Biochemical Pharmacology 97 (2015) 439–444

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Review

The effect of α7 nicotinic receptor activation on glutamatergic transmission in the hippocampus

Qing Cheng*, Jerrel L. Yakel

Neurobiology Laboratory, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC 27709, USA

ARTICLE INFO

Article history:
Received 26 May 2015
Accepted 14 July 2015
Available online 23 July 2015

Keywords:
α7 Nicotinic acetylcholine receptor
Glutamatergic transmission
Hippocampus
Calcium
cAMP

ABSTRACT

Nicotinic acetylcholine receptors (nAChRs) are expressed widely in the CNS, and mediate both synaptic and perisynaptic activities of endogenous cholinergic inputs and pharmacological actions of exogenous compounds (e.g., nicotine and choline). Behavioral studies indicate that nicotine improves such cognitive functions as learning and memory, however the cellular mechanism of these actions remains elusive. With help from newly developed biosensors and optogenetic tools, recent studies provide new insights on signaling mechanisms involved in the activation of nAChRs. Here we will review α7 nAChR's action in the tri-synaptic pathway in the hippocampus. The effects of α7 nAChR activation via either exogenous compounds or endogenous cholinergic innervation are detailed for spontaneous and evoked glutamatergic synaptic transmission and synaptic plasticity, as well as the underlying signaling mechanisms. In summary, α7 nAChRs trigger intracellular calcium rise and calcium-dependent signaling pathways to enhance glutamate release and induce glutamatergic synaptic plasticity.

Published by Elsevier Inc.

Contents

1. Introduction

Nicotinic acetylcholine receptors (nAChRs) belong to the superfamily of cys-loop cationic ligand-gated channels [59,19,21,5]. They are activated by the endogenous ligand acetylcholine (ACh) and various exogenous ligands (e.g., nicotine and choline) to exert their modulatory function on synaptic excitability and plasticity [21,118,119]. The α7 nAChR subtype is prominent in the hippocampus, and has been linked with cognitive deficits and a variety of neurological disorders and diseases, such as Alzheimer's diseases and schizophrenia [37,119,27,95,103]. Schizophrenic patients are often heavy smokers [22], which has been suggested to be a form of self-medication to mitigate their cognitive dysfunctions [71]. The β-amyloid peptide ($A\beta_{1-42}$ or Aβ peptide), a pathological hallmark of Alzheimer's disease, has been shown to affect α7 nAChR's function [113,74,91,66]. Moreover, significant loss of α7 nAChR protein density was observed in the hippocampus of both traumatic brain injury and prenatal restraint stress animal models [52,10]. Either activation of the α7 nAChR with agonists, or potentiation with positive allosteric modulators (PAMs) (e.g., NS-1738), has been shown to improve hippocampal-dependent learning and memory [13,109,117,14]. Conversely,

Abbreviations: ACh, acetylcholine; DG, dentate gyrus; HFS, high frequency stimulation; LTD, long-term depression; LTP, long-term potentiation; nAChR, nicotinic ACh receptor; STP, short-term potentiation; PAM, positive allosteric modulator.

* Corresponding author.

http://dx.doi.org/10.1016/j.bcp.2015.07.015
0006-2952/Published by Elsevier Inc.

genetic deletion and pharmacological inhibition of the α7 nAChR in the hippocampus results in significant learning and memory impairments [69,34,88,121,70], and worsens the learning and memory deficits in a mouse model of Alzheimer's disease [49]. Therefore, it is critical to understand the functional properties of nAChRs in regulating hippocampal circuitry and synaptic plasticity. Below, we will briefly review recent advances, with a particular focus on α7 nAChRs (although α4β2 nAChRs also play an important role), in the regulation of glutamatergic synaptic transmission in the hippocampal formation.

2. α7 nAChR properties and expression in the hippocampus

The nAChRs are widely expressed throughout the brain in both neurons and non-neuronal cells, and participate in a variety of physiological functions [79,84,102]. In the mammalian brain, there are six α (2–10) and three β (2–4) nAChR subunits, which have been shown to form either hetero- or homopentameric nAChRs [111,96,60,7,6]. The most prevalent nAChRs in the hippocampus are comprised of α7 and α4β2 subtypes [59,7,5]. While α7 subunits were initially thought to form mainly homopentameric α7 receptors, they have been shown to co-assemble with other subunits to form functionally distinct native α7-containing receptors [9,122,90,98,73,81,82]. Initially, we found that α7 and β2 subunits co-assembled in vitro [64]; subsequently it was found that basal forebrain cholinergic neurons express functional native α7β2 receptors with an enhanced sensitivity to the amyloid-β (Aβ) peptide associated with AD [73]. Physiological studies have shown that α7 nAChRs have lower affinity for acetylcholine, faster desensitization kinetics, and higher calcium permeability than α4β2 receptors [12,31,5]. Because of its high calcium permeability, α7 nAChRs can function similar to NMDA receptors in the modulation of synaptic plasticity.

In the hippocampal formation, distribution of mRNA for α7 nAChRs, as well as α-bungarotoxin (α-BTX) binding sites (which label α7 nAChRs), are widespread throughout the dentate gyrus (DG), CA3 and CA1 regions [107,29,3]. Functional α7 nAChR-mediated currents have also been reported in CA3 and CA1 pyramidal neurons [57,45,46], mouse dentate granule cells [58] and GABAergic interneurons [60]. Besides neuronal expression, α7 nAChRs are expressed on non-neuronal cells such as astrocytes in the hippocampal CA1 region [102], which could play a role in neuroprotection and inflammation [101]. Ultrastructural studies in the CA1 region revealed immuno-gold particle labeling of α7 nAChRs at both pre- and postsynaptic compartments of both GABAergic and glutamatergic synapses [29]. α7 nAChRs located on presynaptic terminals can regulate release of other neurotransmitters [59,19,21], while α7 nAChRs located on postsynaptic membranes mediate cholinergic synaptic transmission. Taking advantage of their high calcium permeability, functional α7 nAChRs can be mapped with sensitive calcium dyes and genetically-encoded calcium indicators, which provide complimentary information as to the locations of functional receptors beyond the reach of traditional patch-clamp studies. The calcium rise mediated by functional α7 nAChRs has been shown in dendrites of CA1 [31] and CA3 pyramidal neurons [45], and dentate granule cells at their mossy fiber terminals [15]. Optical recordings revealed that the amplitude of the α7 nAChR-mediated calcium response was significantly larger in the dendrites (than in the soma) despite smaller α7 nAChR current responses [32], suggesting that functional α7 nAChRs cluster differentially around neuronal compartments [62]. With the aid of newly developed α7 PAMs, we observed α7 nAChR-mediated calcium rise via GCaMP3 imaging in giant mossy fiber terminals [15], which is consistent with the study using the calcium dye Fura-2 [44]. In addition, α7 nAChRs also distribute perisynaptically to mediate modulating effects of non-synaptically released ACh [61,21,5,101]. The density and distribution of α7 nAChRs changes markedly during early development [2,1], and differs among different mouse strains and species [94,4]. Moreover, genetic polymorphism of the α7 nAChR gene (CHRNA7) linked to schizophrenia generated a partially duplicated α7 nAChR (CHRFAMA7A, *dup*α7) subunit either with or without a 2-bp deletion (CHRFAMA7A-Δ2bp, *dup*Δα7) [41,105], which could change the properties of the α7 nAChR and modify neuronal connections [104]. An in vitro study showed that both *dup*α7 and *dup*Δα7 co-assemble with the α7 subunit to form functional receptors with normal sensitivity to ACh and lower sensitivity to choline, though the calcium permeability of these mutated α7 receptors remains unclear [114].

3. The effect of α7 nAChR's activation by exogenous agonists

Many groups have studied how α7 nAChR activation modulates glutamatergic synaptic transmission with nicotine or selective agonists to activate α7 nAChRs in the hippocampus. We will focus mainly on the direct α7 nAChR-mediated effect on glutamatergic synapses, and not the indirect impact derived from α7 nAChR activation on GABAergic neurons, which also can modulate synaptic plasticity in pyramidal cells.

For spontaneous glutamate release, acute nicotine application increased the frequency of spontaneous miniature EPSCs from dissociated hippocampal neurons [44,93], and CA1 [67] and CA3 pyramidal neurons [100]; this suggests a presynaptic location of nicotine's action. The nicotine-induced frequency increase of mEPSCs was blocked by MLA (an α7-selective antagonist) [44], and absent in α7 knockout mice [67], suggesting that α7 nAChRs mediated this enhancement. Moreover, a brief application of nicotine converted presynaptically silent synapses into conductive ones at immature Schaffer collateral-CA1 connections [76]. Besides its modulatory effect on mEPSC frequency, activation of α7 nAChRs could directly trigger glutamate release from mossy fiber terminals [99]. The direct measurement of glutamate release from hippocampal synaptosomes showed significant release upon choline application [123], which is consistent with electrophysiological findings. In vivo extracellular recordings from CA3 pyramidal neurons showed robust increases in firing induced by nicotine and blocked by MLA; this was found to be due to enhanced glutamate release [53]. The α7 nAChR's effect on spontaneous glutamate release occurred within seconds after agonist application and lasted for several minutes after agonist removal, suggesting that both immediate calcium rise through α7 nAChR activation and longer-term calcium-dependent signaling cascades are involved.

For the evoked release of glutamate, α7 nAChR activation can increase the amplitude of evoked EPSCs in cultured hippocampal neurons [93], for CA3 to CA1 pyramidal neuron synapses, DG to CA3 synapses, and perforant path to DG glutamate synapses [106,89,15]. The increase in amplitude was associated with a significant increase in the probability of release along with a significant decrease of the PPR (paired-pulse ratio) [106]. Our study [15] of CA3 pyramidal neurons showed that α7 nAChR activation enhanced eEPSC amplitude, which persisted for 5–10 min after the removal of agonist. Similar long-lasting effects of nAChR agonists on neurotransmitter release were observed by others as well [68,124]. Studies from both spontaneous and evoked glutamatergic synaptic transmission showed that presynaptic α7 nAChRs mediated enhancement of glutamate release, suggesting that α7 nAChRs could be activating the same calcium-dependent signaling cascades to sustain the nicotinic enhancement of glutamate release. In the prefrontal cortex, nicotine induced an increase in frequency and amplitude of spontaneous EPSCs, but did not affect the amplitude of evoked glutamatergic transmission from layer II/III to layer V pyramidal neurons [17], suggesting that