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Role of nicotinic acetylcholine receptors for modulation of microcircuits in the agranular insular cortex

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ABSTRACT

Background: Acetylcholine (ACh) plays key roles in regulating neuronal excitability throughout the brain by acting muscarinic ACh receptors (mAChRs) and nicotinic ACh receptors (nAChRs). The insular cortex is an important brain region associated with sensory perception, self-awareness, cognitive function, motor control, and drug addiction. The insular cortex receives cholinergic inputs from the basal forebrain, the activation of which stimulates mAChRs and nAChRs in the insular cortex and modulates its microcircuits to perform various functions. Therefore, it is crucial to understand the cholinergic modulation of microcircuits in the insular cortex. To date, we have been focused on the role of nAChRs in modulating neural circuits in the mouse agranular insular cortex.

Highlight: In this review, we present data on cholinergic inputs to neocortical regions, including the insular cortex, and characteristics of mAChRs and nAChRs. In addition, we describe which type of neurons express functional nAChRs in layer III, V, and VI of the mouse agranular insular cortex and how activation of nAChRs regulates synaptic transmission and plasticity in the layer III, V, and VI pyramidal cells.

Conclusion: The activation of nAChRs layer specifically modulates synaptic transmission and plasticity in the mouse agranular insular cortex. These synaptic mechanisms are critical to understand the modulating effects of ACh or nicotine on physiological and pathophysiological functions associated with the insular cortex.

Contents

1. Introduction

The cholinergic system in the central nervous system (CNS) is associated with various aspects of cognitive function, and there is evidence that cholinergic neurons mediate learning and memory processes [1,2]. The release of acetylcholine (ACh) occurs in the

Abbreviations: ACh, acetylcholine; CNS, central nervous system; DHβE, dihydro-β-erythroidine hydrobromide; FS, fast-spiking; LTD, long-term depression; LTP, long-term potentiation; mPFC, medial prefrontal cortex; MLA, methyllycaconitine; mAChR, muscarinic acetylcholine receptor; nAChR, nicotinic acetylcholine receptor

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neocortex in response to a variety of environmental and behavioral conditions, including locomotor activity, wakefulness, stress and exposure to pain, taste, and auditory stimuli [3–8]. The main source of ACh in the cortex are cholinergic neurons located in the basal forebrain, which is comprised of the septum, nucleus basalis, diagonal band of Broca, and the substantia innominata [9,10]. ACh is also produced in the laterodorsal tegmental area and pedunculopontine nucleus [11], and in the sparsely distributed vasoactive intestinal polypeptide-positive interneurons [12]. Although ACh is produced in a relatively small number of neurons, it induces widespread effects in the CNS [13]. Nearly all brain regions receive synaptic inputs from cholinergic neurons, and most neurons and glial cells express acetylcholine receptors (AChRs) [14,15]. In addition, once released, ACh activates muscarinic and nicotinic AChRs (mAChRs and nAChRs, respectively) in neurons and glial cells, and affects neural microcircuits and synaptic plasticity [16]. Recent evidence in humans and animals suggests that cholinergic modulation of neural circuits and synaptic plasticity in the medial prefrontal cortex (mPFC) is layer-specific [17].

It is known that the insular cortex plays essential roles in cognitive function, self-awareness, sensory perception and motor control [18–20]. It has been shown that the insular cortex receives substantial cholinergic innervation, and that the release of ACh within the insular cortex plays a critical role in the formation of taste memory [9,21]. In addition, the insular cortex has been recognized as an area of the brain which is important for the formation of nicotine addiction [22–25]. However, little is known about how ACh and nicotine modulate neuronal microcircuits and synaptic plasticity in the insular cortex. In this review, we discuss recent findings on the roles of nAChRs in synaptic activities in the agranular insular cortex.

2. Cholinergic innervation to the cortex

Cholinergic fibers are densely distributed over the entre cortical mantle [11,12,26]. In rodent and primate brains, the main cholinergic innervation for the cortex arises from the basal forebrain [11,13], although ACh is released from the laterodorsal tegmental nucleus and the pedunculopontine tegmental nucleus, as well as arising from the sparsely distributed local cholinergic interneurons in the cortex [11,27]. In the rodent brain, cholinergic projections from the basal forebrain exhibit a specific topographic organization [16,21,26,28–30]. Early studies suggest that cholinergic neurons in the diagonal band tend to project to the cingulate and visual cortices, while those in the substantia innominate tend to project to the frontal cortex [26,31]. Recent studies reveal that a clear topographical organization exists between cholinergic neurons in the basal forebrain and neocortical regions [16,21,28]. For example, it was reported that the caudal basal forebrain, including the substantia innominata and the caudal globus pallidus, project to the perirhinal and postrhinal cortices, whereas the rostral basal forebrain, including the vertical and horizontal limbs of the diagonal band and the medial septum, project to the entorhinal cortex [28]. In addition, using a viral labelling technique, it was revealed that the rostral basal forebrain, including the horizontal limbs of the diagonal band, mainly innervates the rostral and ventral mPFC, while the caudo-lateral basal forebrain (including the substantia innominate and the nucleus basalis) mainly innervate the dorsal and caudal mPFC [16]. Furthermore, it was shown that the cholinergic neurons in the rostral part of the basal forebrain innervate the superficial layer of the ventral region of the mPFC, while those in the caudal portion innervate the deep layer of the mPFC [16]. Although it was demonstrated that ACh released from the nucleus basalis magnocellularis to the insular cortex is involved in taste recognition [32], currently, details of the topographical organization of basal forebrain neurons projecting to the insular cortex are unknown.

3. Acetylcholine receptors

The neurotransmitter ACh modulates neuronal excitability by activating mAChRs and nAChRs. These receptors function in different ways. mAChRs are a class of G-protein coupled receptors that transduce signals through intracellular signaling cascades [33,34]. There are five main subtypes of mAChRs (M1-M5), and these subtypes can be further grouped into two main families based on their α-subunit isoform, which determines their signaling efficacy. The first group of mAChRs is comprised of M1, M3, and M5 receptors, which couple to Gq/11 proteins, while the second group is comprised of M2 and M4 receptors, which couple to Gi/o proteins [35]. M1-M5 receptors are expressed widely throughout the CNS, but expression of these different subtypes differs by brain regions [34]. M1, M2, and M4 receptors are expressed abundantly in the cortex and striatum, whereas M1-M4 receptors are expressed prominently in the hippocampus [33,36]. mAChRs are located both in presynaptic and postsynaptic regions, and thus, can modulate the neuronal excitability and release probability of various neurotransmitters [34].

In the CNS, activation of mAChRs affects K^+, Ca^{2+} and non-selective cation channels through multiple intracellular signaling cascades [34]. The activation of M1 receptors block several K^+ (Ca^{2+}-activated, voltage-gated and inward rectifier) channels, while M2 and M4 receptors open inward rectifier K^+ channels and block voltage-gated Ca^{2+} channels [37]. In response to phasic application of ACh, layer V pyramidal cells in the rat prefrontal cortex display a transient hyperpolarization through M1 receptor-mediated activation of small-conductance Ca^{2+}-activated K^+ channels [38,39].

The nAChRs are a type of ligand-gated ion channels which respond to ACh and nicotine. These receptors are composed of five subunits, which are arranged around a central pore embedded in the cell membrane. Neuronal nAChRs are composed from 12 different subunits (α2-α10, β2-β4), and, consequently, the different arrangements of these subunits confer distinct structural and functional properties [40]. nAChRs are highly expressed in the CNS [41], and two types of subfamilies exist [42]. The first type are the homomeric receptors, which consist of five α7 subunits, while the second type are the heteromeric receptors, which consist of two α4 subunits, two β2 subunits and a fifth subunit (α4, α5 or β2) (Fig. 1) [43]. In the cortex, homomeric α7-subtype nAChRs and heteromeric

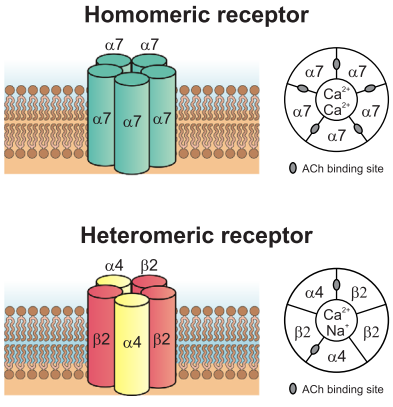

Fig. 1. Structure of nicotinic acetylcholine receptors (nAChRs). Pentameric arrangement of homomeric α7-subtype nAChR (upper) and α4β2-subtype nAChR (lower), and location of the ACh binding site.

α4β2- and α4α5β2-subtype nAChRs are predominantly expressed [44], while α4-, α5-, and β2-nAChR subtypes are preferentially expressed in the deep layers [45,46].

It is well known that the affinity to ACh is different between homomeric and heteromeric nAChRs. The affinity to ACh in homomeric nAChRs is in the micromolar range, while the affinity in heteromeric nAChRs is in the nanomolar rage [45]. This difference in affinity is likely to affect desensitization of both types of nAChRs. α7-Subtype nAChRs exhibit rapid desensitization in response to high concentrations of ACh [47]. Compared to the α7-subtype nAChRs, α4β2-subtype nAChRs desensitize much more slowly, but respond to lower concentrations of ACh [48].

4. Modulation of microcircuits in the agranular insular cortex by nAChRs

nAChRs are expressed abundantly in the rodent cortex and modulate the electrical activity of target neurons [44]. It has been shown that modulation of neocortical microcircuits by nAChRs is layer-specific [17].

In the mPFC, somatosensory cortex, motor cortex and visual cortex of rodent and human brains, layer II/III pyramidal cells do not express functional nAChRs [39,49–52]. Consistent with these observations, we found that a majority of layer III pyramidal cells in the mouse agranular insular cortex do not express functional nAChRs (Figs. 2 and 3) [53]. Furthermore, excitatory synaptic transmission in layer III pyramidal cells was not altered by activation of nAChRs, indicating that glutamatergic inputs onto these neurons do not express functional nAChRs [53].

In addition to pyramidal cells, GABAergic interneurons are modulated by activation of nAChRs. In layer III of the mPFC, distinct types of interneurons display different subtypes of nAChRs, and activation of nAChRs on various types of GABAergic interneurons increases GABAergic synaptic inputs onto pyramidal cells [51]. Likewise, we found that GABAergic synaptic inputs onto layer III pyramidal cells in the agranular insular cortex are augmented by activation of nAChRs, and enhanced GABAergic synaptic transmission is largely abolished by use of the α4β2-subtype nAChR antagonist, DHβE (dihydro-β-erythroidine hydrobromide), and is moderately abolished by use of the α7-subtype nAChR antagonist, MLA (methyllycaconitine citrate) [53]. We then examined whether GABAergic interneurons in layer III of the mouse agranular insular cortex express functional nAChRs. α7-subtype nAChRs are

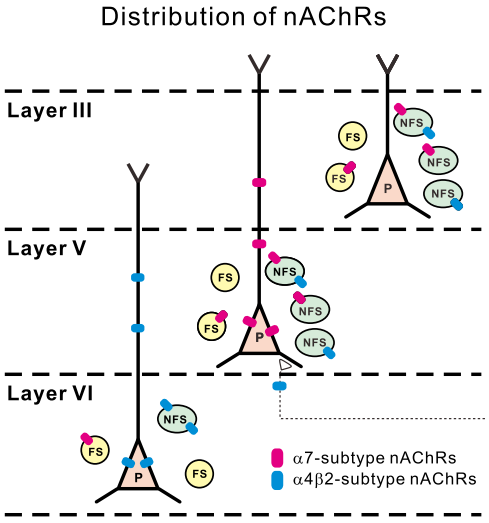

Fig. 3. Distribution of nicotinic acetylcholine receptors (nAChRs) in layers III, V and VI of the mouse agranular insular cortex. Layer III pyramidal cells have no functional nAChRs. Nearly a half of layer V pyramidal cells express functional α7-subtype nAChRs. Layer VI pyramidal cells have functional α4β2-subtype nAChRs. Glutamatergic inputs onto layer V pyramidal cells are modulated by α4β2-subtype nAChRs, which are presumably expressed in thalamocortical fibers. Glutamatergic inputs onto layer VI pyramidal cells are modulated by α4β2-subtype nAChRs. GABAergic inputs onto layer III, V and VI pyramidal cells are modulated largely by α4β2-subtype nAChRs in non-fast-spiking interneurons, and to a minor extent, by α7-subtype nAChRs in fast-spiking and non-fast-spiking interneurons. Abbreviations: P, pyramidal cell; FS, fast-spiking interneuron; NFS, non-fast-spiking interneuron.

expressed in nearly a half of fast-spiking cells, while α7- and/or α4β2-subtype nAChRs are expressed in the majority of non-fast-spiking cells (Fig. 3) [53]. These observations are similar to those observed in layer II/III pyramidal cells of the mouse mPFC [51,54].

Although layer V pyramidal cells in the somatosensory, visual, and motor cortices do not express functional nAChRs [39,50,52], those in the mPFC express functional α7-subtype nAChRs [51]. We found that nearly half of layer V pyramidal cells in the mouse agranular insular cortex express functional α7-subtype nAChRs (Figs. 2 and 3), and that glutamatergic synaptic inputs onto layer V pyramidal cells located in the agranular mouse insular cortex were markedly augmented by activation of nAChRs [55]. However, we found that this enhancement was mediated by α4β2-subtype nAChRs, but not by α7-subtype nAChRs [55], indicating that the

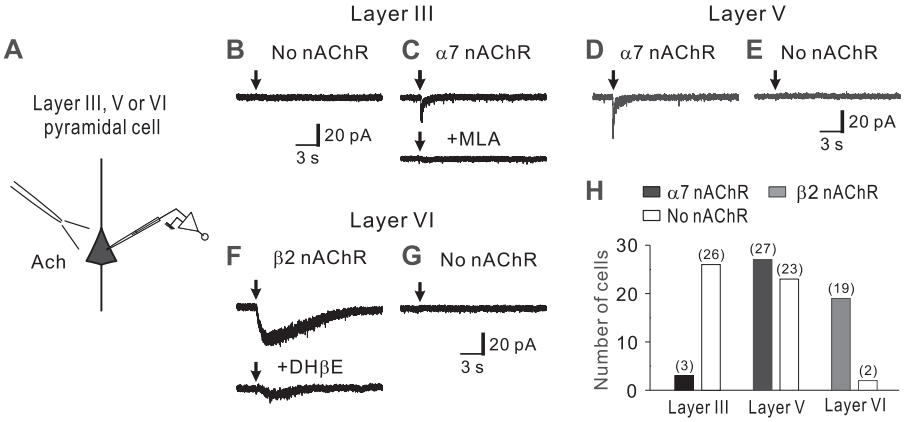

Fig. 2. Puff application of acetylcholine (ACh) onto layer III, V and VI pyramidal cells of the agranular insular cortex. (A) Experimental diagram illustrating puff application of ACh. (B) In a layer III pyramidal cell, no current was induced by puff application of 1 mM ACh. (C) In another layer III pyramidal cell, puff application of ACh induced a rapid inward current which was blocked by 100 nM methyllycaconitine citrate (MLA). (D) In a layer V pyramidal cell, puff application of ACh induced a rapid inward current. (E) In another layer V pyramidal cell, no current was induced by puff application of ACh. (F) In a layer VI pyramidal cell, puff application of ACh induced a slow inward current that was suppressed by 1 μM dihydro-β-erythroidine hydrobromide (DHβE). (G) In another layer VI pyramidal cell, no current was induced by puff application of ACh. (H) Histogram showing the distribution of nAChRs in layer III, V and VI pyramidal cells. (B–G) Arrows indicate puff application of 1 mM ACh. Modified from Refs [53,55].

functional α7-subtype nAChRs in layer V pyramidal cells are not involved in the enhanced excitatory synaptic transmission we observed. Presumably, this is because α7-subtype nAChRs are not activated effectively by a slow increase in ACh concentration (e.g., bath application) [51]. In the mouse mPFC, activation of α4β2-subtype nAChRs strongly enhances excitatory synaptic inputs from thalamic afferents onto layer V pyramidal cells [56]. Considering that the insular cortex receives afferent inputs from the thalamic nuclei [57], and that α4β2-subtype nAChRs are abundantly expressed in the thalamocortical fibers [58], it seems likely that activation of α4β2-subtype nAChRs expressed in thalamocortical axon terminals in the agranular insular cortex are involved in the increases in glutamate release [56].

In layer V of the mouse PFC, distinct types of GABAergic interneurons express several types of nAChRs: nearly a half of fast-spiking cells express α7-subtype nAChRs, and the majority of non-fast-spiking cells (including low-threshold spiking cells, and regular-spiking non-pyramidal cells) express α7-subtype and/or α4β2-subtype nAChRs [51,54]. The GABAergic synaptic inputs onto layer V pyramidal cells of the mPFC are likely to be strongly augmented by activation of nAChRs in the distinct types of GABAergic interneurons [51,54]. In concordance with these findings, we found that in layer V of the mouse agranular insular cortex, the majority of non-fast-spiking cells express α4β2-subtype nAChRs, whereas a minority of non-fast-spiking cells and nearly a half of fast-spiking cells express α7-subtype nAChRs (Fig. 3) [55]. In addition, we found that GABAergic synaptic inputs onto layer V pyramidal cells of the mouse agranular insular cortex are largely augmented by activation of nAChRs, mainly via activation of α4β2-subtype nAChRs, and to a small extent, via activation of α7-subtype nAChRs [55]. Thus, it is likely that the GABAergic synaptic inputs onto layer V pyramidal cells of the mouse agranular insular cortex are enhanced by α4β2-subtype nAChRs in non-fast-spiking cells.

Functional α4β2-subtype nAChRs are highly expressed in layer VI pyramidal cells and in interneurons of the mouse mPFC [51], as well as in layer VI pyramidal cells of the rat

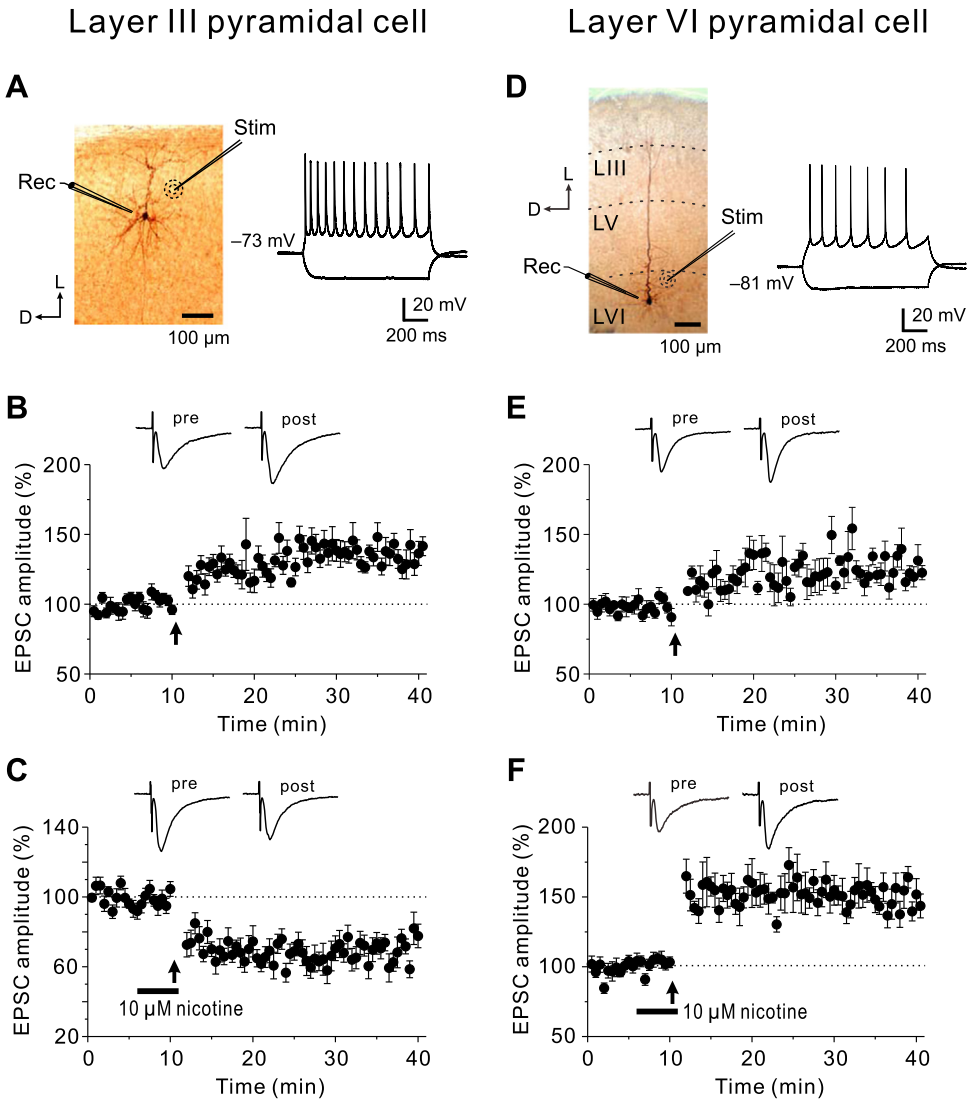

Fig. 4. Effects of nicotine on synaptic potentiation in layer III and VI pyramidal cells of the mouse agranular insular cortex. (A, D) Biocytin-filled layer III and VI pyramidal cells (panels A and D, respectively); schematic illustrates the position of the stimulating (Stim) and recording (Rec) electrodes. D, Dorsal; L, Lateral. Membrane potential responses to hyperpolarizing and depolarizing current pulses (–100 and 100 pA, respectively) applied to layer III and VI pyramidal cells (panels A and D, respectively). Pyramidal cells displayed repetitive action potentials with frequency adaptation. (B, E) Synaptic potentiation was induced in layer III and VI pyramidal cells by paired training (presynaptic 80 pulses at 2 Hz with postsynaptic depolarization at +30 mV) (Panels B and E, respectively). (C, E) In the presence of 10 μM nicotine during the paired training, synaptic depression was induced in a layer III pyramidal cell while robust synaptic potentiation was induced in a layer VI pyramidal cell. (B, C, E, F) Dashed line indicate the mean basal synaptic response. Paired training is indicated by an arrow. Insets show averages of ten consecutive current traces before (pre-) and 25–30 min after (post-) paired training. Data modified from refs [53,55].

entorhinal cortex [46]. We found that a majority of layer VI pyramidal cells in the mouse agranular insular cortex express functional α4β2-subtype nAChRs (Figs. 2 and 3) [53]. Although it was demonstrated that glutamatergic synaptic inputs onto layer VI pyramidal cells in the mPFC are not affected by activation of nAChRs [56,59], we found that those in the agranular insular cortex are enhanced mildly by activation of functional α4β2-subtype nAChRs [53]. Because layer VI pyramidal cells in the neocortex receive sparse but potent excitatory synaptic inputs not only from within layer VI, but also from other cortical layers [60], it is likely that the enhancement of excitatory synaptic transmission by activation of nAChRs is caused by excitatory inputs from neighboring pyramidal cells located in layer VI, as well as excitatory inputs from layer V pyramidal cells.

Although it was shown that inhibitory synaptic inputs onto layer VI pyramidal cells in the mPFC are not controlled by activation of functional nAChRs [51], we found that those in the agranular insular cortex are significantly enhanced by activation of functional α4β2-subtype nAChRs [53]. In layer VI pyramidal cells of the mouse agranular insular cortex, nearly a half of fast-spiking cells express α7-subtype nAChRs, and the majority of non-fast-spiking cells express α4β2-subtype nAChRs (Figs. 2 and 3) [53]. These data uggest that the enhanced GABAergic synaptic transmission observed in these cells is mediated by activation of α4β2-subtype nAChRs in non-fast-spiking cells.

5. Modulation of synaptic potentiation by nAChRs

Long-term potentiation (LTP) is considered to be key mechanisms for cortical plasticity [61,62]. nAChRs can modulate LTP in various brain regions. In the rat dentate gyrus and CA1 regions of the hippocampus, activation of α7-subtype nAChRs enhances LTP [63–65]. In addition, activation of either α7- or α4β2-subtype nAChRs facilitates LTP in the mice amygdala [66], while activation of presynaptic
α7-subtype nAChRs has been shown to enhance LTP in the rat ventral tegmental area [48]. By contrast, in layer II/III and V pyramidal cells of the mPFC in juvenile mice, activation of nAChRs suppresses LTP of excitatory synapses [54,67]. This is because activation of nAChRs on GABAergic interneurons increases inhibitory synaptic transmission, thereby suppressing LTP by reducing Ca^{2+} signals in the dendrites of pyramidal cells [54]. In line with these observations, we found that activation of nAChRs suppresses LTP induced by 80 presynaptic stimuli at 2 Hz with +30 mV postsynaptic depolarization in layer III and V pyramidal cells of the mouse agranular insular cortex (Fig. 4) [53]. As described above, in layer III and V of the mouse agranular insular cortex, most non-fast-spiking cells express α7- and/or α4β2-subtype nAChRs, while nearly half of fast-spiking cells express α7-subtype nAChRs (Fig. 2) [53,55]. These data strongly suggest that in layer III and V pyramidal cells in the agranular insular cortex, activation of nAChRs on various types of GABAergic interneurons enhances GABAergic synaptic transmission, thereby suppressing LTP.

In the rat entorhinal cortex, it has been shown that activation of nAChRs enhances synaptic transmission and plasticity in layer VI pyramidal neurons by acting on non α7-subtype nAChRs (most likely α4β2-subtype nAChRs) [46]. In layer VI of the mPFC, endogenous ACh enhances synaptic potentiation of glutamatergic synapses by activating postsynaptic heteromeric α4β2-subtype nAChRs [49]. Consistent with these findings, activation of α4β2-subtype nAChRs facilitates LTP in layer VI pyramidal cells of the mouse agranular insular cortex (Fig. 4) [53]. Taken together, our data indicate that in different layers of the agranular insular cortex, pyramidal cell activity is oppositely regulated by activation of nAChRs located either on presynaptic GABAergic interneurons located on layer III and V, or on dendrites in layer VI pyramidal cells.

6. Modulation of synaptic depression by nAChRs

Long-term depression (LTD) is a key form of synaptic plasticity which is involved in motor learning and various pathological conditions including drug addiction [68]. The roles of nAChRs on LTD were previously investigated in the striatum [69] and hippocampus [70]. In the rat striatum, high-frequency stimuli-induced LTD was blocked by nAChR antagonists, suggesting that activation of nAChR is involved in induction of striatal LTD [69]. In the rat hippocampal CA1 region, both nicotine and an α7-subtype nAChR antagonist, MLA, facilitate low-frequency stimuli (200 pulses at 1 Hz)-induced LTD by causing nicotine-induced desensitization of α7-subtype nAChRs on GABAergic interneurons [70]. In layer V pyramidal cells of the mouse agranular insular cortex, we found that activation of nAChRs facilitated LTD induced by 300 presynaptic stimuli at 1 Hz with –45 mV postsynaptic depolarization [71]. The facilitated LTD following activation of nAChRs is likely to be induced by potentiation of GABAergic synaptic transmission, which is mediated by activation of α4β2-subtype nAChRs in non-fast-spiking cells [71]. Considering that LTP in the agranular insular cortex displays layer-specific modulation [53,55], it is possible that LTD in the insular cortex also displays layer-specific modulation. It would be necessary in future research to investigate how activation of nAChRs affects LTD in layer III and VI pyramidal cells of the agranular insular cortex.

7. Conclusion

nAChRs in the insular cortex contribute to the regulation of neuronal circuits and synaptic plasticity and play critical roles not only in various physiological functions (including taste learning), but also play roles in pathological conditions including nicotine addiction. Therefore, it is crucial to understand more about the roles that nAChRs play in synaptic activities in the insular cortex. Current evidence suggests that modulation of cortical microcircuits by nAChRs is much more nuanced than previously thought (e.g., layer-dependence). However, it remains unclear how layer-dependent modulation of synaptic activity by nAChRs is associated with various physiological and pathological functions in the insular cortex. More detailed studies of layer-dependent modulation in synaptic activity by nAChRs, and its' relationship to behavior, will be necessary in the future.

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Ethical approval

Ethical approval was not required.

Conflict of interest

The authors have not conflicts of interest to declare.

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