Published in final edited form as:

Biochem Pharmacol. 2015 October 15; 97(4): 439–444. doi:10.1016/j.bcp.2015.07.015.

The effect of $\alpha 7$ nicotinic receptor activation on glutamatergic transmission in the hippocampus

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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 $\alpha 7$ nAChR's action in the tri-synaptic pathway in the hippocampus. The effects of $\alpha 7$ 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, $\alpha 7$ nAChRs trigger intracellular calcium rise and calcium-dependent signaling pathways to enhance glutamate release and induce glutamatergic synaptic plasticity.

Graphical abstract

1. Introduction

Nicotinic acetylcholine receptors (nAChRs) belong to the superfamily of cys-loop cationic ligand-gated channels (Jones *et al.*, 1999; Dajas-Bailador & Wonnacott, 2004; Dani & Bertrand, 2007; Albuquerque *et al.*, 2009a). 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 (Dani & Bertrand, 2007; Yakel, 2012; 2013). The $\alpha 7$ 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 (Freedman & Goldowitz, 2010; Yakel, 2013; Dineley *et al.*, 2015; Sadigh-Eteghad *et al.*, 2015; Sinkus *et al.*, 2015a). Schizophrenic patients are often heavy smokers (de Leon & Diaz, 2005), which has been suggested to be a form of self-medication to mitigate their cognitive dysfunctions (Levin *et al.*, 1996). The β -amyloid peptide ($A\beta_{1-42}$ or $A\beta$ peptide), a pathological hallmark of Alzheimer's disease, has been shown to affect $\alpha 7$ nAChR's function (Wang *et al.*, 2000; Liu *et al.*, 2001; Pettit *et al.*, 2001; Lamb *et al.*, 2005). Moreover, significant loss of $\alpha 7$ nAChR protein density was observed in the hippocampus of both traumatic brain injury and prenatal restraint stress animal models (Hoffmeister *et al.*, 2011; Baier *et al.*, 2015). Either activation of the $\alpha 7$ nAChR with agonists, or potentiation with positive allosteric modulators (PAMs) (e.g. NS-1738), has been shown to improve hippocampal-dependent learning and memory (Bitner *et al.*, 2007; Timmermann *et al.*, 2007; Yaguchi *et al.*, 2009; Blake *et al.*, 2014). Conversely, genetic deletion and pharmacological inhibition of the $\alpha 7$ nAChR in the hippocampus results in significant learning and memory impairments (Levin *et al.*, 2002; Fernandes *et al.*, 2006; Nott & Levin, 2006; Young *et al.*, 2007; Levin *et al.*, 2009), and worsens the learning and memory deficits in a mouse model of Alzheimer's disease (Hernandez *et al.*, 2010). 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 $\alpha 7$ nAChRs (although $\alpha 4\beta 2$ nAChRs also play an important role), in the regulation of glutamatergic synaptic transmission in the hippocampal formation.

2. $\alpha 7$ 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 (McQuiston & Madison, 1999; Nashmi & Lester, 2006; Shen & Yakel, 2012). 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 (Wada *et al.*, 1989; Sargent, 1993; Jones & Yakel, 1999; Alkondon & Albuquerque, 2004; Albuquerque *et al.*, 2009b). The most prevalent nAChRs in the hippocampus are comprised of $\alpha 7$ and $\alpha 4\beta 2$ subtypes (Jones *et al.*, 1999; Alkondon & Albuquerque, 2004; Albuquerque *et al.*, 2009a). While $\alpha 7$ subunits were initially thought to form mainly homopentameric $\alpha 7$ receptors, they have been shown to co-assemble with other subunits to form functionally distinct native $\alpha 7$ -containing receptors (Anand *et al.*, 1993; Yu & Role, 1998; Palma *et al.*, 1999; Shao & Yakel, 2000; Liu *et al.*, 2009; Murray *et al.*, 2012; Mowrey *et al.*, 2013). Initially, we found that $\alpha 7$ and $\beta 2$ subunits co-assembled *in vitro* (Khiroug *et al.*, 2002); subsequently it was found that basal forebrain cholinergic neurons express functional native $\alpha 7\beta 2$ receptors with an enhanced sensitivity to the amyloid- β ($A\beta$) peptide associated with AD (Liu *et al.*, 2009). Physiological studies have shown that $\alpha 7$ nAChRs have lower affinity for acetylcholine, faster desensitization kinetics, and higher calcium permeability than $\alpha 4\beta 2$ receptors (Bertrand *et al.*, 1993; Fayuk & Yakel, 2005; Albuquerque *et al.*, 2009a). Because of its high calcium permeability, $\alpha 7$ nAChRs can function similar to NMDA receptors in the modulation of synaptic plasticity.

In the hippocampal formation, distribution of mRNA for $\alpha 7$ nAChRs, as well as α -bungarotoxin (α -BTX) binding sites (which label $\alpha 7$ nAChRs), are widespread throughout the dentate gyrus (DG), CA3 and CA1 regions (Sudweeks & Yakel, 2000; Fabian-Fine *et al.*, 2001; Adams *et al.*, 2002b). Functional $\alpha 7$ nAChR-mediated currents have also been reported in CA3 and CA1 pyramidal neurons (Ji *et al.*, 2001; Grybko *et al.*, 2011; Gu *et al.*, 2012), mouse dentate granule cells (John *et al.*, 2015) and GABAergic interneurons (Jones & Yakel, 1999). Besides neuronal expression, $\alpha 7$ nAChRs are expressed on non-neuronal cells such as astrocytes in the hippocampal CA1 region (Shen & Yakel, 2012), which could play a role in neuroprotection and inflammation (Shen & Yakel, 2009). Ultrastructural studies in the CA1 region revealed immuno-gold particle labeling of $\alpha 7$ nAChRs at both pre- and postsynaptic compartments of both GABAergic and glutamatergic synapses (Fabian-Fine *et al.*, 2001). $\alpha 7$ nAChRs located on presynaptic terminals can regulate release of other neurotransmitters (Jones *et al.* 1999; Dajas-Bailador & Wonnacott, 2004; Dani & Bertrand, 2007), while $\alpha 7$ nAChRs located on postsynaptic membranes mediate cholinergic synaptic transmission. Taking advantage of their high calcium permeability, functional $\alpha 7$ 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 $\alpha 7$ nAChRs has been shown in dendrites of CA1 (Fayuk & Yakel, 2005; 2007a) and CA3 pyramidal neurons (Grybko *et al.*, 2011), and dentate granule cells at their mossy fiber terminals (Cheng & Yakel, 2014). Optical recordings revealed that the amplitude of the $\alpha 7$ nAChR-mediated calcium response was significantly larger in the dendrites (than in the soma) despite smaller $\alpha 7$ nAChR current responses (Fayuk & Yakel, 2007a), suggesting that functional $\alpha 7$ nAChRs cluster differentially around neuronal compartments (Kawai *et al.*, 2002). With the aid of newly developed $\alpha 7$ PAMs, we observed $\alpha 7$ nAChR-mediated calcium rise via GCaMP3 imaging in giant mossy fiber terminals (Cheng & Yakel, 2014), which is consistent with the study using the calcium dye Fura-2 (Gray *et al.*, 1996). In addition, $\alpha 7$ nAChRs also distribute perisynaptically to mediate modulating effects of non-synaptically released ACh (Kasa *et al.*, 1995; Dani & Bertrand, 2007; Albuquerque *et al.*, 2009a; Shen & Yakel, 2009). The density and distribution of $\alpha 7$ nAChRs changes markedly during early development (Adams *et al.*, 2002a; Adams, 2003), and differs among different mouse strains and species (Rubboli *et al.*, 1994; Adams *et al.*, 2006). Moreover, genetic polymorphism of the $\alpha 7$ nAChR gene (CHRNA7) linked to schizophrenia generated a partially duplicated $\alpha 7$ nAChR (CHRFAMA7A, *dupa7*) subunit either with or without a 2-bp deletion (CHRFAMA7A- 2bp, *dup* $\alpha 7$) (Gault *et al.*, 2003; Sinkus *et al.*, 2009), which could change the properties of the $\alpha 7$ nAChR and modify neuronal connections (Sinkus *et al.*, 2015b). An *in vitro* study showed that both *dupa7* and *dup* $\alpha 7$ co-assemble with the $\alpha 7$ subunit to form functional receptors with normal sensitivity to ACh and lower sensitivity to choline, though the calcium permeability of these mutated $\alpha 7$ receptors remains unclear (Wang *et al.*, 2014).

3. The effect of $\alpha 7$ nAChR's activation by exogenous agonists

Many groups have studied how $\alpha 7$ nAChR activation modulates glutamatergic synaptic transmission with nicotine or selective agonists to activate $\alpha 7$ nAChRs in the hippocampus.

We will focus mainly on the direct $\alpha 7$ nAChR-mediated effect on glutamatergic synapses, and not the indirect impact derived from $\alpha 7$ 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 (Gray *et al.*, 1996; Radcliffe & Dani, 1998), and CA1 (Le Magueresse *et al.*, 2006) and CA3 pyramidal neurons (Sharma & Vijayaraghavan, 2003); this suggests a presynaptic location of nicotine's action. The nicotine-induced frequency increase of mEPSCs was blocked by MLA (an $\alpha 7$ -selective antagonist) (Gray *et al.*, 1996), and absent in $\alpha 7$ knockout mice (Le Magueresse *et al.*, 2006), suggesting that $\alpha 7$ nAChRs mediated this enhancement. Moreover, a brief application of nicotine converted presynaptically silent synapses into conductive ones at immature Schaffer collateral-CA1 connections (Maggi *et al.*, 2003). Besides its modulatory effect on mEPSC frequency, activation of $\alpha 7$ nAChRs could directly trigger glutamate release from mossy fiber terminals (Sharma *et al.*, 2008). The direct measurement of glutamate release from hippocampal synaptosomes showed significant release upon choline application (Zappettini *et al.*, 2010), 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 (Huang *et al.*, 2010). The $\alpha 7$ 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 $\alpha 7$ nAChR activation and longer-term calcium-dependent signaling cascades are involved.

For the evoked release of glutamate, $\alpha 7$ nAChR activation can increase the amplitude of evoked EPSCs in cultured hippocampal neurons (Radcliffe & Dani, 1998), for CA3 to CA1 pyramidal neuron synapses, DG to CA3 synapses, and perforant path to DG glutamate synapses (Sola *et al.*, 2006; Ondrejcek *et al.*, 2012; Cheng & Yakel, 2014). 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) (Sola *et al.*, 2006). Our study (Cheng & Yakel, 2014) of CA3 pyramidal neurons showed that $\alpha 7$ nAChR activation enhanced eEPSC amplitude, which persisted for 5-10 minutes after the removal of agonist. Similar long-lasting effects of nAChR agonists on neurotransmitter release were observed by others as well (Lena & Changeux, 1997; Zhong *et al.*, 2008). Studies from both spontaneous and evoked glutamatergic synaptic transmission showed that presynaptic $\alpha 7$ nAChRs mediated enhancement of glutamate release, suggesting that $\alpha 7$ 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 (Couey *et al.*, 2007), suggesting that multiple calcium-dependent pathways could be involved in its action.

Hippocampal LTP is a well-accepted cellular model for learning and memory. The effect of $\alpha 7$ nAChR's activation on synaptic plasticity is dictated by the timing of its activation and electrical stimulation on glutamatergic synaptic currents. When $\alpha 7$ nAChR agonists were bath perfused, the activation of $\alpha 7$ nAChRs facilitated the induction of LTP (Hunter *et al.*,

1994; Fujii *et al.*, 1999), and enhanced both early and late LTP (Kroger *et al.*, 2011) in the CA1 hippocampal region. When $\alpha 7$ nAChRs were activated via brief application of ACh, which coincided or preceded (by 1-5 s) high frequency stimulation (HFS), this produced LTP under mild presynaptic stimulation conditions at CA1 pyramidal neurons (Ji, 2001). Outside of these time frames, the mismatch of nAChR activity and stimulation led to short-term potentiation (STP) (Ge & Dani, 2005). The $\alpha 7$ nAChR-mediated enhancement of LTP was due to its ability to increase presynaptic release of glutamate and postsynaptic depolarization. Activation of $\alpha 7$ nAChRs has also been shown to suppress LTD induction at CA3-CA1 synapses (Fujii & Sumikawa, 2001; Nakauchi & Sumikawa, 2014). In the DG, acute $\alpha 7$ nAChR activation enhanced HFS-induced LTP, and $\alpha 7$ nAChR PAMs reduced the threshold for LTP induction, an effect which required ERK and PKA activity (Welsby *et al.*, 2009). For mossy fiber LTP, $\alpha 7$ nAChR agonists rescued LTP that was deficient in BACE1 knock-out mice, but had very little effect on LTP in wildtype mice (Wang *et al.*, 2010). The rescue by $\alpha 7$ nAChR agonists was abolished by blockers of ryanodine-sensitive calcium stores, suggesting that calcium-induced calcium release played a key role in this regulation. However, the effect of $\alpha 7$ nAChR activation on STP needs to be tested on mossy fiber transmission. These studies also pointed to a calcium rise induced by $\alpha 7$ nAChR activation as the central mechanism for these actions, and $\alpha 7$ nAChR activation also triggers differential signaling molecules to produce various influences in the hippocampus.

4. $\alpha 7$ activation via cholinergic synapses in the hippocampus

Under physiological conditions, $\alpha 7$ nAChRs are activated by endogenous ACh released from cholinergic neurons. The primary cholinergic input to the hippocampus arises from the medial septum and diagonal band of Broca (Amaral & Kurz, 1985; Dutar *et al.*, 1995), although a small population of cholinergic interneurons do exist in the hippocampus as recently reconfirmed from ChAT-tauGFP and ChAT-CRE/Rosa-YFP transgenic mice (Yi *et al.*, 2015). Initial studies using electrical cholinergic stimulation to dissect the function of endogenous ACh showed prominent muscarinic receptor's effect of Schaffer collateral input to CA1 pyramidal neurons (Fernandez de Sevilla & Buno, 2003). The $\alpha 7$ nAChR-dependent modulation of synaptic plasticity of CA3-CA1 glutamatergic synapses was uncovered with localized application of ACh, which is sensitive to the location and timing of $\alpha 7$ nAChR activation (Ji *et al.*, 2001; Ge & Dani, 2005). The development of optogenetic techniques allows both cell-type specific and temporally precise stimulation of cholinergic inputs to the hippocampus. Taking advantage of this approach, our lab investigated how activation of endogenous cholinergic inputs may regulate hippocampal synaptic plasticity (Gu & Yakel, 2011). We found that $\alpha 7$ nAChRs mediated two forms of hippocampal synaptic plasticity with a timing precision in the millisecond range. When the cholinergic input to the CA1 hippocampal region was activated 100 ms prior to activation of the Schaffer collateral (SC) pathway, this induced an $\alpha 7$ nAChR-dependent form of LTP. When the cholinergic input was activated only 10 ms prior to the SC pathway, this induced an $\alpha 7$ nAChR-dependent short-term depression (STD) that was mediated primarily through the presynaptic inhibition of glutamate release. Furthermore, we observed $\alpha 7$ nAChR-dependent enhancement of calcium responses during this LTP both pre- and post synaptically, and short-term depression of calcium responses during STD (Gu *et al.*, 2012). In aged $\alpha 7$ -nAChR KO mice,

both evoked field synaptic potentials and LTP were significantly reduced in hippocampal CA3-CA1 synapses (Ma *et al.*, 2014), suggesting that cholinergic modulation of LTP required the activation of $\alpha 7$ nAChRs.

5. Second messenger signaling upon activation of $\alpha 7$ nAChRs-

The $\alpha 7$ nAChRs have a high calcium permeability, comparable to that of NMDA receptors (Seguela *et al.*, 1993; Uteshev, 2012); this confers the ability of $\alpha 7$ nAChRs to produce long-lasting modulations of synaptic transmission (Fagen *et al.*, 2003; McKay *et al.*, 2007). The intracellular calcium rise alters the amount of neurotransmitter release directly (Neher & Sakaba, 2008), and triggers multiple signaling cascades to modify the efficacy of synaptic transmission. Indeed, we observed a prominent calcium rise upon activation of $\alpha 7$ nAChRs at mossy fiber terminals (using the genetically-encoded calcium sensor GCaMP3), and found that the peak of the action potential (AP)-evoked calcium transient was enhanced by the $\alpha 7$ nAChR agonist PNU-282987 (Cheng & Yakel, 2014; 2015). Similar actions of presynaptic $\alpha 7$ nAChRs on AP-evoked calcium transients were also reported in CA1 pyramidal neurons (Szabo *et al.*, 2008). Changes in the AP-induced calcium transients would lead to changes in the amount of neurotransmitter released at presynaptic terminals (Jackson *et al.*, 1991). The source of the calcium increase would be mainly comprised of the calcium influx directly through the $\alpha 7$ nAChR itself (Fayuk & Yakel, 2007a; Gilbert *et al.*, 2009), and any calcium-induced calcium release from intracellular calcium stores (Weisskopf & Nicoll, 1995; Sharma & Vijayaraghavan, 2003; Sharma *et al.*, 2008). Although calcium influx through voltage-gated calcium channels (VGCC) previously was shown not to contribute significantly to the $\alpha 7$ nAChR-mediated presynaptic effect (Dickinson *et al.*, 2008), other studies reported that calcium influx through VGCCs could contribute to some degree (Barrantes *et al.*, 1995; Fayuk & Yakel, 2007b; del Barrio *et al.*, 2011). In addition, recent studies showed that $\alpha 7$ nAChR activation enhanced NMDAR-mediated whole-cell currents and glutamate release from hippocampal synaptosomes (Zappettini *et al.*, 2010; Li *et al.*, 2013). Lastly, membrane depolarization induced by $\alpha 7$ nAChR activation could release the magnesium blockade of NMDARs to reduce the threshold for NMDAR-dependent synaptic plasticity.

Although activation of the $\alpha 7$ nAChRs induces transient calcium rises, the kinetics of this do not explain the long-lasting effects caused by $\alpha 7$ nAChR agonists on synaptic plasticity (Lena & Changeux, 1997; Zhong *et al.*, 2008; Zhong *et al.*, 2013). Many calcium signaling cascades have been linked to $\alpha 7$ nAChRs, including the CaMKII (Sharma *et al.*, 2008) and cAMP-PKA pathways (Dajas-Bailador *et al.*, 2002; Welsby *et al.*, 2009). Recently, we reported that the action of $\alpha 7$ nAChRs at mossy fiber terminals depended on PKA activity (Cheng & Yakel, 2014). Since it was shown that the $\alpha 7$ nAChR and adenylyl cyclase 1 (AC1) are associated physically and functionally in epithelium (Maouche *et al.*, 2013), we investigated any connection between the activation of the $\alpha 7$ nAChR and cAMP signaling in hippocampal neurons. Using a FRET-based cAMP sensor, we found that activation of $\alpha 7$ nAChRs significantly increased intracellular cAMP levels. The cAMP rise was abolished by the $\alpha 7$ nAChR antagonist MLA, the calcium chelator BAPTA, the selective AC1 inhibitor CB-6673567, and siRNA-mediated AC1 knockdown; this suggested that the calcium-dependent AC1 is required for linking the activation of $\alpha 7$ nAChRs to a cAMP rise (Cheng

& Yakel, 2015). We also found that the activation of $\alpha 7$ nAChRs leads to the widespread increase of phosphorylated synapsin I (via its PKA site), which is a prominent presynaptic PKA substrate (Huttner & Greengard, 1979) and can regulate neurotransmitter release and calcium-dependent synaptic plasticity (Hilfiker *et al.*, 1999; Hilfiker *et al.*, 2005; Menegon *et al.*, 2006; Fiumara *et al.*, 2007; Cousin & Evans, 2011). The PKA pathway was also shown to be required for the $\alpha 7$ nAChR-mediated enhancement of LTP in dentate granule cells (Welsby *et al.*, 2009). Moreover, $\alpha 7$ nAChR activation was shown to interact with G proteins and G protein-regulated inducer of neurite outgrowth 1 to reduce axonal growth (Nordman & Kabbani, 2014; Nordman *et al.*, 2014). With the advancement of new technologies, novel signaling pathways might be linked to $\alpha 7$ nAChRs to interpret its complex actions in the brain.

6. Significance and conclusion

The changes in $\alpha 7$ nAChR expression and density in the hippocampus have been observed in many cognitive impairment disorders, such as schizophrenia (Freedman & Goldowitz, 2010) and Alzheimer's disease (Dani & Bertrand, 2007; Dineley *et al.*, 2015; Sadigh-Eteghad *et al.*, 2015). However, the physiological mechanism and consequences of these changes are still unclear, in terms of how these receptors regulate neuronal excitability, synaptic plasticity and brain circuit function. Furthermore, the outcome of $\alpha 7$ nAChR activation on the hippocampal circuit is complicated by the extensive distribution of $\alpha 7$ nAChRs on both glutamatergic and GABAergic neurons. With the newly-generated floxed $\alpha 7$ nAChR transgenic mouse (Hernandez *et al.*, 2014) combining with Cre and Cre-ER dependent systems, selective deletion of $\alpha 7$ nAChRs from distinct cell populations at specific developmental stages will allow us to unravel systematically the impact of $\alpha 7$ nAChR activation on hippocampal network both *in vitro* and *in vivo*. This will also help us to understand how the alteration of $\alpha 7$ nAChR function will impact cognitive function.

The agonists and modulators of $\alpha 7$ nAChRs have been attractive candidates for developing therapeutic treatments for these neuronal disorders (Deutsch *et al.*, 2013; Deutsch *et al.*, 2014). Indeed, several drugs targeting $\alpha 7$ nAChRs demonstrated their potential in treating schizophrenic patients (Freedman *et al.*, 2008; Preskorn *et al.*, 2014; Keefe *et al.*, 2015). With the development of improved biosensors and emerging tools such as optogenetics (combined with electrophysiology), we will continue to probe cellular and molecular mechanisms of $\alpha 7$ nAChR's functions in neural circuits. The insights gained from these studies will lead to new treatments to mitigate cognitive impairments.

Acknowledgements

We would like to thank Drs. Serena Dudek and Christian Erxleben for the helpful reading and suggestions on our manuscript. This research was funded by the NIEHS Intramural Research Program/NIH. The authors declare no competing financial interests.

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

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Figure 1.

Mechanisms of $\alpha 7$ nAChR-mediated presynaptic enhancement of glutamate release. The intracellular calcium level at presynaptic terminals is increased by calcium influx through $\alpha 7$ nAChRs, VGCCs, and NMDARs from the outside, and calcium release from intracellular calcium stores. The raised calcium levels could increase vesicular glutamate release directly, and trigger cAMP-PKA-dependent pathways for prolonged enhancement of glutamate release. Phosphorylation of synapsins by PKA leads to synaptic vesicle mobilization from the reserve pool to the readily releasable pool, hence increasing glutamate release. (Purple trapezoids depict unphosphorylated synapsins, while red trapezoids depict phosphorylated synapsins.)