pathology and may be at the origin of some epileptic seizures (115).

SNc: substantia nigra compacta

VTA: ventral tegmental area

GABA: γ-aminobutyric acid

NICOTINIC CHOLINERGIC INFLUENCES OVER THE DOPAMINE SYSTEMS

Anatomy of the Mesostriatal Dopamine System

Midbrain dopamine (DA) neurons in the substantia nigra compacta (SNc) and the ventral tegmental area (VTA) project to the striatum, composing the mesostriatal DA system (48, 116–118). The dopaminergic innervation of the striatum is denser than anywhere else in the brain. The DA axons entering the striatum form large, highly branched arbors with a high density of axonal varicosities (116, 118). Although evidence indicates that DA fibers often make synaptic connections, spillover of DA from the synapses into the extracellular space is common and contributes to dopaminergic volume transmission.

The striatum is a large subcortical structure that is often divided into the dorsal and ventral portions (117). The dorsal striatum (neostriatum) comprises the caudate nucleus and the putamen, and the ventral striatum includes the ventral conjunction of the caudate and putamen, the nucleus accumbens (NAc), and portions of the olfactory tubercle. The phylogenetically older ventral striatum is mainly limbic related and is usually discussed as part of the mesolimbic DA system. Medium spiny projection neurons make up more than 90% of the total striatal neuronal population. These neurons carry the efferent signal from the striatum, and they are inhibitory, using γ-aminobutyric acid (GABA) as their primary neurotransmitter. The other neurons of the striatum can be classified into three groups of interneurons (117). There are burst-firing GABAergic interneurons that express somatostatin and nitric oxide, and there are rapidly firing GABAergic interneurons that express parvalbumin. The third class is the cholinergic interneurons.

The source of DA arises from a relatively small number of DA neurons located in the SNc and VTA of the midbrain. The DA areas receive massively convergent glutamatergic and GABAergic inputs, with the main cholinergic afferents originating

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in the pedunculopontine tegmentum and the laterodorsal pontine tegmentum (47). It is likely that there is significant cholinergic volume transmission in this midbrain region because direct, fast nicotinic transmission is difficult to detect.

Nicotinic Cholinergic Influences within the Mesostriatal Dopamine System

Cholinergic afferents into the midbrain acting via presynaptic (mainly) α7* nAChRs on glutamate terminals boost glutamate transmission (119–123). Nicotinic activity also supplies some excitatory drive to midbrain GABA projection neurons and interneurons via (mainly) β2* nAChRs (120, 123). The DA neurons express a variety of nAChR subunits: α4–α7 and β2, with β2* nAChRs predominating (10, 124, 125). Acting through these excitatory and inhibitory inputs and nAChRs located on the DA neurons, nicotinic receptors influence the firing modes and firing frequency of DA neurons (119, 121).

Within the DA target area of the striatum, cholinergic interneurons contribute only approximately 2% of the striatal neurons, but they are large and have extremely dense axonal arbors that provide denser cholinergic innervation than is seen anywhere else in the brain (48, 126, 127). The action of cholinergic transmission in the striatum is via direct synaptic transmission and volume transmission (128, 129). Measurements using fast cyclic voltammetry have revealed potent nicotinic controls over DA release in the striatum. Nicotine decreases tonic DA release in the striatum that is evoked by single action potentials (127), and nicotine also alters the frequency dependence of DA release that is electrically evoked by stimulus trains (130, 131). By acting at the source of DA (in the midbrain) and at the target of DA fibers (in the striatum), nicotinic mechanisms exert multiple regulatory influences over DA signaling. Via those normal nicotinic mechanisms, the addictive drug, nicotine, exerts modulatory influences over the mesostriatal, mesocortical, and mesolimbic DA systems.

Circuit Mechanisms Contributing to Nicotine Addiction

The DA systems reinforce acquisition of behaviors that are inappropriately reinforced by psychostimulant drugs, such as nicotine (23, 132–134). The rewarding influence of these pathways is supported by the finding that blocking DA release in the NAc of the ventral striatum with antagonists or lesions decreases nicotine self-administration (135).

Tobacco smoke causes inhalation of nicotine that reaches concentrations up to approximately 0.5 μM (107). The nicotine initially activates nAChRs on DA neurons, causing an increase in burst firing and overall firing rate (88, 121, 123, 124, 134). The nAChRs on the VTA DA neurons, which are mainly α4β2* (136–138), largely desensitize over the next few minutes (88, 120, 123, 124, 134). Simultaneously, nicotine activates presynaptic α7* nAChRs, boosting glutamatergic synaptic transmission onto DA neurons (23, 88, 123, 134). Because α7* nAChRs have a relatively low affinity for nicotine, the low concentrations of nicotine achieved by smokers do not significantly desensitize the α7* nAChRs (10). Postsynaptic β2* nAChRs initially depolarize DA

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neurons, causing them to fire action potentials while presynaptic α7* nAChRs boost glutamate release. The combination of enhanced glutamatergic release and strong postsynaptic response produces LTP of the glutamatergic afferents.

While nicotine-induced mechanisms potentiate glutamatergic excitation of DA neurons, nicotine simultaneously decreases inhibition of DA neurons by acting on GABAergic interneurons (23, 120, 123, 134). Cholinergic innervation provides some excitatory drive of GABAergic interneurons, and the low concentration of nicotine obtained from tobacco slowly desensitizes mainly the β2* nAChRs that mediate the cholinergic drive. Consequently, the GABAergic inhibition of DA neurons declines. Among its many actions throughout the brain, nicotine derived from smoking enhances excitation and decreases inhibition to the DA neurons. As a consequence, DA neurons fire more frequently.

Nicotine also alters DA signaling in the target areas of the striatum by desensitizing β2* nAChRs on presynaptic DA terminals (127, 130, 131, 139). By acting both at the source of DA in the midbrain and the target area in the striatum, nicotine alterations of DA signaling contribute to the overall process of addiction (23).

NICOTINIC CHOLINERGIC INFLUENCES IN COGNITION AND DISEASE

Nicotine or nicotinic receptors have been implicated in a wide range of neuronal dysfunctions and mental illness (17, 19, 20, 22, 23). Nicotinic mechanisms contribute to cognitive function, and the decline of nicotinic mechanisms or loss of nAChRs has been observed in AD, dementia with Lewy bodies, Down syndrome, autism, and Parkinson's disease (20, 140). Genetic evidence has linked nicotinic receptors to epilepsy and schizophrenia, and studies with mutant mice have implicated nAChRs in pain mechanisms, anxiety, and depression. In addition, nicotinic-based therapies have been proposed for Tourette's syndrome and attention deficit/hyperactivity disorder (ADHD) (17, 141). This review only briefly considers a few conditions.

Learning, Memory, and Attention

In general, nicotinic agonists improve certain forms of memory, and nicotinic antagonists and cholinergic lesions impair memory (5, 141–145). For example, local infusion of the α7 antagonist, methyllycaconitine (MLA), or the β2* antagonist, dihydro-β-erythroidine (DHβE), into the basolateral amygdala, the ventral hippocampus, or the dorsal hippocampus impairs the working memory of rats seeking food reward within a 16-arm radial maze (146–148). In animal studies, acute and chronic nicotine administration improves working memory, and nicotinic agonists were found to improve learning and memory in humans and nonhuman primates (145).

Disparate findings in the literature indicate that nicotinic mechanisms significantly influence only particular forms of memory, and only under certain conditions. Rodents studied using the radial maze revealed nicotinic action improved working memory, not reference memory or response latency (145, 148). Behavioral studies using agonists, antagonists, and selective cholinergic lesions indicate that the greatest

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Aβ: amyloid-β

nicotinic influences occur when the subject is performing a difficult task or is cognitively impaired (144). Results with young and old animals also show varied results. Nicotinic agonists improved memory in aged rats (149) and aged monkeys (150), but in another study, chronic nicotine did not improve working memory in aged rats (149). The variable age-related decline of cholinergic transmission and decrease in nAChR numbers contribute to the differing results. While slight cholinergic impairments may be improved by nicotinic treatments, more severe decline may not be treatable when sufficient nAChRs are no longer present to respond to the treatment. Experimental factors also influence the outcome because nicotinic agonists are highly dose dependent, having no influence at the lowest concentrations and potentially producing seizures at the highest concentrations. Furthermore, nicotinic manipulations can produce artifacts by altering autonomic and motor function.

During attention tasks, the nicotinic antagonist, mecamylamine, impaired accuracy or reaction time (151, 152) and nicotinic agonists improved accuracy (153). In some tasks and using some rodent stains, there was little nicotinic influence over attention. The results suggest that the nicotinic action is significant only when the rodent has low baseline abilities or when the task is difficult (145). This hypothesis provides a basis for analyzing the influence of nicotinic mechanisms over learning, memory, and attention. If the task is relatively easy, nicotinic influences do not seem necessary. However, when the subject is impaired or the task is particularly difficult, then nicotinic mechanisms often provide a significant modulatory influence over attention and certain forms of learning and memory.

Alzheimer's Disease

The most common form of degenerative dementia is AD, which affects more than 15 million people worldwide and grows as the proportion of elderly persons increases (154). Amyloid plaques arising from amyloid-β (Aβ) peptides and neurofibrillary tangles arising from aggregates of hyperphosphorylated tau protein are hallmarks of AD, which is characterized by progressive cognitive dysfunction, particularly in learning and memory. AD advances to affect limbic structures, subcortical nuclei, and cortical regions, and in that way influences multiple neurotransmitter systems. The most well-appreciated neuronal loss, however, is in the cholinergic system (155, 156), particularly the basal forebrain cholinergic system comprised of the medial septal nucleus, the horizontal and vertical diagonal bands of Broca, and the nucleus basalis of Meynert (157). The decline of cortical cholinergic activity as measured in postmortem brains correlates with the severity of AD symptoms and with the intellectual deterioration observed in life (155, 158). As AD worsens, cholinergic neurons are progressively lost and the number of nAChRs declines, particularly in the hippocampus and cortex (140, 158).

Nicotinic deficits during the progression of AD arise from the decline of synaptic and circuit mechanisms. The most commonly prescribed treatments for AD are acetylcholinesterase inhibitors, which decrease the hydrolysis rate of ACh and, thereby, enhance cholinergic signaling. One such drug, galantamine (Reminyl®), also

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potentiates nAChRs (66). Consistent with these treatments, nicotinic agents improve cognitive deficits of AD patients (20, 158).

Although Aβ peptides negatively alter the cholinergic system at multiple sites, including ACh synthesis, ACh release, and muscarinic receptors (157), the discovery that $A\beta_{1-42}$ binds to α7 nAChRs with high affinity suggested the potential for a causal role of nAChRs in AD (159, 160). This prospect was supported by the finding that α7 nAChRs were found in plaques (159), and α7 and α4 subunits positively correlated with neurons that accumulated Aβ and hyperphosphorylated tau in AD brain tissue (161). In a triple transgenic mouse model of AD (3xTg-AD), which expresses aspects of AD neuropathology and an age-related decline in LTP and cognition, there was a loss of α7 nAChRs (160). Despite some disagreement, the accumulation of evidence also indicates that $A\beta_{1-42}$ inhibits currents mediated by α7 nAChRs (162, 163). Therefore, the decline of nAChRs and additional inhibition by Aβ provides a mechanism (at least in part) (14, 157) to explain Aβ decreasing synaptic induction of LTP (164). The loss of cholinergic projections and decline of nAChRs during AD disrupts normal nicotinic mechanisms that contribute to proper neurotransmitter release, circuit activity, and synaptic plasticity. Overall, these mechanisms contribute to the cognitive decline observed during the progression of AD.

Autosomal dominant nocturnal frontal lobe epilepsies (ADNFLE): this form of nAChR-based epilepsy exhibits seizures that originate in the frontal lobe and occur mainly during non-REM sleep

Epilepsy

Epilepsies are characterized by recurrent seizures manifested from transient abnormal neuronal activity. Seizures lasting from seconds to minutes occur repetitively or in isolation, and they can be focal or spread across the entire brain causing motor, sensory, or cognitive disturbances. Epilepsies that have no obvious origin are called idiopathic epilepsies, and they arise mainly from genetic origins. Multiple genes have been identified as being responsible for idiopathic epilepsies, and many of them code for ion channels.

A mutation in the gene encoding the α4 nAChR subunit (CHRNA4) causes a genetically transmissible form of epilepsy, which was the first discovery of a human disease associated with a neuronal nAChR (165, 166). The mutation has been identified as a single base substitution converting a serine into threonine (S248F) in the TM2 domain of the α4 subunit (165). The nAChR-based epilepsy exhibits seizures occurring mostly during non-REM (rapid eye movement) sleep (167). Presenting a focal origin in the frontal lobe, these kinds of epilepsy are called autosomal dominant nocturnal frontal lobe epilepsies (ADNFLE). Subsequent to the original discovery, several other families suffering from typical ADNFLE or nocturnal frontal lobe epilepsy (NFLE) have been found to have a mutation either in α4 or β2 (encoded by CHRNB2) (165, 166, 168–170). ADNFLE patients are heterozygous for the mutation, carrying only a single copy of the modified gene. Because α4 and β2 subunits combine to make a major nAChR subtype in the brain ($\alpha4\beta2^*$), mutations in either subunit produce comparable epileptic symptoms. Onset occurs at approximately age 12 and can extend through the entire life span, but ADNFLE has a low penetrance, which means that only a fraction of persons that harbor the mutation display a clinical

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phenotype (166). Thus, a mutation in the gene encoding either α4 or β2 is sufficient to cause ADNFLE, but additional factors may attenuate or accentuate the onset and gravity of the disease.

The function of the mutant α4 or β2 subunit has been analyzed in the *Xenopus* oocyte expression system (168, 171–175). Although each mutant displays slightly different characteristics, a shared trait is an increased sensitivity to ACh (173). The mutated nAChRs show the complex dose-response curve of control receptors, which have a high and low affinity component, but the mutants have a larger proportion of the high-affinity component (172). The next step is to understand how increased ACh sensitivity leads to abnormal synchronization of neuronal networks producing epileptic seizure.

ADNFLE seizures take place in the frontal lobe during sleep. While profound sleep is dominated by slow-wave EEG, other phases yield sleep spindles and high-voltage slow waves that reflect changes in the excitability of the cortical and thalamic circuitry (176, 177). There are cyclic REM and non-REM phases that reflect differential activities in sleep-controlling cholinergic nuclei. Two major branches compose the cholinergic ascending pathway that controls arousal. The first branch activates the thalamic relay neurons that control transmission of sensory information to the cortex. The thalamic-relay nuclei and the reticular nucleus of the thalamus receive input from two groups of cholinergic neurons in the upper brainstem: the pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT) (177). The neurons from the PPT/LDT nuclei discharge at a higher frequency during wakefulness and REM sleep, which corresponds to a higher level of ACh being released in the thalamus and the reticular nucleus. The second branch of the ascending arousal system bypasses the thalamus and activates the lateral hypothalamic area of the basal forebrain and projects throughout the cerebral cortex. Most cholinergic neurons of the basal forebrain are active during both waking and REM sleep, and their activity is synchronized with theta oscillations (178).

The major cell groups of the hypothalamus and brain stem that participate in arousal also receive monoaminergic fibers from a small group of cells from the ventrolateral preoptic nucleus (VLPO). Neurons from the VLPO that are primarily active during sleep are inhibited by nicotine through the activation of high-affinity nAChRs (i.e., β2*) that are sensitive to the antagonist DHβE but not to MLA (selective for α7) (179). This inhibition is thought to arise from the presynaptic facilitation of noradrenaline release by heteromeric α4β2* nAChRs. In agreement with these observations, mice lacking the β2 subunit (β2−/−) display equivalent proportions of REM and non-REM sleep as their wild-type littermates, but they exhibit longer REM sleep periods and reduced fragmentation of non-REM sleep (180). Moreover, although nicotine increases wakefulness in wild-type mice, it does not affect β2−/− mice. Overall, stimulation of nAChRs promotes arousal and REM sleep.

Hypersynchrony of the cortical network is triggered in the frontal lobe and, depending on the gravity of the disease, spreads to other cortical areas (181). The thalamic-relay nucleus and reticular neurons connect to the cortex, which projects

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back to the thalamus forming a feedback loop. The α4β2 nAChR subtype is densely expressed in the thalamus and is diffusely distributed in the cortex onto GABAergic interneurons and pyramidal cells. The underlying genetic mutations produce a range of effects from slight to profound. However, the normal brain performance and absence of evident brain reorganization suggest that ADNFLE seizures originate from network tuning but not from gross abnormalities. The question that must be answered is the following: Can we explain the abnormal neuronal synchrony based on the increase in ACh sensitivity arising from the ADNFLE-inducing mutations in CHRNA4 (α4) or CHRNB2 (β2)?

The present information suggests the following hypothesis: Regulated ACh release causes changes in the phases of sleep. The CHRNA4 or CHRNB2 mutations cause a hypersensitivity of the α4β2* nAChRs that increases the positive response of the pyramidal cells, boosting feedback onto the thalamic neurons. Concomitantly, an increase in ACh-induced GABAergic interneuron activity influences the excitability of large groups of pyramidal cells, tending to synchronize their activity. These two alterations progressively interact to produce a discharge, which is triggered by events that would normally give rise to the K-complex or spindles. This hyper-synchronized discharge, like the K-complex or spindles, produces a complex phasic activity observed in the EEG during non-REM sleep. Synchronous neuronal activity reinforces the thalamo-cortical loops and causes further invasion of seizure-type events in the cortex. Following these initial steps, the spreading of the seizure-type discharges depends on the reactivity of the neighboring neurons. Spreading of the seizure to the motor control area causes the typical epileptic tonico-clonic muscle contractions of an epileptic attack.

Genetically engineered knockin mice have been created to investigate further the contribution of the α4 subunit. The variant introduced a leucine to serine mutation (L9'S) into the pore-lining TM2 domain, creating an α4 gain of function with increased agonist sensitivity and decreased desensitization (182). These mice have a higher sensitivity to nicotine-induced seizures but do not have spontaneous seizures (183). However, they display an increase in brief awakenings (microarousal), supporting a role for α4* nAChRs in sleep regulation.

Thus, introduction of ADNFLE mutations into mice causes changes in circuit excitability but does not induce the spontaneous seizures expected of an ideal ADNFLE model. This shortcoming may arise for a number of reasons. The low penetrance of ADNFLE indicates that a single mutation in CHRNA4 or CHRNB2 is necessary but not sufficient to cause seizures. Additional exposures (such as other genetic, environmental, or developmental factors) must contribute to create this form of epilepsy. Alternatively, differences between the human and the mouse in the structural organization of the frontal cortex and neuronal networks may underlie the present limitation in mice models. In addition, although human and mouse α4 subunits show a high degree of homology, there are amino acid differences and detectable differences in human and rat α4β2 nAChR function (65). The mouse models thus far have been helpful, but additional understanding and effort is needed to produce an ideal animal model for nAChR-based epilepsies.

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PERSPECTIVE

Nicotinic receptors are widely expressed throughout the CNS, influencing electrical events in nearly every area of the mammalian brain. They enhance neurotransmitter release, modify circuit excitability, and influence synaptic plasticity. The synaptic physiological roles of nAChRs continue to be delineated, but important issues at the higher systems level have received less attention. This need is highlighted by nAChR participation in a diverse array of neuronal pathologies, including AD, Parkinson's disease, schizophrenia, epilepsy, and addiction. The complex systems-level nature of those diseases underscores nicotinic influences over local circuits and the long-range communication involved in attention and cognition.

The final goal of better nicotinic treatments requires advances on multiple fronts. More ideal animal models are needed to investigate nicotinic-based dysfunctions. Advances with nicotinic ligands would be helpful in the laboratory and, eventually, in the clinic. Nonselective ligands may be created to control the general activation and desensitization of nAChRs. Nicotinic receptor subtypes are distributed onto many different neuronal targets and cannot be linked to only one signaling pathway. Despite that problem, more subtype-selective ligands that easily cross the blood-brain barrier would provide valuable experimental tools for in vivo studies to investigate subtype-selective influences over neuronal function and dysfunction. Allosteric ligands that alter nAChR functions without eliminating them may avoid some side effects associated with classic agonists and antagonists. Continued advances in basic research coupled with improved animal models will enhance the transfer of information to clinical settings and, ultimately, provide improved nicotinic therapies.

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Errata

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