Role of α7 nicotinic acetylcholine receptor subtype in neuroprotection: An overview

Muthuraju S., Abdullah J.M*.  
Department of Neurosciences, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, 16150 Kelantan, Malaysia

ABSTRACT

Neuronal cell death results from various circumstances such as hypoxia, ischemic and neurodegenerative diseases (NDs). In these events, the resulting modification of neurotransmitters, either excitatory or inhibitory, mediate much of the neuronal damage. However, this consequence depends upon their pre and post synaptic receptor activities which are the key mechanism for signal regulation. Among these, acetylcholine (ACh) is a well known neurotransmitter which is predominantly involved in neuroprotection as well as cognitive functions through its receptors activity, particularly the nicotinic subtypes. Several lines of evidence suggest that among these subtypes, α7 nicotinic acetylcholine receptor (α7nAChR) offers much promise for neuroprotective role in relation to the central nervous system (CNS) disorders like schizophrenia and Alzheimer’s disease (AD). Several lines of evidence exist to show the potential mechanisms in which this nAChR subtype and its agonists such as nicotine, that trigger the α7nAChR-mediated suppression of neuronal cell death. This review focuses on the potential role of α7nAChR in neuroprotection by examining recent experimental data, both in vitro and in vivo, that argue for the neuroprotective role of α7nAChR in the CNS.

Keywords neuroprotection, α7nAChR nicotinic acetylcholine receptor, hypoxia, glutamate, Ethanol, oxygen-glucose deprivation

* Corresponding author: Prof. Dr Jafri Malin Abdullah MD Ph.D., Department of Neurosciences, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kuching, Kelantan, Malaysia.  
E-mail: brainsciences@gmail.com

Introduction

Recently, several studies provided evidence to implicate the involvement of cholinergic neurons in neuroprotection and cognitive functions in neurodegenerative disease (NDs), ischemic and hypoxia (Muthuraju et al., 2009 and 2010). Acetylcholine (ACh) is a neurotransmitter in cholinergic neurons which is released into synaptic cleft to bind to ACh receptors as a result of an action potential. Acetylcholine receptors in the mammalian nervous system are divided into two groups: muscarinic and nicotinic receptor. Muscarinic receptor is G-protein coupled receptor which is divided in five subtypes (M1-M5) and mostly present in the neocortex and the hippocampus, basal forebrain, and cerebellum (Kao I et al., 1977). Nicotinic receptors, in contrast, are ligand-gated ion channel receptors (Miyazawa et al., 2003) and are divided as α and β subtypes (α2-α10 and β2-β4) that are present in cerebral cortex, thalamus and hippocampus. These subunits are known to differ in their pharmacological profiles and sub-cellular localizations. The α7nAChR subtype, for instance, is found in the cortex, hippocampus, lateral geniculate nucleus, superior colliculus, striatum and the dorsal horn of the spinal cord (Arneric et al., 1994). Even though pharmacological diversity of nAChR in the CNS is well documented, the physiological and cellular functions of nAChR in the brain remain poorly understood. Both α and β nAChR subtypes appear to play certain roles in neuroprotection, cognitive processes and modulation of neurotransmitter release. However, among these, the α7 nAChR activation appears to protect the neurons against a wide variety of cytotoxic stimuli such as glutamate (Gahring LC et al., 2003), amyloid-β (Whitehouse et al., 1982), oxygen and glucose deprivation (Wang et al., 2007), and ethanol (Li Y et al., 2002). For these reasons, this review attempts to elaborate the growing evidence for the neuroprotective role of α7nAChR in the setting of such neuronal stressors.

Neuroprotective roles of α7nAChR in various neurotoxic-inducing conditions:

a). α7nAChR and Ethanol Exposure (figure 1)

Mitochondria are the primary intracellular calcium store (Richter 1993), source of reactive oxygen species (Piantadosi and Zhang 1993), and sensor of oxidative stress (Melov 2000). Mitochondrial dysfunction as a result of hypoxia, ischemia and neurodegenerative diseases is known to cause neuronal damage (Beal 1998). In 1988, Deshmukh and...
Johnson reported that cytochrome C is released from mitochondria into cytoplasm following a cellular impairment. In the cytosol, cytochrome C binds to caspase activating protein Apaf-1 that stimulates its binding to pro-caspase 9 (Krajewski et al., 1999). 3-(2-4)-Dimethoxybenzylidine anabaseine (DMXB, also known as GTS-21) is an agonist for α7nAChR which showed α7nAChR mediated neuroprotection through modulation of cytochrome C release. In addition, DMXB also activates protein kinase C (Li et al., 1999) that phosphorylate Bcl-2 which in turn could suppress apoptosis by modulating the release of cytochrome C during apoptosis (Ruvolo et al., 1998). Nicotine is another agonist of α7nAChR which can facilitate the α7nAChR receptor to protect mitochondrial dysfunction against cytochrome C release and modulate caspase activation as shown in cultured spinal cord neurons (Garrido et al., 2001). Therefore, this serves as one of the potential mechanisms by which activation of α7nAChR can protect against stress-induced alteration in mitochondrial functions.

b). α7nAChR and Glutamate-induced Neurotoxicity (figure 2)

Glutamate is considered an excitatory neurotransmitter to mainly involve in neuronal damage in stress as well as disease conditions. Cortical cholinergic neurodegeneration has been attributable to glutamate excitotoxicity. Recent studies reported that glutamate stimulation induces Ca2+ influx into the cells through NMDA receptor channels, triggering nitric oxide (NO) formation resulting in glutamate related cell death (Gahring L.C et al., 2003). This attracts studies on neurotransmitter related agents that can halt these downstream changes to rescue the neurons from glutamate related cell death. In 1997, Kaneko examined the effects of nicotine on glutamate induced cytotoxicity using primary cultures of rat cortical neurons. The results suggested that the nicotine protects cultured cortical neurons against glutamate induced cytotoxicity via α7nAChR. Further studies revealed that α7nAChR can support neuronal survival after an excitotoxic stimulus, through a Ca2+ dependent mechanism that operates downstream of NMDA receptor activation. (Dajas-Bailador FA et al., 2000)

c). α7nAChR and β Amyloid (βA)-induced Neurotoxicity (figure 2)

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized pathologically by the depletion of cholinergic neurons and accumulation of β amyloid (Whitehouse et al., 1982). These cholinergic deficits are the basis for current treatment strategies. Multiple evidences, from molecular, cellular and epidemiological data, have implicated nicotinic transmission in the pathogenesis of AD. Kihara T et al., 2001 found that levels of phosphorylated Akt, an effector of PI3K, and Bcl-2 were increased by nicotine. This is because of α7nAChR is physically associated with the PI3K p85 subunit and Fyn. This finding indicates that α7nAChR transduces signals to PI3K in a cascade, which partially contributes to a neuroprotective effect by upregulating Bcl-2. Moreover, nicotine stimulation of α7nAChR transduces signals to phosphatidylinositol 3-kinase and Akt via Janus kinase 2 (JAK2) in a cascade, which also results in neuroprotection. These reports recognize novel mechanisms of receptor communications related to neuronal viability and recommended therapeutic strategies for neuroprotection (Shaw S et al., 2002). In 2003, Mario B et al. showed that 2-(3-pyridyl)-1-azabicyclo[3.2.2]nonane (TC-1698), a novel α7nAChR selective agonist, exerts neuroprotective effects via activation of the JAK2/PI-3K cascade. This finding supports the mechanism that JAK2 plays a central role in the nicotinic α7nAChR induced activation of the JAK2-PI-3K cascade which ultimately contribute to nAChR-mediated neuroprotection.
d). α7nAChR and Oxygen-Glucose Deprivation

Nicotine is also considered neuroprotective against oxygen-glucose deprivation induced neurotoxicity, preventing neuronal death and apoptosis. In this instance, activation of α7nAChR is thought to mediate neuroprotection (Hejmadi et al., 2003) with lines of evidence lend by Rose et al., 2006 in oxygen – glucose deprivation (OGD) model of rat and mouse hippocampal slices using nicotine. Therapeutic acetylcholinesterase inhibitor drugs such as galantamine and Huperzine A also mediated neuroprotection through the activation of α7nAChR. Galantamine protects neuron against tumor necrosis factor through activation of α7nAChR (Gahring et al., 2003). The effect of Huperzine A against OGD induced injury in C6 cells appeared to inhibit activation of NF-kappa B attenuated iNOS, COX-2 and NO over expression and nitric oxide (NO) over expression that promoted survival. This protective effect of Huperzine A was partly mediated by cholinergic anti inflammatory pathway through α7nAChR (Wang et al., 2007).

e). α7nAChR and Hypoxia Exposure

Brain neurons are extremely susceptible to changes in oxygen availability. Any temporary incidences of hypoxia/ischemia encourage pathophysiological changes such as disturbances in energy metabolism (Paschen and Djuricic, 1995) and modifications in synaptic communication (Luhmann, 1996). Hypoxia/ischemia-induced neurotoxicity is assumed to be necrotic because of the correlation between energy failure and necrotic cell death (Grow and Barks, 2002). Using PC12 cells, Toghi H et al., 2000 had showed that hypoxia induced membrane degradation and DNA fragmentation of these cells are inhibited by nicotine administration through α7nAChR. This finding is supported by Utsugisawa K et al., 2002 study that reported α7nAChR over expression increases tolerance against G1- arrest and DNA fragmentation along with changes in Akt expression n PC12 cells after hypoxia. Interestingly, In addition, Hejmadi M.V et al., 2003 demonstrates that acute hypoxia-induced cell death in cortical cultures is primarily apoptotic, as shown by TUNEL staining, DNA damage, and caspase-3/7 activity assays.

Figure 2  A schematic diagram displays the neuroprotection through enhancement of α7nAChR in glutamate and β-Amyloid exposure.
Future perspective (figure 3)

This review focused on the role of α7nAChR in various neurotoxic events such as glutamate excitotoxicity, ethanol, hypoxia and β amyloid. Nicotinic acetylcholine receptors appear to be crucial in the survival of cortical neurons as supported by multiple lines of evidence. The regulation of the mitochondrial dysfunction involving the α7nAChR indicates its potential protective role in free radical and associated cellular oxidative stress events. For instance, in traumatic brain injury, neurons generally undergo insufficient of oxygen supply which leads to further free radical formation. Hence, nicotine and other agonist of α7nAChR may offer a therapeutic strategy for preventing further neuronal damage following traumatic brain injury. Similarly, this nicotinic ACh receptor subtype also protects neurons in glucose oxygen deprivation condition indicating that selective agonists for this receptor may have potential therapeutic neuroprotection in stroke. In addition, recent data also provide further evidence that α7nAChR could be a candidate target for treatment against hypoxia-induced acute membrane degradation and delayed DNA fragmentation in neurons. Overall, this minireview highlights key evidences that support the therapeutic potentials of α7 nicotine acetylcholine receptors in neuroprotection that involves, partly by inhibiting the mechanisms involved in apoptosis.

References


