HHS Public Access

Author manuscript

Biochem Pharmacol. Author manuscript; available in PMC 2016 October 15.

Published in final edited form as:

Biochem Pharmacol. 2015 October 15; 97(4): 399–407. doi:10.1016/j.bcp.2015.06.014.

Alpha7 nicotinic receptors as therapeutic targets for Parkinson's disease

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Abstract

Accumulating evidence suggests that CNS α7 nicotinic acetylcholine receptors (nAChRs) are important targets for the development of therapeutic approaches for Parkinson's disease. This progressive neurodegenerative disorder is characterized by debilitating motor deficits, as well as autonomic problems, cognitive declines, changes in affect and sleep disturbances. Currently L-dopa is the gold standard treatment for Parkinson's disease motor problems, particularly in the early disease stages. However, it does not improve the other symptoms, nor does it reduce the inevitable disease progression. Novel therapeutic strategies for Parkinson's disease are therefore critical. Extensive pre-clinical work using a wide variety of experimental models shows that nicotine and nAChR agonists protect against damage to nigrostriatal and other neuronal cells. This observation suggests that nicotine and/or nAChR agonists may be useful as disease modifying agents. Additionally, studies in several parkinsonian animal models including nonhuman primates show that nicotine reduces L-dopa-induced dyskinesias, a side effect of L-dopa therapy that may be as incapacitating as Parkinson's disease itself. Work with subtype selective nAChR agonists indicate that α7 nAChRs are involved in mediating both the neuroprotective and antidyskinetic effects, thus offering a targeted strategy with optimal beneficial effects and minimal adverse responses. Here, we review studies demonstrating a role for α7 nAChRs in protection against neurodegenerative effects and for the reduction of L-dopa-induced dyskinesias. Altogether, this work suggests that α7 nAChRs may be useful targets for reducing Parkinson's disease progression and for the management of the dyskinesias that arise with L-dopa therapy.

Graphical Abstract

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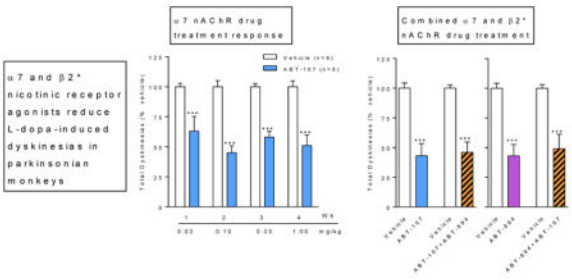
Conflict of interest

There are no conflicts of interest.



Keywords

Alpha7; L-dopa-induced dyskinesias; Neuroprotection; Nicotinic receptors; Parkinson's disease

1. Introduction

The idea that nicotine may be useful as a therapy for Parkinson's disease initially stemmed from the results of epidemiological studies [1–6]. An extensive literature demonstrated a reduced risk of Parkinson's disease among current and former smokers, which correlated with smoking duration, intensity, and recentness [7, 8]. This decline in Parkinson's disease was also observed with other forms of tobacco and with environmental smoke exposure [9, 10]. Moreover, the incidence of Parkinson's disease within twin pairs was less in the twin that smoked compared to the nonsmoker [11]. A recent report suggested that the apparent neuroprotective effect may be due to the propensity of Parkinson's disease patients to quit smoking early rather than to neuroprotection [12]. However, the greater majority of studies are consistent with the idea that the reduced frequency of Parkinson's disease is due to a true biological effect of tobacco use.

The results of the above studies, coupled with the finding that nicotine, a key component in tobacco products, stimulates dopamine release [13–16] led to the premise that nicotine may underlie the beneficial effect of smoking in Parkinson's disease. Extensive studies now substantiate this hypothesis. Experimental evidence shows that nicotine partially protects against nigrostriatal and other forms of CNS damage. Moreover, nicotine administration reduces the abnormal involuntary movements or dyskinesias that arise as a side effect of L-dopa treatment for Parkinson's disease motor symptoms. Multiple nAChR populations exist in the brain, with several subtypes implicated in these beneficial effects of nicotine. This review will focus on the role of α7 nAChRs and discuss the potential utility of α7 nAChR agonists as a novel treatment strategy for Parkinson's disease to reduce disease progression and alleviate L-dopa-induced dyskinesias (LIDs).

2. α7 nAChRs

Neuronal nAChRs are pentameric ligand-gated ion channels composed of diverse combinations of α and β transmembrane subunits [17–19]. There is a mandatory requirement for an α subunit, which binds the naturally occurring neurotransmitter acetylcholine and also exogenous agonists such as nicotine. In addition, β subunits may be present in the receptor complex; these do not express a neurotransmitter recognition site although they contribute

significantly to receptor properties. The main nAChR subtypes in the brain expressing both α and β subunits are the α4β2*, α6β2* and α3β4* populations, with the asterisk indicating the possible presence of other nAChR subunits in the receptor complex. Another primary nAChR subtype in the brain is one composed only of α7 subunits (Fig. 1). Not only are α7 nAChRs structurally different from the other subtypes, they are also phylogenetically and functionally distinct [18, 20]. They display the lowest nicotine sensitivity and exhibit the fastest desensitization kinetics of all nAChRs, a property which initially made their functional characterization very difficult. They have a very high calcium permeability which allows them to regulate numerous calcium-dependent cellular mechanisms important for optimal CNS function [21, 22].

α7 nAChRs are uniquely localized throughout the brain, although there is substantial overlap in their distribution with other nAChR subtypes. α7 nAChRs are very widespread, with a dense localization in regions such as the hypothalamus, geniculate nuclei, colliculi, hippocampus, medial habenula, thalamus, cortex, amygdala, and sparse expression in striatum, forebrain, medulla and various brain nuclei (Fig. 1) [23–29]. Consistent with their extensive CNS localization, α7 nAChRs are implicated in numerous functions including development, maintenance, survival, synaptic plasticity, neurotransmitter release and/or immune responsiveness. Their acute and long term effects on these cellular processes may modulate behaviors such as anxiety, attention, learning, memory, movement and sensory gating, with consequent implications for Alzheimer's disease, Parkinson's disease, schizophrenia, traumatic brain injury, autism, addiction, pain and immune/inflammatory disorders [30–36].

3. α7 nAChRs and neuroprotection

3.1. Trophic role and protection against toxic insults

A trophic role for α7 nAChRs was originally suggested several decades ago [37, 38]. Studies using cultured cells showed that drugs acting at α7 nAChRs modulated neuritic outgrowth via α7 nAChR-mediated alterations in intracellular calcium [39–41]. Further support for a trophic action stemmed from experiments in intact animals, which demonstrated that α7 nAChR expression was modified with neuronal development, growth, maintenance and survival [42–45].

The idea that α7 nAChRs had a role in neuroprotection initially arose from results showing that α7 nAChR antagonists prevented nicotine, choline or acetylcholinesterase inhibitor-mediated protection against toxic insults in neuronal cell cultures (Table 1). α7 nAChR antagonists such as methyllycaconitine (MLA) or α-bungarotoxin (α-BTX) attenuated nAChR-mediated protection against amyloid-β, glutamate and NMDA toxicity, as well as growth factor and oxygen-glucose deprivation in cell lines and primary neuronal cultures [46–58].

Conversely, α7 nAChR agonists afforded neuroprotection. For example, the α7 nAChR allosteric modulator galantamine decreased amyloid-β and glutamate-induced toxicity in cell lines or cortical cultures [48, 59, 60]. Additionally, the α7 nAChR agonist TC-1698 reduced amyloid-β toxicity in pheochromocytoma (PC12) cells, while PNU-282987 protected SH-

SY5Y cells against oxidative stress and okadaic acid-induced toxicity [61–63]. Another agonist 3-[2,4-dimethoxybenzylidene]anabaseine (DMXB) attenuated amyloid-β and ethanol-induced toxicity, as well as growth factor deprivation, in both cell lines and primary cultures [47, 64–66]. Furthermore, DMXB protected cholinergic neurons against septohippocampal axotomy in mice, demonstrating effectiveness *in vivo* [67].

The use of α7 knockout mice also proved valuable in demonstrating a protective role for α7 nAChRs. Nicotine failed to protect against oxygen-glucose deprivation in hippocampal slices from α7 knockout mice and against NMDA toxicity in cortical cultures from transgenic mice expressing dominant-negative α7 nAChRs [68–70]. In addition, while combined neostigmine/anisodamine treatment was protective in a mouse model of ischemia, no effect was observed in α7 nAChR knockout mice [71]. Deletion of α7 nAChRs also worsened ethanol-induced toxicity in primary cortical cultures and exacerbated early-stage cognitive declines in a mouse model of Alzheimer's disease [72, 73].

Overall, results using several different approaches including the use of receptor targeted drugs and genetically modified mice implicate α7 nAChRs in neuroprotection against varying toxic insults in multiple neuronal systems.

3.2. Protection against nigrostriatal damage in parkinsonian animal models

A role for α7 nAChRs in protection against dopaminergic degeneration initially stemmed from studies using the general nAChR agonist nicotine [74–76]. The first of these by Janson and coworkers showed that nicotine administered before or at the time of lesioning significantly improved both striatal and nigral dopaminergic markers in rats with a hemi-transection of the medial forebrain bundle [77–79]. Since then the neuroprotective effect of nicotine has been demonstrated in numerous rodent models of dopaminergic nigrostriatal damage. This includes protection against 6-hydroxydopamine (6-OHDA)-induced nigrostriatal damage in rats [80–83] and against MPTP-induced nigrostriatal degeneration in mice. However, neuroprotection in this latter animal model did not consistently occur raising questions about nicotine's protective potential [76, 84–88]. Subsequent work in parkinsonian nonhuman primates again showed that nicotine improved various striatal dopaminergic measures, including tyrosine hydroxylase, the dopamine transporter, the vesicular monoamine transporter and dopamine levels [89, 90]. These latter findings in a model exhibiting symptoms closely resembling those of the human disease, coupled with the rodent work, provide strong evidence for nicotine's neuroprotective potential.

With respect to the nAChR subtypes involved in neuroprotection against nigrostriatal damage, pharmacological studies showed that the α4β2* nAChR agonist ABT-089 protected against 6-OHDA-induced nigrostriatal damage in rats (Table 2) [91]. By contrast, nicotine-mediated protection against nigrostriatal damage was not observed in α4 nAChR knockout mice, which lack α4β2* nAChRs (Table 2) [81]. Thus, drug and genetic studies support the idea that β2* nAChRs are important. Nicotine may exert its neuroprotective effect by chaperoning β2* nAChRs to the surface of the cell. This may induce changes in the structure and function of the endoplasmic reticulum, the Golgi apparatus and secretory vesicles of cells thereby reducing ER stress and enhancing cell survival [92, 93].

The use of subtype selective α7 nAChR agonists and antagonists also supports a protective role for α7 nAChRs (Table 2) [74, 75, 94]. Drugs with varying agonist properties, such as the α7 nAChR allosteric modulator galantamine, and the α7 agonists DMXB and ABT-107 all protected against 6-OHDA-induced nigrostriatal damage in rats [95–97]. Additionally, the α7 agonist PNU-282987 protected against nigrostriatal damage in the MPTP-lesioned mouse [98], while α7 nAChR antagonists such as methylycaconitine blocked the neuroprotective effect of nicotine [99]. These studies with α7 nAChR agonists and antagonists provide compelling evidence for a role for these receptors in protection against nigrostriatal damage.

In summary, both α7 and β2* nAChR agonists reduce nigrostriatal damage in several parkinsonian animal models, suggesting that drugs targeting these receptors may be useful for attenuating progression of the motor symptoms that arise in Parkinson's disease. As mentioned earlier, nicotine and nAChR agonists also reduce numerous other forms of neuronal toxicity. nAChR drugs may therefore also ameliorate non-motor symptoms that arise with Parkinson's disease by reducing/halting other neurodegenerative processes in the brain.

4. α7 nAChR agonists reduce L-dopa-induced dyskinesias (LIDs)

In addition to a putative neuroprotective role, nicotine treatment may also be useful in the management of LIDs. These are debilitating abnormal involuntary movements that occur with L-dopa administration, the gold-standard therapy for Parkinson's disease [100–103]. Although L-dopa very successfully treats Parkinson's disease motor symptoms, LIDs develop in the majority of patients by 10 years on L-dopa treatment. The only approved pharmacological therapy is with amantadine; however, the beneficial effects of this drug are variable across patients and are generally lost with sustained treatment [103–105]. Although new drugs are under study, effective treatments for LIDs remain elusive.

Recent preclinical work in rodents and nonhuman primates indicates that drugs interacting with nAChRs may be of benefit in reducing LIDs (Table 3) [34]. Initial studies with the general nAChR agonist nicotine showed a 60% reduction in LIDs in parkinsonian monkeys and rodents, indicating effectiveness across species [106–111]. Importantly, nicotine's effects persisted with long term treatment, with one study in nonhuman primates carried out for over a year [108]. Nicotine reduced LIDs whether given orally via the drinking water, by systemic injection or by minipump, showing the effect is independent of treatment mode. Varenicline, another general nAChR agonist [112–114] also reduced LIDs by ~50% (Table 3) [115]. At least a month was required for the antidyskinetic effect of nicotine to maximally develop [108]. Notably, such a time period was also required for the nicotine-mediated antidyskinetic effect to dissipate after drug discontinuation [115]. These combined observations suggest that long term molecular changes are most likely involved in the nicotine-mediated reduction in LIDs.

These data with nicotine prompted work to investigate the nAChR subtypes that contributed to the antidyskinetic effect. Two approaches that proved valuable included the use of genetically modified mice and drugs targetting the different nAChR subtypes. Genetic

deletion of α7 nAChRs increased LIDs in L-dopa-treated parkinsonian mice compared to wildtype littermates suggesting that α7 nAChRs exert an inhibitory influence on expression of these abnormal movements [116]. However, nicotine still reduced LIDs in α7 nAChR null mutant mice, indicating that α7 nAChRs are not essential for nicotine's antidyskinetic action. Similar studies with mice lacking the β2, α4 and α6 nAChR subunits yielded somewhat different results. Nicotine exerted no antidyskinetic effect in any of these knockout mice, suggesting that the α4β2* and α6β2* nAChRs are essential. In addition, mice lacking the β2 or α6 nAChR subunits expressed fewer LIDs compared to their wildtype littermates. Overall, the results indicate that α7 and β2* nAChRs regulate the expression of LIDs but in somewhat unique manners.

Pharmacological studies also support the idea that drugs interacting at α7 or β2* nAChR subtypes influence the occurrence of LIDs. Drugs that selectively act at α7 nAChRs decreased LIDs, with no change in parkinsonism when the animals were administered L-dopa (on L-dopa) or in the absence of the drug (off L-dopa) (Table 3). This includes work in *Saimiri sciureus* in which the α7 agonist ABT-107 reduced LIDs ~60% (Table 3, Fig. 2). The decrease persisted with several months of treatment [115]. Notably, the ABT-107-induced antidyskinetic effect persisted for about a month after its discontinuation suggesting that long term molecular changes were involved. A study with another α7 agonist ABT-126 yielded similar results (Table 3) [117]. Administration of the α7 nAChR agonist AQW051 to *Macaca fascicularis* also resulted in ~60% decrease in LIDs, with no worsening of parkinsonism [118], demonstrating the effectiveness of α7 nAChR agonists in another nonhuman primate.

The antidyskinetic effect was not unique to α7 nAChRs drugs, as β2* nAChR agonists also improved LIDs (Table 3). This includes TC-8831, which reduced LIDs by 50% in macaques and squirrel monkeys without affecting parkinsonism, although a drawback of this drug was induction of emesis [119, 120]. Another β2* nAChR agonist AZD1446 also attenuated LIDs in macaques, although it was not as effective with only a 30% decline possibly due to a lower nAChR affinity [121]. In addition, the β2* nAChR agonists ABT-089 and ABT-894 decreased LIDs, with the most pronounced effect with ABT-894 which resulted in a 60% decline in LIDs in squirrel monkeys (Table 3) [122]. Neither ABT-089 nor ABT-894 was associated with emesis. Like ABT-107, the decline in LIDs was dose dependent, did not diminish with time and required about a month to washout [122].

Notably, the reduction in LIDs observed with either an α7 or β2* nAChR drug on its own was not increased by administration of both nAChR subtype drugs together. Combined administration of ABT-894 with the α7 agonist ABT-107 resulted in a reduction in LIDs similar to that observed with either drug alone (Fig. 2). These findings suggest that drugs acting at either α7 or β2* nAChRs are sufficient to achieve the antidyskinetic effect observed with general agonists such as nicotine. These data also indicate that α7 and β2* nAChR agonists reduce LIDs via some final common mechanism.

In summary, both α7 and β2* nAChR drugs reduce LIDs up to 60% with no detrimental effects on parkinsonism. Because α7 nAChR agonist appear to be associated with few side

effects and are linked to positive effects on cognition (which may be deficient in Parkinson's disease), they may represent ideal candidate drugs to improve LIDs in Parkinson's disease.

5. Mechanisms underlying α7 nAChR-mediated effects in the brain

A question that arises is the molecular and cellular mechanisms whereby an interaction at α7 nAChRs modulates behaviors. One of the first steps in α7 nAChR-mediated transduction involves changes in calcium signaling (Fig. 3). α7 nAChRs exhibit a greater relative calcium permeability than other nicotinic receptors and readily flux calcium [40, 45, 123, 124]. Resultant changes in intracellular calcium may enhance cholinergic transmission in the short term, with consequent long term changes in neuronal plasticity.

Several intracellular mechanisms have been shown to mediate protective effect of α7 nAChR activation against toxic insults (Fig. 3). For instance, nicotine reduces Aβ-induced toxicity by enhancing phosphatidylinositol 3-kinase to lead to increased levels of phosphorylated AKT, and also Src, B-cell lymphoma (Bcl) 2 and Bcl-x with a consequent protection [51, 125]. The mitogen-activated protein kinase/extracellular signal-regulated kinases pathway and the JAK2/STAT3 pathway have also been implicated in α7 nAChR-mediated neuroprotection against a variety of toxic insults in PC12 cells, spinal cultures and keratinocytes [126–129]. Other downstream mechanisms associated with α7 nAChR-mediated protection include increases in phospholipase C [126], nerve growth factor [130], hemeoxygenase [61] and proinflammatry cytokines (tumor necrosis factor-α and interleukin-1β) [131], while nitric oxide [49], caspases, reactive oxygen species [61] are linked to toxicity.

With respect to α7 nAChR-mediated protection against nigrostriatal damage, the first step appears to be an increase in calcium influx via the α7 nAChR and also voltage-gated calcium channels [132]. This may then result in activation of a survival pathway involving the calcium effector protein calmodulin, phosphatidylinositol 3-kinase and phosphorylated AKT with subsequent upregulation of Bcl-2 [132, 133]. In addition, α7 nAChRs on astrocytes may contribute to nicotine's protective effect against nigrostriatal damage. α7 nAChRs have been identified on astrocytes and shown to mediate changes in intracellular calcium mobilization [134, 135]. α7 nicotinic cholinergic signaling may subsequently alter expression of a variety of astrocytic transduction mechanisms including extracellular signal-regulated kinase1/2, p38, tumor necrosis factor-α, glial derived neurotrophic factor, glial fibrillary acidic protein, CD68, and caspase 9 [96, 99, 136] to modulate nigrostriatal plasticity.

The mechanisms linked to the α7 nAChR-mediated improvement in LIDs are less studied but probably include long and short term molecular and cellular changes. One of these may consist of alterations in striatal dopamine release. It is well established that LIDs are associated with an aberrant dopamine release from striatal terminals [137]. Nicotine decreases dopamine release via β2 nAChR-mediated nAChR desensitization and down regulation [138]. Striatal α7 nAChRs on glutamatergic afferents from the cortex may be similarly involved. Stimulation of these α7 nAChRs increases glutamate release, which in turn acts at glutamate receptors on dopamine terminals to modulate dopamine release/

turnover [139]. Additionally, α7 nAChRs in the substantia nigra may influence the release of striatal dopamine [140].

Long term mechanisms most likely also play a role in the nAChR-mediated antidyskinetic effect. This possibility is based on findings that one to two months of treatment with nicotine or nAChR drugs are required for an optimal antidyskinetic effect and also for its decline with drug discontinuation [107, 108]. LIDs have been associated with structural changes in spine morphology in the striatum. This includes the appearance of aberrant spines, the development of new spines or a loss of existing spines in neurons of the corticostriatal, direct and/or indirect pathways [141–144]. Nicotine may restore aberrant signaling that contributes to LIDs by modulating spine formation/morphology as it is well known to modulate neuronal morphology via an interaction at α7 nAChRs [39, 41, 145].

6. Summary

Emerging studies suggest that α7 nAChR drugs may be useful in the management of Parkinson's disease. Of particular importance is the finding that α7 nAChR agonists have disease modifying potential as they protect against nigrostriatal deficits in parkinsonian nonhuman primate and rodent models. In addition, α7 nAChRs mediate neuroprotective effects against numerous other toxic insults and thus be of benefit against some of the other CNS deficits associated with Parkinson's disease. Preclinical studies in nonhuman primates also show that α7 nAChR agonists reduce LIDs, a serious side effect of L-dopa therapy. Altogether, these data suggest that α7 nAChR agonists, which may exhibit fewer side effects than other subtype selective nAChR agonists [146, 147], may be useful for reducing Parkinson's disease progression and also decreasing LIDs.

Acknowledgments

This work was supported by NIH grants NS59910.

Abbreviations

Bcl	B-cell lymphoma
α-BTX	α-bungarotoxin
DMXB	3-[2,4-Dimethoxybenzylidene]anabaseine
LIDs	L-dopa-induced dyskinesias
MLA	methyllycaconitine
nAChR	nicotinic acetylcholine receptor
PC	pheochromocytoma
*****	indicates the possible presence of other subunits in the receptor complex

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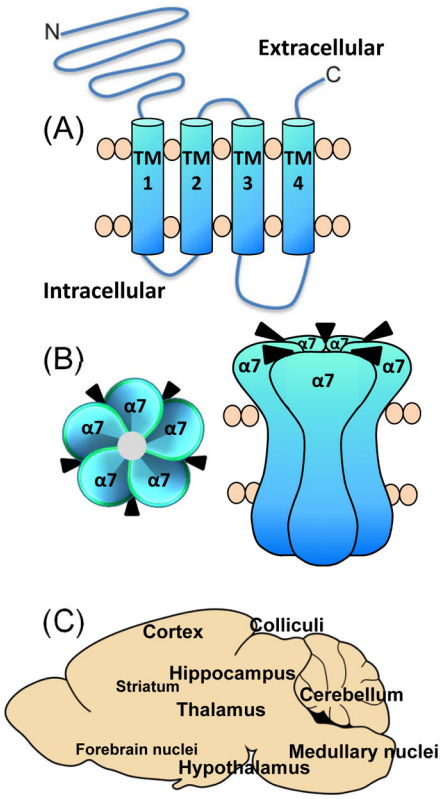

Fig. 1.

Schematic representation of α7 nAChR structure and localization. The α7 nAChR subunit consists of a large extracellular N-terminal region, four transmembrane (TM) domains and an extracellular carboxy-terminal (A). The α7 receptor is membrane bound and composed of 5 identical α subunits, with five agonist binding sites, with (B) depicting a top view and a side view of the receptor in the cell membrane. α7 nAChRs are very widely distributed in numerous brain regions (C). The smaller font size represents a lower density of α7 nAChRs in the various brain areas.

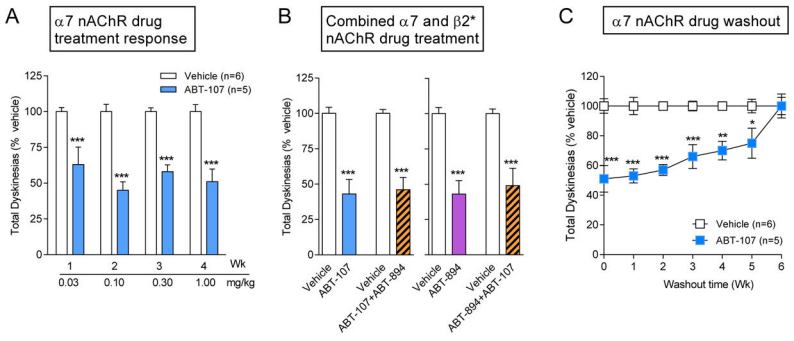

Fig. 2.

The α7 nAChR agonist ABT-107 reduces LIDs in parkinsonian monkeys. MPTP-lesioned monkeys were gavaged with L-dopa plus carbidopa twice daily 5 days per week, with the α7 nAChR agonist ABT-107 given orally 30 min before L-dopa. The left panel (A) shows that ABT-107 significantly reduced LIDs by 60%. The middle panel (B) shows that the reduction in LIDs with combined ABT-107 plus ABT-894 treatment was similar to that with ABT-107 or ABT-894 alone. The right panel (C) shows ABT-107 discontinuation leads to a return of LIDs to vehicle-treated levels by 6 wk. Values are the mean ± SEM of 5–6 monkeys. Significance of difference from vehicle, *p < 0.05, **p < 0.01, ***P < 0.001 using two-way ANOVA. Taken in modified form from [149].

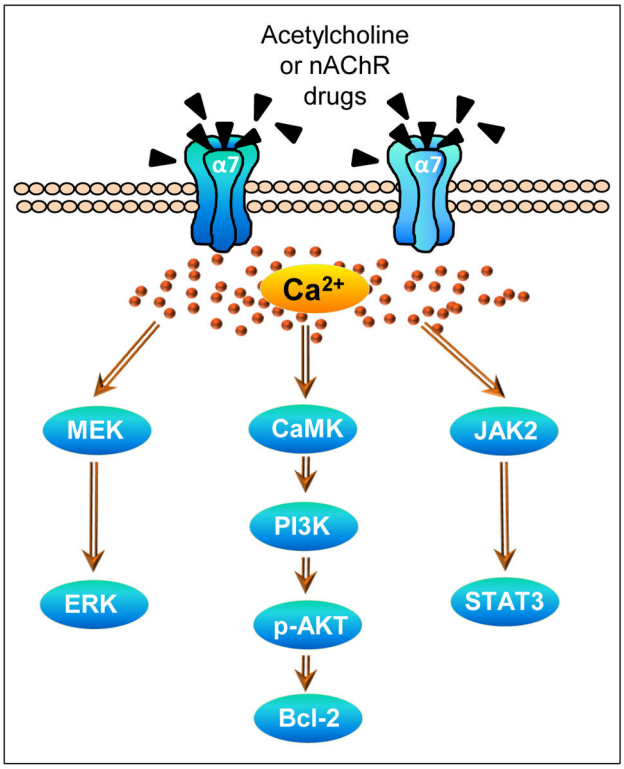

Fig. 3.

Various intracellular signaling pathways have been linked to α7 nAChR activation as described in the text. These lead to secondary events within the same cell or others, with consequent alterations in synaptic plasticity, development, maintenance, survival, apoptosis, neurotransmitter release, immune responsiveness or others. These subsequently modulate movement, addiction, anxiety, attention, learning, memory, sensory gating, inflammation, and neuroprotection. Bcl, B-cell lymphoma; CaMK, Ca2+/calmodulin-dependent protein kinase; ERK, extracellular signal-regulated kinases; MEK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; p-AKT, phosphorylated AKT.

Table 1

α7 nAChR-mediated protection against induced toxicity in culture and *in vivo*.

Toxic insult	Model	Cholinergic drug	Neuroprotection prevented by	References
Amyloid-β	Rat cortical cultures	Nicotine	α-BTX, MLA	[47, 48, 51, 52]
	Rat cortical cultures	DMXB	---	[47]
	SH-SY5Y cell line	Galantamine	α-BTX, MLA	[59, 60, 148]
	PC12 cell line	TC-1698	---	[62]
Glutamate	Rat cortical cultures	Nicotine	α-BTX, MLA	[48, 49, 51, 55]
	Rat spinal cultures	Nicotine	α-BTX	[53]
	Rat cortical cultures	Galantamine	---	[48]
	Rat cortical cultures	Donepezil	MLA	[46, 57]
NMDA	Rat hippocampal cultures	Nicotine	α-BTX, MLA	[56]
	Mouse cortical cultures	Nicotine	Dominant negative α7 knockin	[70]
Growth factor deprivation	PC12 cell line	Nicotine	MLA	[54]
	PC12 cell line	DMXB	MLA	[64]
	PC12 cell line	Pyrrolidinecholine	MLA	[58]
Ethanol	Rat hippocampal cultures	DMXB	MLA	[65, 66]
	Mouse cortical cultures	---	α7 knockout	[72]
Oxygen-glucose deprivation	Mouse hippocampal slices	Nicotine	α7 knockout	[69] [68]
Okadaic acid	SH-SY5Y cell line	PNU-282987	PNU-120596	[63]
Oxidative stress	SH-SY5Y cell line	PNU-282987	MLA	[61]
Amyloid-β	Mouse i*n vivo*	---	α7 knockout	[73]
Ischemia	Mouse i*n vivo*	Neostigmine + anisodamine	α7 knockout	[71]
Septohippocampal axotomy	Mouse i*n vivo*	4OH-GTS-21	---	[130]

Not done (---)

Table 2

α7 and β2* nAChR-mediated protection against nigrostriatal toxicity *in vivo*

nAChR subtype	Model system	Neuroprotection induced by nAChR agonist	Neuroprotection prevented by nAChR antagonist	References
β2*	6-OHDA lesioned rat	ABT-089	---	[91]
	Methamphetamine-treated α4 knockout mice	Nicotine	---	[81]
α7	MPTP-treated mouse	Nicotine	Methylycaconitine	[99, 136]
	MPTP-treated mouse	PNU-282987	---	[98]
	6-OHDA lesioned rat	DMXB	Methylycaconitine	[95, 96]
	6-OHDA lesioned rat	ABT-107	---	[95]

Table 3

α7 and β2* and nAChR drugs decrease LIDs in parkinsonian nonhuman primates

nAChR subtype	nAChR drug	Monkey model	Mode of treatment	% decline in LIDs	References
Multiple	Nicotine	*Saimiri sciureus*	Drinking water	≤ 60%	[106–108]
	Varenicline	*Saimiri sciureus*	Oral	≤ 50%	[115]
α7	ABT-107	*Saimiri sciureus*	Oral	≤ 60%	[149]
	ABT-126	*Saimiri sciureus*	Oral	≤ 60%	[117]
	AQW051	*Macaca fascicularis*	Oral	≤ 60%	[118]
β2*	TC-8831	*Saimiri sciureus*	Oral	≤ 50%	[115]
	TC-8831	*Macaca fascicularis*	Oral	≤ 50%	[119]
	ABT-089	*Saimiri sciureus*	Oral	≤ 50%	[122]
	ABT-894	*Saimiri sciureus*	Oral	≤ 60%	[122]
	AZD1446	*Macaca fascicularis*	Oral	30%	[121]