1. INTRODUCTION

Protection of neuronal cells from damage and cell death associated with neurodegenerative disease is a major challenge in neuroscience research. Donepezil, galantamine and tacrine are acetylcholinesterase inhibitors used for the treatment of Alzheimer’s disease, and were believed to be symptomatic drugs whose therapeutic effects are achieved by slowing the hydrolysis of acetylcholine at synaptic termini. However, recent accumulated evidence strongly suggests that these acetylcholinesterase inhibitors also possess neuroprotective properties whose mechanism is independent of acetylcholinesterase inhibition. We have shown that acetylcholinesterase inhibitors protect neurons from glutamate-induced neurotoxicity in the primary culture of rat cortical neurons. It was also found that acetylcholinesterase inhibitor treatment induces up-regulation of nicotinic receptor expression levels, a property which may also have some bearing on their therapeutic effects. We next showed that α4 and α7-nicotinic receptors play important roles in acetylcholinesterase inhibitor-induced neuroprotection and nicotinic receptor up-regulation. Our results also demonstrate the important roles of the phosphatidylinositol 3-kinase pathway downstream of nicotinic receptors in protecting neurons from death and up-regulating nicotinic receptors. This review summarizes recent findings on the roles of the nicotinic receptor in acetylcholinesterase inhibitor-induced neuroprotection and nicotinic receptor up-regulation.

Key words nicotinic receptor; neuroprotection; Alzheimer’s disease; phosphatidylinositol 3-kinase
long-standing belief was that acetylcholinesterase inhibitors are symptomatic agents that ameliorate cholinergic deficits by slowing the hydrolysis of acetylcholine at synaptic nerve terminals; however, recent studies have shown that acetylcholinesterase inhibitors have other pharmacological properties, for example, neuroprotection against toxic insults, such as glutamate and up-regulation of nicotinic receptors.

Glutamate is a neurotransmitter with roles such as long-term potentiation and synaptic plasticity of the brain via N-methyl-D-aspartate receptors (NMDA), and is also an excitotoxin whose neurotoxicity has been associated with numerous neurodegenerative diseases, such as AD, vascular dementia, Parkinson disease, and amyotrophic lateral sclerosis. The mechanism of glutamate-induced neuronal death has been extensively studied: glutamate induces neuronal death via stimulation of NMDA receptor through which Ca$^{2+}$ enters the cell and activates Ca$^{2+}$-dependent nitric oxide (NO) synthase, resulting in excess nitric oxide formation, production of radicals, mitochondrial dysfunction and cell death. Although the extent of the role glutamate neurotoxicity plays in AD is not yet clear, it has been reported that amyloid-$\beta$, a protein that plays important roles in neurodegeneration in AD, enhances neurons’ vulnerability to glutamate neurotoxicity, indicating that glutamate may play important roles in amyloid-$\beta$-induced cytotoxicity in the cerebral cortex. It has been shown that glutamate induces neuronal death associated with necrosis and apoptosis. Necrosis is caused by catastrophic cell damage and is characterized by cell swelling, injury to cytoplasmic organelles and rapid collapse of internal homeostasis, leading to the lysis of membranes and the release of cellular contents, resulting in inflammation. On the other hand, apoptosis is a process characterized by cell shrinkage, membrane blebbing, nuclear pyknosis, chromatin condensation and genomic fragmentation.

It has been established, through many previous studies, that stimulation of nicotinic receptor protects against glutamate and amyloid-$\beta$ protein-induced neuronal death. Nicotinic receptors are members of a heterogeneous family of ligand-gated cation-selective ion channels that are assembled as a homomeric or heteromeric pentamer from 12 types of subunits: nine $\alpha$ ($\alpha 2$-$\alpha 10$) and three $\beta$ ($\beta 2$-$\beta 4$). The $\alpha 4$- and $\alpha 7$-nicotinic receptor subtypes are the most abundantly expressed subtypes in CNS and their loss during AD has been documented many times. It has been shown that nicotinic receptors can exist in functionally different conformations: one with high ligand affinity and conductance, and the other with low ligand affinity and conductance. In relation to the effects of smoking, particular interest has been paid to the effects of prolonged chronic nicotine treatment on the nicotine receptor state and expression levels. It has been reported that chronic treatment with nicotine or nicotinic receptor agonists desensitizes nicotinic receptors; lowering their ligand affinity and conductance. Nicotinic receptor stimulation is also known to up-regulate the expression level of nicotinic receptors, and this effect is often associated with desensitization; however, the results of analyses regarding the functional conditions of up-regulated nicotinic receptors are not yet conclusive, likely due to multiple desensitized states, differences in kinetics, or ligand-specific differences.

Over recent years, new results have emerged demonstrating that acetylcholinesterase inhibitors used for the treatment of AD have additional pharmacological properties; protection against neurotoxic agents, such as glutamate, and up-regulation of nicotinic receptors.

2. NEUROPROTECTIVE PROPERTIES OF ACETYLCHOLINESTERASE INHIBITORS

Direct evidence of neuroprotection by acetylcholinesterase inhibitors first came from studies on the effects of donepezil against glutamate neurotoxicity in rat primary culture of cerebral neurons. Cell viability was measured by the trypan blue exclusion method, in which viable cells exclude trypan blue and are not stained but non-viable cells cannot exclude trypan blue and are darkly stained. In this study, pretreatment with donepezil (10 $\mu M$) for 24 h significantly inhibited glutamate (1 mM)-induced loss of viability. On the other hand, simultaneous treatment with donepezil and glutamate did not protect neurons from neurotoxicity. Donepezil, galantamine and tacrine also protected against neuronal death induced by moderate (100 $\mu M$) glutamate treatment-induced neuronal death associated with apoptosis. Protective effects of pretreatment with six other acetylcholinesterase inhibitors were tested and not only donepezil but also galantamine and tacrine as well as neostigmine and pyridostigmine also protected against glutamate neurotoxicity; however, physostigmine, despite having the strongest potency among the acetylcholinesterase inhibitors tested, did not protect against glutamate. Donepezil, galantamine and tacrine significantly protected against glutamate neurotoxicity in a concentration-dependent manner from 0.1 to 10 $\mu M$, a clinically relevant physiologic concentration. These three acetylcholinesterase inhibitors also significantly protected neurons against glutamate in a treatment time-dependent manner from 12 to 24 h.

Around the same period, neuroprotective effects donepezil was examined in an oxygen-glucose deprivation (OGD) model of ischemia using rat PC12 cells and rat primary neuronal culture of the cerebral cortex. Pretreatment with donepezil (1 $\mu M$) for 2 h before OGD inhibited OGD-induced cell injury in PC12 cells measured by cell morphology. Donepezil pretreatment also markedly inhibited OGD-induced decrease in the reduction of 3-(4,5-dimethylthiazol-2-yi)-2,5-diphenyl tetrazolium bromide (MTT). Pretreatment with donepezil at concentrations higher than 0.1 $\mu M$ significantly and dose-dependently inhibited OGD-induced cell in-
jury measured by lactate dehydrogenase release in primary culture of the rat cerebral cortex, however, significant protection against OGD-induced neuronal damage was not observed with galantamine, tacrine or rivastigmine pretreatment. These data showed that pretreatment with donepezil has protective effects against artificial ischemia in PC12 cells and primary culture of rat cortical neurons and, at least in the OGD model of ischemia, donepezil has the most potent protective effect against neuronal damage. The potency of donepezil has been confirmed with in vivo studies on spatial cognitive impairment in a rat hypoperfusion model of ischemia using the escape latency model. These studies suggest, from several points of view, that the neuroprotective effects of acetylcholinesterase inhibitors are not due to AChE inhibition: (1) Donepezil but not other acetylcholinesterase inhibitors could not protect neurons from OGD-induced injury, (2) physostigmine, the strongest AChE inhibitor among those tested, did not protect neurons in our study, (3) the neuroprotective action of donepezil, galantamine and tacrine was observed in a concentration-dependent manner at concentrations much higher than their half-maximal inhibitory concentration (Fig. 1), (4) acetylcholinesterase inhibitors have no effect when administered at the same time as glutamate. Thus, in the following studies, we focused on the mechanism of donepezil-, galantamine- and tacrine-induced neuroprotection.

3. MECHANISM OF ACETYLCHOLINESTERASE INHIBITOR-INDUCED NEUROPROTECTION

Involvement of nAChR in neuroprotection against neuronal insults, including that by glutamate, had been indicated for some time prior to our study in the mechanism of acetylcholinesterase inhibitor-induced neuroprotection; Akaike et al. demonstrated that stimulation of nAChR by nicotine (10 μM) significantly inhibited glutamate or NMDA treatment-induced neuronal death and Kaneko et al. demonstrated that α7-nAChR mediated the protective action of nicotine. The proposed mechanism of neuroprotection by nicotine was its stimulation of α7 and α4-α7-nAChR and inhibition of the intracellular process of glutamate-induced NO production. Furthermore, preclinical electrophysiological experiments proposed that galantamine potentiates ligand action on nAChR possibly through allosteric modulation of nAChR. Several studies have indicated that donepezil may also interact and regulate nAChR function, although the results were not conclusive. These studies prompted us to examine the involvement of nAChR in acetylcholinesterase inhibitor-induced neuroprotection.

We examined the effects of acetylcholine receptor antagonists on acetylcholinesterase inhibitor-induced neuroprotection against glutamate (1 mM) treatment-induced neurotoxicity and observed that nicotinic receptor antagonists but not muscarinic receptor antagonists inhibit neuroprotection against glutamate neurotoxicity (Table 1). The antagonistic effects of dihydro-β-erythroidine (DHβE) and methylyccoinmine (MLA), inhibitors of α4- and α7-nAChRs, respectively, suggest the participation of these receptor subtypes in donepezil- and galantamine-induced neuroprotection. Neuroprotection by tacrine was inhibited by mecamylamine but not subtype selective antagonists, suggesting that other subtypes may be involved in the neuroprotection. These results strongly suggested that nAChR mediate the neuroprotective effects of acetylcholinesterase inhibitors. Since the mechanism of glutamate-induced neurotoxicity involves the increase of intracellular levels of Ca2+ and activation of Ca2+-dependent neuronal NO synthase (nNOS), we examined the effects of acetylcholinesterase inhibitor on neurotoxicity induced by ionomycin and S-nitrosoysestane, a calcium ionophore and NO donor, respectively. First we confirmed that treatment with ionomycin (3 μM) or S-nitrosoysestane (SNOC) (300 μM) induces neurotoxicity. Donepezil, galantamine and tacrine all protected against ionomycin-induced neurotoxicity, but only tacrine protected against SNOC-induced neurotoxicity, suggesting that donepezil and galantamine protects neurons at points after the influx of calcium and before the activation of nNOS, and tacrine protect neurons at points after the activation of nNOS. None of the three acetylcholinesterase inhibitors have been reported to directly stimulate nAChR and open its channel and thus, the effects of acetylcholinesterase inhibitors may modify nAChR mediated signaling, which in turn may regulate nNOS activation (donepezil and galantamine) or cell survival pathways (tacrine).

We previously showed, using primary cultures of rat cortical neurons, that acute (1 mM) and moderate (100 μM) glutamate treatment induces neuronal death associated with necrosis and apoptosis, respectively. In contrast to the acute glutamate treatment (1 mM, 10 min) used in the above studies, a low concentration of glutamate (100 μM) over an extended period (24 h) induces neuronal death associated with apoptosis, as observed by nuclear fragmentation using Hoechst 332358 dyes. Moderate (100 μM) glutamate-induced neurotoxicity was inhibited by caspase-3 inhibitor DEVDC CHO, supporting the association with apoptosis. First, we demonstrated that acetylcholinesterase inhibitors protect neurons from glutamate-induced apoptotic death in a treatment time- and concentration-dependent manner, and then the effects of acetylcholine receptor antagonists on acetylcholinesterase inhibitor-induced neuroprotection were examined. Nicotinic receptor antagonist but not muscarinic receptor antagonist significantly inhibited neuroprotection, suggesting that, similar to neuroprotection against acute glutamate-induced neuronal death, acetylcholinesterase inhibitor-induced neuroprotection against apoptosis is mediated by nAChRs. Significant inhibition of donepezil- and galantamine-induced neuroprotection was observed with DHβE or MLA co-treatment with acetylcholinesterase inhibitor, sug-

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<th>nAChR antagonist</th>
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Table 1. Effects of AChR Antagonists on AChE Inhibitors-Induced Neuroprotection Against Glutamate Neurotoxicity

Viability of the cells was compared between cortical neuron pretreated with 10 μM AChE inhibitors and those pretreated with AChE inhibitors and acetylcholine receptor antagonists (mecamlyamine and scopolamine: 10 μM; DHβE and MLA: 10 μM) prior to glutamate treatment. Viability of the cells was examined by trypan blue staining. +: effective, -: not effective.
gesting that the effects of donepezil and galantamine are mediated by \( \alpha 4 \)- and \( \alpha 7 \)-nAChRs. Similar to protection against acute glutamate neurotoxicity, DHE \( \beta E \) and MLA did not inhibit tacrine-induced neuroprotection, suggesting the involvement of other nAChR subtypes in neuroprotection by tacrine.

Phosphatidylinositol 3-kinase (PI3K) promotes the survival of neuronal cells \textit{via} activation of the Akt-Bcl-2 pathway\(^{51} \) and it has been shown that, upon stimulation, \( \alpha 7 \)-nAChR activates PI3K \textit{via} activation and direct association with non-receptor-type tyrosine kinase Fyn and janus-activated kinase 2 (JAK2) and protects neurons against A\( \beta \)-induced neuronal death\(^{31,52} \). With the involvement of nAChR in acetylcholinesterase inhibitor-induced neuroprotection, we examined the involvement of this pathway in acetylcholinesterase inhibitor-induced neuroprotection. Treatment with PP2, AG490, LY294002 and wortmannin, inhibitors of Fyn, JAK2 and PI3K, respectively, significantly inhibited neuroprotection by donepezil and galantamine, but not tacrine, which is in good accordance with the results of MLA treatment described above.\(^{44} \) The level of phosphorylated Akt increases upon nicotine treatment and is suppressed with PI3K inhibitor or JAK2 inhibitor treatment.\(^{31,52} \) Activation of Akt in turn increases the expression level of Bcl-2 transcript. We observed that treatment with donepezil and galantamine, but not tacrine, also increases the phosphorylation level of Akt and the expression level of Bcl-2 transcript.\(^{44} \)

We examined the mechanisms of neuroprotection against neuronal death induced by two different conditions of glutamate treatment, acute (1 mM, 10 min) and moderate (100 \( \mu \)M, 24 h) that are associated with necrotic and apoptotic death. The proposed mechanism of neuroprotection against acute glutamate-induced death is summarized below (Fig. 2). The mechanism of neuroprotection against moderate glutamate-induced death inferred from our results is as follows (Fig. 3). First, donepezil and galantamine stimulate nAChR. In the case of galantamine, this is likely to occur \textit{via} binding to nAChR at an allosteric site distinct from the acetylcholine-binding site. It is not clear how donepezil stimulates nAChRs. While it has been shown that donepezil modulates nAChR function,\(^{53} \) and the possibility of allosteric binding has been proposed in several studies,\(^{46} \) the results are not yet conclusive. Second, upon stimulation by donepezil and galantamine, \( \alpha 7 \)-nAChR activates PI3K through association with Fyn and JAK2, leading to the activation of Akt by phosphorylation. This may involve acetylcholinesterase inhibitor-induced formation of a complex between \( \alpha 7 \)-nAChR and JAK2 and activation of JAK2 by Fyn and, as it has been shown that nicotine can induce the formation of such a complex, activation of JAK2 requires tyrosine phosphorylation and Fyn is a non-receptor type tyrosine kinase that binds to \( \alpha 7 \)-nAChR.\(^{31,52} \) This is an interesting scenario, but remains to be confirmed in future studies. How the stimulation of \( \alpha 4 \)-nAChR leads to neuroprotection is not yet clear and remains an area of strong interest. Regarding tacrine, nAChR sub-

Fig. 2. A Schematic Model of the Mechanism of Neuroprotection by AChE Inhibitors (Donepezil, Galantamine and Tacrine) against Glutamate Neurotoxicity

Fig. 4. A Schematic Model of the Mechanism of nAChR Upregulation by Donepezil \textit{via} \( \alpha 7 \)-nAChR
types involved in tacrine-induced neuroprotection and intracellular mechanisms involved are not clear. Our results indicate that the mechanism of tacrine-induced neuroprotection differs from that of donepezil and galantamine. Although tacrine, due to its side effects, is currently not used clinically, investigation of its neuroprotective mechanism may provide another treatment strategy against AD that differs from those envisioned for donepezil and galantamine.

4. NICOTINIC RECEPTOR UP-REGULATION BY ACETYLCHOLINESTERASE INHIBITOR

Loss of nAChR is a hallmark of AD pathology and thus, inhibition or reversal of loss of nAChR, if possible, may contribute to the modification of disease progression. Furthermore, nAChRs are considered to play important roles in neuroprotection.54) Simultaneously with our studies on the involvement of nAChR in neuroprotection by acetylcholinesterase inhibitors, several clinical and preclinical data demonstrated that the administration of acetylcholinesterase inhibitors, donepezil and galantamine, increases the level of nAChR in rat and human brains.55–58) We tested the possibility that the previously observed neuroprotection by acetylcholinesterase inhibitors, donepezil and galantamine, increases the level of nAChR in rat and human brains.55–58) We examined the expression levels of α4- and α7-nAChR by immunoblotting and immunocytochemistry following acetylcholinesterase inhibitor treatment. Treatment with donepezil, galantamine or tacrine (0.1—10 μM) did not significantly up-regulate α4- and α7-nAChR after 24-h treatment.59) Thus, the neuroprotective action observed with acetylcholinesterase inhibitor treatment (10 μM, 24 h) in previous studies does not involve nAChR up-regulation; however, we observed significant up-regulation of α4- and α7-nAChR protein levels with longer treatment, after 4 days’ chronic treatment with donepezil.59,60) We also observed a significant increase in the proportion of neurons expressing α4- and α7-nAChR after chronic treatment with donepezil and galantamine. These results are in good accordance with an in vivo study which showed that chronic administration of donepezil and galantamine at dose levels analogous to those used to treat patients with Alzheimer’s disease significantly increased nAChR density in the frontal cortex and hippocampus of aged rats.55)

The difference between the actions of donepezil and galantamine regarding nAChR up-regulation is a point of interest. Although galantamine treatment increases the proportion of cells expressing α4- and α7-nAChR, we did not observe a significant increase in the α4-nAChR protein level in neurons treated with galantamine and only a modest increase in the α7-nAChR.59) These results are supported by in vivo and in vitro studies which demonstrated that treatment with donepezil induced a significantly greater increase of nAChR density than treatment with galantamine in the frontal cortex of aged rats55) and M10 cells stably expressing α4-nAChR.53) The reasons for the difference between donepezil and galantamine are not yet clear, but may be associated with the difference in the therapeutic effects of these drugs which has been noted in several clinical studies and should be the target of future studies.38)

It is well known that chronic nicotine treatment also up-regulates nAChRs, but previous studies do not show consensus on the functional state of up-regulated nAChRs; several report that nAChRs are desensitized61) while others report that they are fully functional.62,63) In treatment with acetylcholinesterase inhibitors, prolonged treatment with donepezil, galantamine and tacrine (1—10 μM) significantly potentiated the nicotine-induced increase in intracellular calcium concentration ([Ca2+]i), suggesting that chronic acetylcholinesterase inhibitor treatment does not desensitize nAChR.59) These results are interesting given that chronic administration of donepezil and galantamine extends the decay time of long-term potentiation (LTP) which, in the same study, was demonstrated to be significantly correlated to cognitive function.55) It was suggested that the increased density of functional nAChR enhances LTP, but the functional state of nAChR was not examined in the previous study.55) Our results, by showing that acetylcholinesterase inhibitor treatment functionally up-regulates nAChR, support this interesting discussion on the effects of chronic acetylcholinesterase inhibitor administration.

Contrarily to the results of the up-regulation of nAChR levels, we did not observe differences among donepezil, galantamine and tacrine on the functional modification of nAChR by chronic treatment. In summary, prolonged donepezil treatment induces functional up-regulation and increases in protein levels of nAChRs while galantamine and tacrine induce functional up-regulation. Galantamine may induce up-regulation of the expression of nAChRs but the results of immunoblotting and immunocytochemistry are not conclusive. Finally, donepezil likely increases the number of functional nAChR in chronically treated neurons, which may contribute to its unique therapeutic effects and could point the way to a future therapeutic strategy against AD.

5. MECHANISM OF NICOTINIC RECEPTOR IN ACETYLCHOLINESTERASE INHIBITOR-INDUCED UP-REGULATION

The mechanism of nAChR up-regulation by nicotine has been studied extensively using cell lines stably expressing α4- or α7-nAChRs. These studies suggested that nAChRs are up-regulated by post-translational mechanisms64) involving receptor stabilization,65) changes in endocytic trafficking and receptor turn-over,66) exocytic trafficking of nAChRs from the endoplasmic reticulum to the cell surface67) or enhanced intracellular maturation68) through the chaperone function of nicotine.69)

The mechanism of donepezil-induced nAChR up-regulation has been studied using primary cultures of rat cortical neurons.59,60) Chronic treatment with donepezil did not alter the level of α4- and α7-nAChR mRNAs examined by reverse transcription polymerase chain reaction, demonstrating that donepezil up-regulates nAChR by post-translational mechanisms.59) Next, we examined the involvement of nAChR functions in up-regulation using antagonists for nAChRs. Treatment with MLA (10 nM), a selective antagonist of α7-nAChR, significantly inhibited the cholinic donepezil (10 μM) treatment-induced up-regulation of α7-nAChR, as examined by immunoblotting.60) Then, using specific inhibitors, we investigated the involvement of the α7-nAChR-Pi3K pathway in the up-regulation of nAChR. Treatment with PP2 (10 μM), AG490 (10 μM), LY294002 (10 μM)
and inhibitors of Fyn, JAK2 and PI3K, respectively, significantly inhibited donepezil-induced up-regulation, suggesting the involvement of the α7-nAChR-PI3K pathway.\textsuperscript{60} Furthermore, donepezil-induced up-regulation was significantly inhibited by treatment with PD98059 (50 μM), an inhibitor of kinase of mitogen-activated protein kinase (MAPK). Donepezil-induced functional up-regulation of nAChR as shown by the enhancement of nicotine-induced increase of \([Ca^{2+}]\), was also significantly inhibited by MLA (10 nM), PP2 (10 μM), AG490 (10 μM), LY294002 (10 μM) and PD98059 (50 μM) treatment.\textsuperscript{60} The proposed model of nAChR up-regulation from our results is summarized in Fig. 4. Our results indicate that functional up-regulation of nAChR may be due to the up-regulation of nAChR at the cell surface, but it is not yet conclusive whether donepezil modulates the function of nAChR.\textsuperscript{53} Our recent unpublished data support our notion of the contribution of nAChR in up-regulating the function of nAChR. Another point of interest is how galantamine and tacrine functionally up-regulate nAChR without an apparent increase in nAChR density. Up-regulation by galantamine likely involves allosteric modulation of nAChR function. On the other hand, the mechanism of tacrine-induced up-regulation is not clear and it is not known whether tacrine physically interacts with nAChR and modulates its functions.

6. EFFECTS OF NICOTINIC RECEPTOR UP-REGULATION ON ACETYLCOLINESTERASE INHIBITOR-INDUCED NEUROPROTECTION

Surprisingly, we observed that chronic treatment with donepezil and galantamine made neurons more sensitive to the neuroprotective effect of donepezil and galantamine.\textsuperscript{59} It has been previously shown that donepezil and galantamine do not significantly protect neurons against glutamate neurotoxicity at concentrations below 100 nM and 10 nM, respectively\textsuperscript{15,43}; however, following chronic treatment with donepezil or galantamine, donepezil (10 nM) and galantamine (1 nM) pretreatment significantly protected neurons from glutamate (1 mM, 10 min or 100 μM, 24 h) neurotoxicity.\textsuperscript{45,50,59,60} No such effect was observed for tacrine. The mechanism of this enhancement of sensitivity to donepezil remains relatively unstudied, but we have shown that chronic simultaneous treatment with donepezil and an nAChR antagonist, PI3K pathway inhibitor, significantly inhibits the enhancement of sensitivity.

7. CONCLUSION AND FUTURE PROSPECTS

Over recent years, nAChRs have attracted the attention of many scientists because of their involvement in the pathology of AD and many other neurodegenerative diseases. We and several others have demonstrated the involvement of nAChRs in neuroprotection, especially those induced by nicotine and acetylcholinesterase inhibitors.\textsuperscript{28,43,60,70} nAChRs are up-regulated by prolonged chronic administration of acetylcholinesterase inhibitors, and it has been shown that nAChRs are involved in the mechanism of up-regulation. An intracellular second messenger system, such as the PI3K and MAPK signaling systems, plays important roles in neuroprotection and up-regulation. Despite being in the early stages, these studies on the mechanism of nAChR-mediated effects have produced surprising and interesting new results. Unraveling the precise molecular mechanisms of these effects could lead to novel strategies for the prevention and treatment of neurodegenerative diseases by targeting nAChR-related mechanisms.

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