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The α7 Nicotinic Acetylcholine Receptor in Neuronal Plasticity

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Abstract

A growing body of evidence indicates that neuronal nicotinic acetylcholine receptors (nAChRs), in addition to promoting fast cholinergic transmission, may modulate other neuronal activities within the central nervous system (CNS). In particular, the α7 nAChR is highly permeable to Ca^{2+} and may serve a distinct role in regulating neuronal plasticity. By elevating intracellular Ca^{2+} levels in discrete neuronal locations, these ligand-gated ion channels may influence numerous physiological processes in developing and adult CNS. In this article, we review evidence that both pre- and postsynaptic α7 nAChRs modulate transmitter release in the brain and periphery through Ca^{2+}-dependent mechanisms. The possible role of α7 nAChRs in regulating neuronal growth and differentiation in developing CNS is also evaluated. We consider an interaction between cholinergic and glutamatergic transmission and propose a hypothesis on the possible coregulation of intracellular Ca^{2+} by *N*-methyl-D-aspartate (NMDA) receptors and α7 nAChRs. Finally, the clinical significance of alterations in the normal function of α7 nAChRs is discussed as it pertains to prenatal nicotine exposure, schizophrenia, and epilepsy.

Index Entries: α-Bungarotoxin; nicotine; acetylcholine; cholinergic; plasticity; thalamocortical; cortex; trophic factors.

Introduction

Neuronal development and plasticity are influenced greatly by external signals acting as cues for particular cellular responses. In addition to the influence of growth factors in these processes, there is a growing body of evidence that neurotransmitters may serve as neurotrophic agents in the peripheral (PNS) and central nervous system (CNS; reviewed in *1–3)*. Studies have shown that neurotransmitters can modulate the levels of a specific

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second messenger(s), such as intracellular free Ca^{2+}, and thereby influence various aspects of cellular plasticity *(4)*.

Numerous investigations have indicated a possible role for cholinergic systems in mediating trophic actions in the developing and adult CNS *(5–8)*. Although a great deal of evidence has implicated muscarinic receptors *(5,9)*, there has been relatively little attention paid to the role of nicotinic acetylcholine receptors (nAChRs) in neuronal plasticity. However, an increasing number of studies are demonstrating that nAChRs, in addition to mediating fast cholinergic transmission, may also play a broader role in the development and modulation of neuronal synapses *(10)*. One particular nAChR subtype that has received much attention in recent years is the α7 nAChR. Since its initial cloning *(11)*, followed by an instrumental review *(12)*, which helped propel this receptor into recognition, there has been a plethora of studies attempting to analyze the functional role of α7 nAChRs in the CNS.

This article relates the available evidence on the potential role(s) of α7 nAChRs in neuronal plasticity. It is not intended to be an historical perspective of the α7 nAChR, since such qualified accounts already exist *(12–14)*. We begin by summarizing the molecular, pharmacological, and physiological diversity of neuronal nAChRs, while focusing on the α7 nAChR. Next, we discuss the roles of pre- and postsynaptic α7 nAChRs as they relate to synaptic plasticity. This is followed by an analysis of α7 nAChRs in the developing CNS, along with the cholinergic source(s) for their activation. In addition, we consider the interaction between cholinergic and glutamatergic transmission as it pertains to the α7 nAChR. Finally, we discuss the possible clinical significance of alterations in the normal function of α7 nAChRs. Although there are also numerous studies on the functional roles of other neuronal nAChR subtypes, we focus here specifically on the α7 nAChR. For more comprehensive descriptions of nAChRs, the reader is referred to several excellent reviews *(10,14–19)*.

Background

The α7 nAChR is a member of a large family of neuronal nAChRs found in the vertebrate PNS and CNS. These ligand-gated ion channels are pentamers, generally composed of α and β subunits (2 α and 3 β). To date, 11 nAChR subunits have been identified in vertebrates and designated as either α-type (α2–α9) or β-type (β2–β4) based on their homology to the muscle α1 subunit. The α8 subunit has been found in avians, but not in mammals *(20)*, and the α9 subunit is only expressed in certain endocrine cells and sensory end organs *(21)*. Heterologous expression of nAChR subunits in *Xenopus* oocytes indicates that many (but not all) of the α and β subunits can coassemble to form functional nAChR channels that are distinct in their biophysical and pharmacological properties *(14,16)*. Moreover, expression of α7, α8, or α9 subunits alone gives rise to functional homo-oligomeric, acetylcholine- (ACh) gated channels that are blocked by nanomolar concentrations of the snake toxin, α-bungarotoxin (α-BTX; *20–22*).

Whereas data from in vitro expression studies have identified potential nAChR subtype candidates, more recent studies have helped characterize possible subtypes of native neuronal nAChRs in the CNS *(17–19)*. Although physiological and pharmacological studies have confirmed the existence of distinct functional nAChRs in different regions of the brain, they appear to belong to two major classes: α-BTX-insensitive and α-BTX-sensitive. Receptors containing α3 , α4 , or β2 subunits form the bulk of α-BTX-insensitive nAChRs in the vertebrate brain and account for the vast majority of high-affinity nicotinic agonist binding *(23–26)*. On activation by ACh, these ion channels become permeable to Na^+, K^+, and Ca^{2+} ions and show a relatively slow decaying inward current *(16)*. The α-BTX-insensitive channels are found in brain regions, such as the nigrostriatal and mesolimbic pathways, where they modulate dopamine release *(18,27,28)*, and mediate the locomotor and reinforcing properties of nicotine *(29–31)*.

Neuronal nAChRs of the α-BTX-sensitive class contain α7 subunits and account for most of the α-BTX binding in the vertebrate brain *(32,98)*. In the chick CNS and PNS, there is strong evidence for heteroligomeric complexes of α7 along with α8 *(34,35)*, and more recently with α5 *(36)*. However, in mammals, α7 nAChRs appear to be predominantly homomeric ion channels *(32)*. These channels have a high relative permeability to calcium and are blocked by nanomolar concentrations of α-BTX *(22,37)*. Furthermore, activation of α7 nAChRs can produce a rapidly decaying inward current that can quickly elevate intracellular levels of free calcium in neurons, either directly through the channel, or indirectly via depolarization and consequent activation of voltage-gated Ca^{2+} channels *(39,40,84)*.

Presynaptic α7 nAChRs

A general problem in addressing nAChR function in the brain has been the inability to demonstrate clearly ACh-evoked synaptic responses from these receptors, and has been aggravated by the lack of specific agonists and antagonists for each of the receptor subtypes *(14)*. However, the functional characterization of nAChRs has improved immensely in recent years because of subtype-selective ligands, as well as advances in physiological recording techniques that have enabled the analysis of nAChR currents expressed in single neurons *(16,17,41)*. Therefore, a growing body of evidence suggests that nAChRs found at presynaptic terminals in the CNS may have an important role in modulating neurotransmitter release *(10,18)*. Because of their high Ca^{2+} permeability and rapid desensitization, α7 nAChRs provide a unique mechanism for cholinergic regulation of transmitter release throughout the brain. Indeed, recent studies have shown that activation of presynaptic α7-containing nAChRs can enhance and sometimes elicit release of the excitatory amino acid transmitter, glutamate, from synaptic terminals in developing and adult brains through a calcium-dependent mechanism. These results were obtained in culture and slice preparations from various brain regions expressing high levels of α7 nAChRs, including the chick medial habenula *(42)*, and lateral geniculate nucleus *(43)*, rat hippocampus *(41)*, olfactory bulb *(44)*, and sensory neocortex *(45)*. Thus, α7 nAChRs may be involved in modulating sensory processing and cognitive tasks, such as learning and memory.

By mediating glutamatergic transmission, α7 nAChRs may also indirectly regulate other neurotransmitter systems. Studies in animals have demonstrated that nicotine increases release of dopamine in the nucleus accumbens by activation of nAChRs in the ventral tegmental area (VTA; *29,30,46,47)*. These nAChRs include presynaptic α7 nAChRs located on glutamatergic afferents in the VTA, which increase glutamate release and, in turn, stimulate mesolimbic dopamine neurons *(48)*. These results indicate that α7 nAChRs may also have an important role in modulating the reinforcing effect of natural rewards as well as that of various drugs of abuse, such as nicotine.

In addition to facilitating glutamate release, activation of α7-containing nAChRs on presynaptic sites can potentiate the release of several other neurotransmitters. A recent study in rat brainstem slices has demonstrated nicotine-stimulated release of norepinephrine from dorsal raphe neurons *(49)*. The effect on norepinephrine release was calcium-dependent and inhibited by methyllycaconitine. Although this suggests the presence of presynaptic α7-containing nAChRs, the high concentration of methyllycaconitine used in this study may also indicate the involvement of other nAChR subtypes. Activation of presynaptic α7 nAChRs in PNS ganglion neurons has been shown to stimulate ACh release *(42,50)*, presumably acting as a positive feedback mechanism for cholinergic transmission. The potentiation of γ-aminobutyric acid (GABA) release from hippocampal interneurons by presynaptic α7 nAChRs has also been proposed *(51)*. However, since most of the α7 nAChRs in interneurons are believed to play a postsynaptic role *(see* Postsynaptic α7

nAchRs; refs. *52–55)*, such findings are still preliminary. Nevertheless, these data indicate that a major role for presynaptic α7 nAChRs in the vertebrate CNS is to modulate neurotransmitter release and thereby contribute to cholinergic modification of information processing throughout the brain. Further studies will most likely focus on the secondary mechanism(s) involved in this process.

Postsynaptic α7 nAChRs

Although cholinergic transmission mediated by postsynaptic nAChRs is well established in the periphery, it has been considerably more difficult to demonstrate these nicotinic responses in the CNS *(10)*. The α7 neuronal nAChR has been especially elusive in this regard, presumably because of its fast-desensitizing currents and low agonist affinity. However, with recent advances in recording techniques that make it possible to detect synaptic events on a faster time scale, an increasing number of laboratories have now demonstrated evoked synaptic currents in both PNS and CNS neurons, mediated by post- and perisynaptic α7 nAChRs. By general definition, these postsynaptic responses were evoked under pharmacologically isolated conditions by application of specific receptor agonists and blocked by selective receptor antagonists.

Initial studies of chick ciliary ganglion neurons have shown that these cells express a large number of α7-containing nAChRs *(56)*. Despite their perisynaptic localization *(57,58)*, α7-containing nAChRs have been shown to produce a large fraction of the synaptic currents within these ganglion neurons *(59–61)*. In the rat brain, fast cholinergic transmission mediated by postsynaptic α7 nAChRs has recently been observed within the hippocampus *(52–55)*, and the olfactory bulb *(44)*, and associated with modulation of GABA release. These results are the first to indicate that α7 nAChRs may also participate in mediating cholinergic neurotransmission in the brain. A more recent study, however, suggests that the GABAergic circuitry in the hippocampus may be slightly more complicated, consisting of inhibitory and disinhibitory responses that are modulated by nicotinic receptors at both pre- and postterminal regions *(62)*. Thus, neuroanatomical investigations may be required to help determine the precise cellular localization of α7 nAChRs in this area of the brain.

All together, these studies suggest that pre- and postsynaptic α7 nAChRs can play significant roles in cholinergic modulation of transmitter release in the CNS by mediating the release of both excitatory and inhibitory signals through Ca^{2+}-dependent mechanisms. This would have important implications for neuronal plasticity. For example, because of their capacity to regulate neurotransmission in the hippocampus, α7 nAChRs may play a role in modulating the induction of long-term potentiation. Such a role has been suggested by several studies *(63,64)* and is consistent with the proposed functions of α7 nAChRs in the hippocampus *(17)*. Furthermore, α7 nAChRs may be involved in cholinergic facilitated reorganization of cortical maps in the adult brain *(65–68)*.

α7 nAChRs in the Developing CNS

In addition to their role in modulating synaptic neurotransmission, α7 nAChRs may play an important role in regulating neuronal growth and differentiation. This hypothesis is supported by three separate, but related lines of evidence. First, several studies have demonstrated that α7 nAChR expression is highly regulated in the developing brain during a critical period of synaptic plasticity. In both the chick and rodent, there is strong expression of α7 mRNA and protein in embryonic brain *(11,69,70)*, with a subsequent reduction in many brain regions during postnatal development *(70–73)*. Within the rodent neocortex, for example, transient α7 mRNA and protein expressions delineate sensory regions, with a spatiotemporal correspondence to ingrowing thalamic afferents.

Moreover, this increased α7 nAChR expression is tightly regulated by thalamic afferent activity *(74)*. Additionally, other factors associated with neuronal activity, such as neurotrophic factors *(75)*, protein kinases *(76,77)*, arachidonic acid *(84)*, and Ca^{2+} ions *(78)*, have clearly been shown to regulate the expression and properties of α7 nAChRs, suggesting that the developmental regulation of α7 nAChR expression may involve a complex set of mechanisms. These observations, along with the transient increased expression of α7 nAChRs in the developing CNS, are consistent with a putative role for this receptor in developmental processes.

A second series of studies have shown that α7 nAChRs may modulate the plasticity of neuronal circuitry. Early experiments in the toad optic tectum have demonstrated that α-BTX binding sites modulate the development and maintenance of retinotectal connections *(79)*. Subsequent studies have shown that activation of α7-type nAChRs leads to neurite retraction in both PC12 cells and isolated ciliary ganglion neurons, which is dependent on Ca^{2+} influx *(80,81)*. Finally, in a more recent study, activation of α7 nAChRs on cultured neurons of rat olfactory bulb was reported to produce neuritic elongation *(82)*. Although the results of these studies may appear contradictory, it is reasonable to predict that different neuronal cell types may possess diverse Ca^{2+}-sensitive biochemical signaling pathways and, thus, can react differently to increased intracellular Ca^{2+} *(83)*. In addition, these processes may depend on the spatial distribution of α7 nAChRs on the cell membrane. Nevertheless, these observations indicate that α7 nAChRs are involved in establishing and regulating neuronal circuitry, probably through Ca^{2+}-dependent mechanisms.

Varying levels of intracellular Ca^{2+} can have graded effects on developing neurons, from altering gene expression to apoptotic cell death *(4,83,98)*. Given the high Ca^{2+} permeability of α7 nAChRs *(22,37,38,40)*, these channels are likely to influence many aspects of neuronal differentiation. Indeed, this has been implicated in a series of past and recent studies. First, α-BTX-sensitive nAChRs have been reported to regulate mRNA production of neurotrophic growth factors in the adult rat hippocampus *(85)*. Consistent with this observation, activation of α-BTX-sensitive nAChRs resulted in cell proliferation in a neuroendocrine cell line *(86,87)*. Other studies have demonstrated a neuroprotective role for the α7 nAChR. Preactivation of α7-type nAChRs protected rodent cultured neocortical neurons against *N*-methyl-D-aspartate (NMDA)-mediated glutamatergic excitotoxicity *(88,89)*. Similar neuroprotective properties of α7 nAChRs were observed in models of ischemia and lesion-induced atrophy *(89,90)*.

Finally, a series of studies have implicated α7 nAChRs in opposing processes of apoptosis and neurodegeneration. Blockade of α-BTX-sensitive nAChRs was previously reported to rescue embryonic chick motoneurons from naturally occurring cell death *(91,92)*. More recently, activation of these receptors by nicotine was demonstrated to induce apoptotic cell death of rat hippocampal progenitor cells *(93)*. Furthermore, an α7 nAChR mutation (L247T) resulting in a gain of channel function *(94,95)* has been demonstrated to cause neurodegenerative apoptosis in the Caenorhabditis elegans *(96)* and the developing murine nervous systems *(97)*. These contrasting neuroprotective and neurodegenerative effects of α7 nAChRs on developing neurons can again be explained by the appearance of diverse biochemical signaling pathways, but also by the expression of Ca^{2+}-buffering mechanisms *(93)*, which may change the effect of α7 activation from damaging to beneficial. Taken together, these data provide strong evidence that α7 nAChRs can mediate diverse effects on developing neurons ranging from local regulation of neurite growth cones to a more general modulation of cellular growth and differentiation.

Given the increasing evidence for the involvement of α7 nAChR in neuronal development and plasticity, it is surprising to learn that knockout of the α7-subunit yields animals that survive normally with no apparent physical or neuroanatomical deficits *(33)*. Moreover, these

mice show no obvious difference in the barrel formations within their somatosensory cortex (SS1), a region delineated by α7 nAChR expression during cortical development *(70)*. However, preliminary studies have shown that α7 nAChR knockout mice display an anomalous synchronization on electroencephalography recordings *(99)*, suggesting that loss of the α7 nAChR may cause more subtle phenotypic abnormalities in the intrinsic circuitry of the brain. In the absence of α7 nAChRs, other mechanisms may take over to help modulate intracellular Ca^{2+} levels *(see* α7 nAChRs and Glutamatergic Systems*)*, resulting in apparently normal anatomical structures. Therefore, future studies may need to analyze these α7-deficient mice on an ultrastructural level. Furthermore, the absence of the α7 nicotinic receptor subunit may only become evident when there is a compromise of neuronal function, such as in aging or some neurological disorder. This has recently been demonstrated for mice lacking the β2 nicotinic receptor subunit *(100)*. Additionally, other animal models expressing alterations of the α7 nAChR resulting in a "gain of function" *(97)* may help to elucidate the functional role of these receptors in the brain.

Early Cholinergic Circuitry

If α7 nAChRs are truly involved in modulating neuronal development, an established source of endogenous agonist, such as ACh, must be present within developing regions of the CNS that express α7 nAChRs. For this topic, we shall focus our discussion on the rodent sensory cortex, which expresses high levels of α7 nAChRs during brain development *(70,71,73)*. The rodent cortex receives its primary cholinergic projection from ACh-containing neurons located in the basal forebrain *(101,102)*. A transient expression of cholinergic neurons within rat sensory cortex has been reported to peak during the perinatal period *(103)*. Interestingly, α7 mRNA and protein expression can also be observed during this time-point within the embryonic neocortex *(70)*. Cortical ingrowth of basal forebrain afferents in the rodent has been observed as early as postnatal d 0 (P0) *(104,105)*. These tracing studies have indicated that the early postnatal development of basal forebrain fibers coincides temporally with a transient expression of α7 nAChRs in the sensory cortices *(70,74)*. Whereas previous studies were not able to detect choline acetyltransferase-(ChAT) positive expression in these basal forebrain afferents before P5 *(106)*, in a more recent study, ChAT-immunopositive axons were detected in the rat cerebral cortex at birth *(107)*. This directly coincides with the first detectable expression of α7 nAChR mRNA and protein in the sensory cortex *(74)*.

Although these results are in agreement, there is still an apparent discrepancy between the high levels of α7 nAChR expression and the relatively low levels of ChAT expression in the developing cortex. This becomes even more pronounced considering the high levels of acetylcholinesterase (AChE) activity in these developing cortical regions *(108)*. However, recent investigations suggest that ACh may not be the primary activator of α7 nAChRs during brain development. These studies have demonstrated that choline, a precursor of ACh and a product of ACh hydrolysis by AChE, acts as an efficient and selective agonist of α7 nAChRs expressed in *Xenopus* oocytes and neuronal cell and slice cultures *(62,109–111)*. Thus, high levels of choline, possibly owing to increased AChE expression, may play a prominent role in regulating α7 nAChR activity during development. Although the precise concentration and spatiotemporal distribution of choline in the brain remain to be determined, these findings indicate that α7 nAChRs may be functionally active during the critical period of neuronal growth and differentiation.

α7 nAChRs and Glutamatergic Systems

One issue that warrants further consideration is the consistent association of α7 nAChRs with glutamatergic transmission. This issue becomes particularly interesting given the elec-

trophysiological response profiles of α7 nAChRs and NMDA receptors *(112)*. Although both receptor channels are highly permeable to Ca^{2+}, they are differentially regulated by Mg^{2+} and show opposing current–voltage relationships. ACh-induced α7 nAChR currents exhibit an inward rectification, which is dependent on the presence of intracellular Mg^{2+} *(113,114)*. In contrast, the outward rectification of NMDA-evoked currents is dependent on the presence of extracellular Mg^{2+} *(115)*. Thus, α7 nAChRs can mediate a substantial Ca^{2+} entry into neurons at resting or hyperpolarizing membrane potentials, whereas NMDA receptors gate Ca^{2+} entry into neurons at depolarized conditions. Additionally, NMDA receptor activation has been shown to induce an elevation in intracellular Mg^{2+} levels *(116)* that would ensure blockade of α7 nAChRs and prevent Ca^{2+} overload of neurons owing to simultaneous activation of both receptor types. These observations indicate complementary, nonoverlapping roles for α7 nAChRs and NMDA receptors in the regulation of intracellular Ca^{2+} concentrations, a concept that may be referred to as a "ying-and-yang" hypothesis. This hypothesis, initially put forth by Albuquerque and colleagues *(112)*, suggests a mutual physiological interaction between the two transmitter systems that may serve to fine-tune cellular activity.

Perhaps one of the best examples of this putative interaction between cholinergic and glutamatergic systems can be seen in the developing rodent sensory cortex. Sensory regions of the cortex provide a useful model for analysis of synaptic plasticity, because they exhibit dynamic changes during early postnatal development. These cortical areas are innervated by afferents from the thalamus and basal forebrain, which provide the primary glutamatergic and cholinergic transmission to the cortex, respectively *(102,117,118)*. Furthermore, these two transmitter pathways innervate the sensory cortex during a critical period of development *(106,119–121)*. Studies have demonstrated that disruption of either the cholinergic *(5,6,68)* or glutamatergic *(122,123)* pathways during this early period can have marked consequences on cortical development and plasticity.

Both α7 nAChRs and glutamatergic receptors are active and exhibit discrete patterns of expression in the sensory cortices at around the same postnatal period *(45,70,71,73,124, 125)*. In the developing rat SS1, studies have demonstrated that α7 nAChR expression on cortical neurons is tightly regulated by the ingrowing thalamocortical afferents *(74)* and that this regulation may be mediated by glutamate acting via NMDA receptors *(126)*. Moreover, activation of presynaptic α7 nAChRs in the developing rat auditory cortex has recently been shown to enhance NMDA receptor-mediated glutamatergic transmission *(45)*. These data imply that glutamatergic signals from ingrowing thalamocortical afferents cause an increase in postsynaptic and perhaps presynaptic α7 nAChR expression in the developing cortex. Together with NMDA receptors, postsynaptic α7 nAChRs may serve to regulate intracellular Ca^{2+} levels in cortical neurons *(112)* whereas presynaptic α7 nAChRs could serve as a feedback mechanism for modulating glutamatergic transmission *(18)*. Such a scheme is presented in Fig. 1. In support of this overall hypothesis, several recent studies have demonstrated that activation of α7 nAChRs protected rat neuronal cultures from NMDA receptor-mediated excitotoxicity *(88,89,127, 128)*. These results indicate a close interaction between cholinergic and glutamatergic pathways, mediated by α7 nAChRs and NMDA receptors, that can have significant effects on neuronal plasticity throughout the developing and adult brain.

Clinical Implications

Over the past two decades, accumulating knowledge of nAChRs in vertebrates has led to the demonstration that alterations of these receptors may be responsible for a variety of familial disorders of the CNS and PNS (reviewed in ref. *129*). Consequently, these

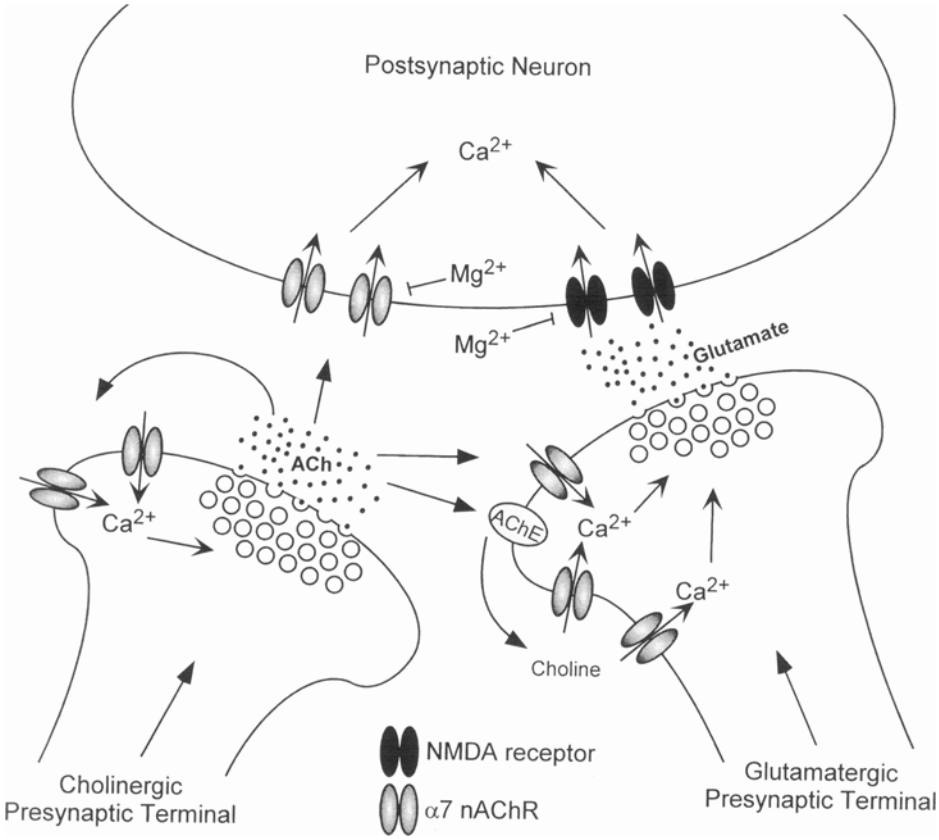

Fig. 1. Schematic diagram depicting the hypothetical roles for α7 nAChRs in the CNS. Presynaptic α7 nAChRs can modulate the release of neurotransmitters, whereas postsynaptic receptors can help regulate the levels of intracellular Ca^{2+}. Also presented is the putative interaction between the cholinergic and glutamatergic systems. Together, α7 nAChRs and NMDA receptors can regulate intracellular Ca^{2+} levels, with Mg^{2+}-mediated rectification as the limiting factor. This diagram represents a potential model for cholinergic/glutamatergic interactions throughout the brain. Adapted from Albuquerque et al. *(17)*. Acetylcholinesterase, AChE.

receptors are also being considered as relevant targets for nicotinic therapies of brain disorders. Because of the potential for α7 nAChRs to modulate neuronal plasticity, their aberrant function may underlie many of these disorders. Indeed, the recent cloning of the human α7 nAChR *(130)* has generated increased interest in identifying disorders involving this receptor.

One topic that has attracted considerable interest in recent years is the problem of tobacco abuse. Although the underlying mechanisms that cause tobacco abuse are not well understood, accumulated evidence indicates that nicotine is the primary component of tobacco that motivates continued use *(29,30)*. Numerous studies have indicated that nicotine may have adverse effects on the developing CNS. The incidence of cigaret smoking among pregnant women is approx 20–50%, resulting in infant health problems, such as prematurity, low birthweight, and sudden infant death syndrome *(131)*. In animal studies, prenatal nicotine exposure has been associated with abnormal neuronal maturation, defects in multiple neurotransmitter systems, and alterations in cognitive performance of the offspring *(132–135)*. Moreover, fetal nicotine exposure has been observed to cause abnormal cortical

development *(136)*. Anatomical analysis of the SS1 in exposed rat pups shows a reduction in cortical thickness and cell size, as well as decreased dentritic branching. Given the evidence presented, these observations implicate the involvement of nAChRs, including the α7 nAChR subtype, in mediating the adverse effects of nicotine in the developing brain, and warrant further investigation of this role.

Characterizing the functional role(s) of α7 nAChRs in the brain and the secondary mechanisms they could activate may also help in our understanding of a variety of neurological disorders. One such disorder where α7 nAChRs have received considerable attention is schizophrenia. This polygenetic disorder is partially characterized by an auditory gating deficit, an abnormal electrophysiological response to repeated auditory stimuli involving the hippocampus *(137)*. Studies have shown that increased cigaret smoking in schizophrenic patients normalizes this aberrant trait *(138)*. Recent investigations in both animal models and humans *(139,140)*, in conjunction with familial linkage data *(141)*, have indicated that decreased function of hippocampal α7 nAChRs could underlie the auditory gating deficit in schizophrenia. Although α7-deficient mice appear to have normal sensorimotor gating *(142)*, it is possible that what is important is not the number of nAChRs, but how they function. Thus, future studies may examine the gating responses of mice with mutations in the α7 gene that produce a receptor with altered function *(97)*. Despite the usual appearance of characteristic symptoms in late adolescence or early adulthood, schizophrenia is increasingly seen as a deficit in brain growth and development, possibly involving a disruption of neuronal migration within the cortex (reviewed in *143–145)*. Therefore, the involvement of α7 nAChRs in neuronal growth and differentiation could allow them to influence this aspect of the pathogenesis of schizophrenia as well.

Finally, recent genetic studies in humans have found a significant link between the chromosomal region encompassing the α7 nAChR gene and several different forms of idiopathic epilepsy *(146,147)*. In addition, animal studies have identified polymorphisms in the α7-subunit gene among strains of mice that are associated with sensitivity to nicotine-induced convulsions *(148,149)*. Moreover, α7-deficient mice show epileptiform-like wave patterns in the hippocampus *(99)*. Together, these results suggest that α7 nAChRs may play a crucial role in regulating general neuronal activity.

Conclusions

A growing body of evidence has indicated that neuronal nAChRs may play a broader role than merely promoting fast cholinergic transmission. In particular, the α7 nAChR may have a distinct function in regulating synaptic plasticity. By modulating intracellular Ca^{2+} levels in discrete locations on neuronal cell bodies, dendrites, and terminal fields, these ligand-gated ion channels can regulate a myriad of physiological processes in the developing and adult brain. With the ongoing development of new pharmacological and molecular tools, the functional roles of this nicotinic receptor subtype may finally be elucidated.

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