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α7 nicotinic acetylcholine receptor in memory processing

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Abstract

Information storage in the brain involves different memory types and stages which are processed by several brain regions. Cholinergic pathways through acetylcholine receptors actively participate on memory modulation and their disfunction is associated with cognitive decline in several neurological disorders. During the last decade, the role of α7 subtype of nicotinic acetylcholine receptors in different memory stages has been studied. However, the information about their role in memory processing is still scarce. In this review, we attempt to identify brain areas where α7 nicotinic receptors have an essential role in different memory types and stages. In addition, we discuss recent work implicating -or not- α7 nicotinic receptors as promising pharmacological targets for memory impairment associated with neurological disorders.

Keywords

Acetylcholine, basal forebrain, prefrontal cortex, amygdala, hippocampus

Abbreviations

ACh: acetylcholine

BF: basal forebrain

CINs: cholinergic interneurons

CNS: central nervous system

CS: conditioned stimulus

HDB: horizontal limb of diagonal band of Broca

IPN: interpeduncular nucleus

LDT: laterodorsal tegmental nucleus

LTM: long-term memory

LTP: long-term potentiation

mAChR: muscarinic acetylcholine receptor

mHb: medial habenula

MLA: methyllycaconitine

MS: medial septum

mPFC: medial prefrontal cortex

nAChR: nicotinic acetylcholine receptor

NB: nucleus basalis magnocellularis

PFC: prefrontal cortex

PPT: pedunculopontine nucleus

SI: substantia innominata

STM: short-term memory

US: unconditioned stimulus

VDB: vertical limb of the diagonal band of Broca

1. Introduction

Learning is the process by which we and other organisms acquire information about the world. Memory is the storage of that information and is not a unitary process: Information storage in the brain is a temporally graded process involving different memory types and stages. During these stages new information is consolidated and stored (Dudai, 2004; McGaugh, 2000; Medina et al., 2008). Memory processing has several stages including acquisition, consolidation, retrieval and its consequences, extinction and reconsolidation (Dudai, 2004; Kandel, 2001). In addition, according to duration, memory in mammals can be divided into at least two mechanistically and temporally distinct stages: 1-an early and short phase, which seems to depend on transient covalent changes of preexisting proteins such as phosphorylation of receptor subunits and ion channels (Kandel, 2001) and do not depend on de novo protein and RNA-synthesis; it lasts seconds to minutes to 1-3 hours (short-term memory, STM); 2- a long phase which depends on the activation of brain transcriptional and translational machinery (long-term memory, LTM) that lasts many hours, days, weeks or even a lifetime (Davis and Squire, 1984; McGaugh, 2000, 1966). During the last 20 years studies of the molecular basis of memory processing demonstrated that several signaling molecules are involved in several stages of memory. Specific signaling pathways and patterns of gene expression modulated by neurotransmitters are required in neurons and glia for the formation, stabilization and long-term persistence of synaptic and connectivity changes that underlie LTM (reviewed by Asok et al, 2019; Gonzalez et al., 2019; Josselyn and Tonegawa, 2020; Medina and Viola, 2018).

Acetylcholine (ACh) is a key neuromodulator for learning and memory. It is also involved in arousal, attention, and plasticity (Picciotto et al., 2012). ACh acts through metabotropic

muscarinic (mAChRs) or ionotropic nicotinic receptors (nAChRs). mAChRs were not object of study in this review, but the reader is referred to recent articles addressing their role in memory processing (Fernández de Sevilla et al., 2021; Fuenzalida et al., 2021). Among ionotropic nAChRs, the α7 subtype is one of the most prominent in the central nervous system (CNS). The α7 nAChR subtype is highly expressed in cortical and limbic areas of the mammalian brain, where it is expressed in neurons (presynaptically and postsynaptically), and in no neuronal cells (Castro and Albuquerque, 1995; Fabian-Fine et al., 2001). Particularly important is the role of α7 nAChR in controlling the release of glutamate and dopamine in cortical and hippocampal nerve terminals (Cheng and Yakel, 2014; Dickinson et al., 2008; Koukouli and Maskos, 2015; Quarta et al., 2009). This receptor has the highest calcium permeability compared with other nAChRs subtypes, which make α7 nAChR subtype a key player in plasticity processes, such as long-term potentiation (LTP), and then, in learning and memory (Koukouli and Changeux, 2020). Indeed, activation of α7 nAChR facilitates LTP at the hippocampal-prefrontal cortex synapses in vivo (Stoiljkovic et al., 2016) and suppresses LTP induction in hippocampal slices (Nakauchi and Sumikawa, 2014). These contradictory findings also highlight the need to deepen the investigation of cellular and molecular mechanisms induced by the activation of α7 nAChRs.

α7 nAChRs has been implicated in disorders associated with memory impairment such as Alzheimer's disease (AD), schizophrenia and substance use disorder (Ballinger et al., 2016; Koukouli and Changeux, 2020; Picciotto et al., 2012). Thus, α7 nAChRs are a pharmacological target of high therapeutic interest. In this article, we first reviewed cholinergic pathways in the CNS and potential mechanisms which might be associated with α7 nAChRs activation. Given the important role of α7 nAChRs in healthy individuals and their involvement in

several neurological disorders, the main goal of this review was to analyze the described role of α7 nAChRs in selected brain regions on different memory stages and its implication in neurological disorders.

2. Cholinergic pathways in the central nervous system

In the CNS, there are three primary groups of cholinergic neurons: 1) those originating in ventral areas of the forebrain, which form the region known as basal forebrain (BF); 2) those originating in the pons, which form brain nuclei known as the pedunculopontine (PPT) and the laterodorsal tegmental (LTD) nuclei; and 3) small interneurons in different brain areas (Woolf, 1991). Most of the regions of the mammalian brain are innervated by one of those cholinergic pathways, and many of them express α7 nAChRs, as was recently reviewed by several authors (Bertrand and Wallace, 2020; Bloem et al, 2014a; Letsinger et al, 2022; Wills et al, 2022).

The BF innervates all cortical areas and limbic regions in the mammalian brain (Mesulam et al., 1983; Woolf, 1991). The BF is not a uniform structure, but rather is composed of several nuclei (Figure 1). The medial septum and the vertical limb of the diagonal band of Broca (VDB) comprise the anterior part of the BF and project mainly to the hippocampal formation and in a lesser extent to cortical areas including the retrosplenial cortex and the mPFC (Kondo and Zaborszky, 2016). Moreover, the BF projects to the neocortex in a layer-specific manner (Bloem et al., 2014a; Li et al., 2018; Obermayer et al., 2017). The horizontal limb of the diagonal band of Broca (HDB) and the nucleus basalis magnocellularis, which includes the substantia innominata, project to the neocortex and the amygdala (for references, see Solari and Hangya, 2018). A recent anatomical study elegantly showed in a whole brain scale

that BF cholinergic projections to the cortex are highly specific in neuronal types and connections (Gielow and Zaborszky, 2017). Additionally, by using genetic labeling and tomography-based whole-brain imaging technology, Li et al (2018) created a 3D atlas of the cholinergic system. BF cholinergic neurons were first recorded in behaving mice by Hangya et al (2015). Using optogenetics, they described that cholinergic neurons from the auditory-projecting nucleus basalis and prefrontal-projecting HDB nuclei respond to innate rewarding (water) and aversive (air puff) stimuli. Interestingly, cholinergic neurons respond stronger to an unexpected than an expected reward. This posits the BF as a hub for integrating bottom-up and top-down information. The complexity of the BF is also related to its different neuronal types. The BF consists of cholinergic, glutamatergic, and GABAergic neurons, which form reciprocal connections within the BF (Xu et al., 2015; Yang et al., 2014).

Pontine cholinergic nuclei comprise the PPT and the LDT nuclei, which innervate several structures throughout the brain (Figure 1). The PPT projects to the thalamus, the midbrain, the basal ganglia and also to the brainstem and spinal cord (Inglis and Winn, 1995; Oakman et al., 1995). LDT cholinergic neurons project to the ventral tegmental area and make excitatory synapses on meso-accumbens dopaminergic neurons (Bolton et al., 1993; Lammel et al., 2012; Omelchenko and Sesack, 2005). These synapses are involved in rewarding memory processing (Lammel et al., 2012). Additionally, PPT and LDT contain glutamatergic and GABAergic neurons (Clements and Grant, 1990; Wang and Morales, 2009).

Cholinergic interneurons (CINs) have been described primarily in striatal areas, where they represent 1% of striatal neurons (Bolam et al., 1984; Wilson et al., 1990). Despite representing a minor percentage of local neurons, CINs control local circuit activity which can significantly influence behavior. CINs receive glutamatergic inputs from thalamostriatal

and corticostriatal afferents and dopaminergic inputs from the midbrain (Ding et al., 2010; Thomas et al., 2000). Although firing tonically, CINs pause in response to rewarding or aversive stimuli, mediating associative learning (Apicella, 2002; Zhang and Cragg 2017). This pause was termed the "conditioned pause response". Acute silencing of cholinergic interneurons in the NAc by optogenetics disrupted cocaine-associated memory (Witten et al., 2010), highlighting their role in rewarding memory processing. Gabaergic projecting neurons of the VTA selectively innervate cholinergic interneurons in the NAc. This pathway has been proposed as a key player in associative learning (Brown et al., 2012). In cortical areas, CINs have also been described, where they represent about 1% of all cortical neurons (Eckenstein and Thoenen, 1983). Cortical CINs also express vasoactive intestinal peptide (VIP), indicating that they are a subclass of gabaergic VIP+ interneurons (Cauli et al., 1997; Eckenstein and Baughman, 1984). Cortical CINs have been less studied than striatal CINs. Recently, Obermayer et al (2019) reported that CINs directly excite interneurons and pyramidal neurons in the mPFC through the activation of nAChRs. These authors showed that mPFC CINs are involved in sustained attention.

3. Potential mechanisms associated with α7 nAChRs activation: insights from cellular and molecular mechanisms of memory.

In the last decades there have been significant advances in our understanding of the cellular and molecular mechanisms underlying synaptic plasticity and connectivity that subserve memory formation. Memory formation or consolidation involves different molecular events including the activation of several signaling cascades in specific brain regions (Izquierdo et al., 2006). Typically, activation of these cascades in the dorsal

hippocampus, that occur during the acquisition and formation of one-trial avoidance task in rats, is initiated by receptor activation including AMPA, metabotropic and particularly NMDA glutamate receptors, BDNF and monoamines receptors (see for references Izquierdo et al., 2006). Similarly to what happens with LTP induction and maintenance in the hippocampal CA1 region, the activation of NMDA receptors causes an increase of intracellular calcium concentration, followed by the activation of some second messengers and protein kinases (CaMKII/IV, PKA, ERKs, PKC, mTORC1). Several waves of transcription and translation occur thereafter (Medina et al., 2008; Katche et al., 2013) to regulate protein synthesis expression necessary for functional changes at selected synapses. It is important to mention here that different molecular cascades in different sites of the brain control memory consolidation of avoidance training (Izquierdo et al., 2006). Moreover, different molecular components and sequence of events occur after appetitive, spatial, recognition, or other aversive tasks (Kandel, 2001; Tonegawa et al., 2018).

Memory retrieval refers to the complex and active process of re-accessing previously stored information and its expression in the brain. There is a consensus that the neuronal activity and synapses that are reactivated when the animals are demanded to retrieve are those that have been changed through the molecular processes that underlie memory formation (Josselyn and Tonegawa, 2020; Frankland et al., 2019). Memory recall has a very short timescale compared to other memory processes that could take from hours to days or even weeks like cellular or systems consolidation (Tonegawa et al., 2018; Pereyra et al., 2021). The information about the molecular mechanisms of memory retrieval is surprisingly scarce and fragmentary (see Lopez et al., 2015). AMPA receptors and some protein kinases including ERK1/2 and mTORC1 are critically involved in the hippocampus and amygdala to retrieve aversive information (Lopez et al., 2015; Pereyra et al., 2018, 2021).

The cellular responses to α7 nAChR activation vary according to cell types and brain regions. For instance, α7 nAChR activation in hippocampal pyramidal neurons leads to LTP (Chen et al., 2006; Townsend et al., 2016), while α7 nAChR activation in GABAergic interneurons leads to long-term depression (Ji et al., 2001). In the prelimbic cortex, activation of these receptors induced inhibitory and excitatory effects on network integration and synaptic plasticity (Udakis et al., 2016). Moreover, contradictory findings were obtained when *in vivo* or *in vitro* conditions were applied. Indeed, activation of α7 nAChR facilitates LTP at the hippocampal-prefrontal cortex synapses in vivo (Stoiljkovic et al., 2016) and suppresses LTP induction in hippocampal slices (Nakauchi and Sumikawa, 2014).

The activation of α7 nAChRs leads to a net flux of calcium into neurons which induces the depolarization of the membrane (Dajas-Bailador and Wonnacott, 2004). This may trigger the activation of voltage-dependent calcium channels with the subsequent calcium influx raising cytoplasmic calcium levels even further. In addition, the increase in intracellular calcium levels may induce a process called calcium-induced calcium increase from two sources: the endoplasmic reticulum via the ryanodine receptors and IP3 receptors from intracellular stores (Tsuneki et al., 2000; Dajas-Bailador and Wonnacott, 2004; Shen and Yakel, 2009).

Therefore, the activation of α7 nAChRs may trigger a plethora of calcium-dependent intracellular processes (Figure 2). Depending on the cell type (Cheng et al., 2021) and the spatial-temporal pattern of intracellular calcium concentration several protein kinases important for synaptic plasticity and memory processing may be activated. CaMKII, PKC, PKA, and ERK1/2 are a few examples of them (Dajas-Bailador et al., 2002; Moriguchi, et al., 2020). On the other hand, modest increases in intracellular calcium concentration trigger

the activation of some phosphatases like calcineurin (Borroni and Barrantes, 2021). Based on some reports showing that α7 nAChRs interact with small G proteins like RhoA (King and Kabbani, 2016) which modulates cytoskeletal dynamics, Borroni and Barrantes (2021) postulated that α7 nAChRs may control dendritic spine shape and strength through modulation of actin dynamics.

In summary, there is still scarce direct evidence about the precise cellular and molecular mechanisms associated with α7 nAChRs activation (Cheng et al., 2021; Cheng and Yakel, 2014; 2015). However, some of the described molecular mechanisms of memory induced by the increase on calcium concentration might be related to those triggered by α7 nAChRs activation.

4. The role of α7 nAChRs in brain regions involved in memory processing

The homomeric α7 nAChR subtype is highly expressed in the hippocampus, the amygdala and the mPFC (Changeux, 2009; Gotti and Clementi, 2004; Wonnacott et al., 2005), three essential brain regions for memory processing. Due to their complex electrophysiology and rapid kinetic properties, it has been difficult to study their role in learning and memory processes. Functionally, nAChRs can exist in different conformational states (open, closed, or desensitized) and nAChRs agonists may induce a sustained desensitization of the target receptor (Couturier et al., 1990; Role, 1992). However, positive allosteric modulators which reinforce the endogenous cholinergic neurotransmission have been developed to solve this problem (Hurst et al., 2005).

Most pharmacological experiments assessing the role of nAChRs in memory processing have been performed by using agonist, antagonist or allosteric modulators via systemic administration (Palandri et al., 2021; Potasiewicz et al., 2021; Wang et al., 2020). However, α7 nAChRs are also expressed in peripheral cells, including lymphocytes, macrophages and endothelial cells (Ayala Peña et al., 2011; Sato et al., 1999; Zanetti et al., 2016). This could be a confounding factor in those experiments, considering that the relationship between the brain and peripheral systems as well as with the gut microbiota are increasingly relevant events that may influence cognitive functions (Chakrabarti et al, 2022). Thus, peripheral α7 nAChRs may affect in some way the results obtained. Fewer studies assessed the role of nAChRs in specific brain areas. In this section, we reviewed the role of mPFC, hippocampal and amygdalar α7 nAChRs in memory processing, assessed by different behavioral tasks (summarized in Table 1).

The role of α7 nAChRs in the mPFC: ACh phasic release in the mPFC is involved in the detection of environmental cues with rewarding and aversive emotional value (Gritton et al., 2016; Parikh et al., 2007). This mechanism is essential for acquiring and retrieving associative memories and guiding behavior. The mPFC is also involved in the consolidation of object recognition, a form of episodic memory (Tuscher et al., 2018), although the underlying mechanisms are not fully understood. α7 nAChRs are expressed through the mPFC in a layer-specific manner (Bloem et al., 2014b; Poorthuis et al., 2013), where they mediate ACh function. In this section, we summarize different types of memory tasks which were recently used to assess the role of prefrontal α7 nAChRs in memory processing (Table 1).

Trace fear conditioning is a behavioral model for studying aversive associative memory, where a time gap is introduced between the end of the conditioned stimulus (CS) and the start of the unconditioned stimulus (US). This behavioral model is useful for evaluating the mental representation of the CS which the brain needs to form after the CS has ended. The mPFC and the hippocampus are involved in this process (Gilmartin and Helmstetter, 2010; Han et al., 2003; Raybuck and Gould, 2010; Runyan et al., 2004). As shown by the group of Gould, the infusion of the α7 nAChR selective antagonist methyllycaconitine (MLA) in the mPFC before the retention test decreased the contextual fear response (Raybuck and Gould, 2010), describing a role for these receptors in fear conditioning memory retrieval. In addition, Miguelez-Fernández et al (2021) found no effect of mPFC MLA administration on trace fear conditioning retrieval. However, this discrepancy is likely related to the difference in the rodent model and MLA concentration used by those researchers. Miguelez-Fernández et al (2021) showed that prefrontal cortical α7 nAChRs are involved in trace fear conditioning acquisition in an age-dependent manner. By using MLA, these authors found a decrease of freezing behavior during conditioning in adults but not in adolescent rats, when MLA was infused in the mPFC before the conditioning session. Also only in adult rats, mPFC infusion of MLA enhanced the level of freezing response during extinction, which was suggested to be mediated by a disinhibition process (Miguelez Fernández et al., 2021), although more research is needed to clarify the meaning of those results.

Associative memories between rewarding effects of drugs of abuse and the context in which they are consumed are critical for the development of substance use disorder (Berke and Hyman, 2000). These memories are well studied with the conditioning place preference (CPP) model (Tzschentke, 2007). By using this model and a pharmacological approach in rats, prefrontal α7 nAChRs were found to be essential for the acquisition and retrieval of

cocaine-associated memory, but not for its consolidation (Pastor et al., 2021). Following extinction, drug-cue associative memory can be reinstated by the exposure to a subthreshold dose of the drug. With this approach, Wright et al (2019) found no involvement of prefrontal α7 nAChRs in morphine-associated memory reinstatement.

Novel object recognition test is based on the rodents´ innate preference for novelty, which makes them spend more time exploring a novel object than a familiar one. This test is used for studying episodic memory in rodents (Dere et al., 2007). Nicotine administration increases the acquisition of object recognition memory in mice, an effect blocked by the prefrontal infusion of nAChRs antagonists, including the α7 subtype (Esaki et al., 2021). Thus, prefrontal α7 nAChRs are also involved in the acquisition of episodic memory.

The role of α7 nAChRs in the hippocampus: nAChRs are involved in NMDA-independent LTP in the hippocampus (Griguoli et al., 2013; Nicholson and Kullmann, 2021). Pharmacological studies showed that hippocampal α7 nAChRs are involved in working memory (Nott and Levin, 2006) and in rewarding and aversive memory processing (Table 1). Regarding the acquisition of aversive memories, nicotine has been shown to increase trace and contextual fear conditioning in a dose-dependent manner. However, this effect was attributed to non-α7 nAChRs activation in the dorsal hippocampus (Raybuck and Gould, 2010). In contrast, nicotine systemic administration along with blocking α7 nAChRs in the ventral hippocampus before training enhanced contextual fear conditioning (Kenney et al., 2012), suggesting that α7 nAChRs are involved in nicotine-induced modulation of fear memory acquisition. Following storage, retrieval may labilize a memory, which can be extinguished or re-stabilized by a process called reconsolidation (Przybyslawski and Sara, 1997). In the dorsal

hippocampus, α7 nAChRs activation was necessary for aversive memory reconsolidation in an inhibitory avoidance task (Blake et al., 2013; Boccia et al., 2010). Hippocampal α7 nAChRs are also involved in rewarding memory processing. As was shown in a CPP task, the reinstatement of morphine-associated memory following extinction requires the activation of α7 nAChRs in the ventral hippocampus (Wright et al., 2019).

The role of α7 nAChRs in the amygdala: The amygdala receives cholinergic inputs from brainstem nuclei and the BF (Woolf, 1991; Woolf and Butcher, 1982), and these two pathways were recently suggested to drive opposing learning behaviors (Aitta-aho et al., 2018). The basolateral amygdala (BLA) is critical for associating environmental cues with appetitive or aversive stimuli (LeDoux et al., 1990). Cholinergic tone in the BLA contributes to associative learning in a fear conditioning paradigm, by inducing synaptic plasticity in cortical afferents (Jiang et al., 2016). α7 nAChRs were described in the amygdala, both in glutamatergic neurons and gabaergic interneurons, where they can increase or decrease their activity depending on which subregion of the amygdala is being analyzed (Klein and Yakel, 2006; Pidoplichko et al., 2013). Amygdalar α7 nAChRs were first found to modulate working memory (Addy et al., 2003), although their role in memory processing has not been extensively studied. In rats exposed to morphine, a conditioned place aversion (CPA) can be precipitated with the opiate antagonist naloxone. This behavior was decreased by the infusion of an agonist of α7 nAChRs in the central amygdala (Ishida et al., 2011). Moreover, naloxone-precipitated CPA was inhibited by intra-amygdala administration of nicotine, and this effect was reversed by the antagonism of α7 nAChRs in the central amygdala (Ishida et

al., 2011). These results suggest that the inhibition of α7 nAChRs in the central amygdala may promote aversive behaviors.

Other brain areas involved in memory processing are also modulated by nAChRs. In the ventral tegmental area, α7 nAChRs are required for long-term memory persistence of a fear memory, an effect which seems to depend on hippocampal dopamine signaling (Lima et al., 2013). The habenula is an epithalamic complex which consists of different subnuclei with diverse neuronal populations. For example, the interpeduncular nucleus receives strong cholinergic innervation from the medial habenula through the fasciculus retroflexus (Aizawa et al., 2012). This habenula-interpeduncular pathway is involved in drug-addiction, fear memory and depression (Kobayashi et al., 2013; Xu et al., 2018). A large diversity of nAChR subunits has been described in the habenula-interpeduncular circuit (Wills et al., 2022), including functional α7 nAChRs in GABAergic neurons of the interpeduncular nucleus (Jin and Drenan, 2022). However, the function of these neurons is not clear yet. Future studies on the role of α7 nAChRs in the habenula-interpeduncular pathway would add to the knowledge of pathophysiology of memory and emotional disorders.

It is interesting to mention here that α7 nAChRs are also expressed in glial cells, although the knowledge about their function in memory processing is only recently starting to emerge. It was shown by an *in vitro* study that α7 nAChRs activation on astrocytes induced the recruitment of glutamatergic AMPA receptors in postsynaptic hippocampal neurons (Wang et al., 2013). These results suggest that glial α7 nAChRs may convert silent synapses to functional ones by promoting the insertion of AMPA receptors in the postsynaptic membrane. In the auditory cortex, Zhang et al (2021) found that aversive sensory stimulation activates α7 nAChRs in a subpopulation of astrocytes. These authors showed

that conditional genetic deletion of α7 nAChRs in astrocytes affected fear memory persistence.

From what is observed in these preclinical studies reviewed here, it can be deduced that knowledge of the α7 nAChR function in memory processing is scarce and fragmented. Moreover, a limitation of the studies reviewed here is that they did not consider that different cognitive aspects (e.g., aversive and reinforcing memories) may involve overlapping brain regions. It seems not to constitute a coherent scenario that the available evidence can serve as a conceptual basis for understanding the pharmacological application of α7 nicotinic agents as therapeutic tools in mental illnesses like schizophrenia (Letsinger et al., 2022; Recio-Barbero et al., 2021; but see below in Section 5 the role of α7 nAChR as a promising target for the treatment of AD).

5. α7 nAChR as a pharmacotherapy tool in memory deficits and cognitive decline

Memory processing is impaired in AD and other neurological disorders such as schizophrenia (Khan et al., 2014). As we reviewed in Section 2, cholinergic pathways from the BF to the cortex and the hippocampus are important for memory processing and their impairment is associated with cognitive decline (Kuhl et al., 1996). Thus, the cholinergic system has been postulated to be responsible for the cognitive decline associated with AD and other neurological disorders (Hampel et al., 2018; Koukouli and Changeux, 2020). In this sense, the study of pharmacological strategies directed to modify cholinergic tone -such as anticholinesterase inhibitors- have dominated preclinical and clinical studies in the AD field.

Although extensive research was intended to prevent cognitive decline associated with AD, there remains no effective treatment. In the last few years, a more specific approach targeting nAChRs has evolved. α7 nAChRs are localized to astrocytes, microglia, macrophages, and endothelial cells. In this way, cholinergic inputs via α7 nAChRs may regulate pro-inflammation states and several humoral factors controlling cerebral blood flow (Disney and Higley, 2020). Considering that neuroinflammation was postulated as a pathological mechanism in AD (Kinney et al., 2018), several studies attempt to point out that α7 nAChRs may be a key element in AD pathophysiology (Hoskin et al., 2019). Moreover, α7 nAChRs influence the expression of glutamate receptors and neurotrophic factors, making them a key element for targeting cognitive decline in AD (Cai et al., 2022; Medeiros et al., 2014; Roberts et al., 2021; Wei et al., 2022).

Beta-amyloid (Aβ) has been recognized as one of the hallmarks of AD (Selkoe and Hardy, 2016). Despite existing evidence about molecular interaction between Aβ and α7 nAChRs (Wang et al., 2000), contradictory results have been reported about the contribution of α7 nAChRs to the pathophysiology of AD (Dziewczapolski et al., 2009; Hernandez et al., 2010). Roberts et al (2021) showed in cell culture that selective co-activation of α7 and α4β2 nAChRs reversed Aβ-induced reduction in AMPA receptor phosphorylation and surface expression in hippocampal neurons, and Aβ-induced disruption of LTP. Additionally, these authors provided direct molecular evidence for selective interaction of Aβ with α7 and α4β2 nAChR subtypes. A recently described heteromeric α7β2 nAChR subtype has unique functional characteristics (Liu et al., 2009; Nielsen et al., 2018; Wu et al., 2016). Although their role has not been studied in detail, they were found to interact with Aβ in cholinergic neurons (George et al., 2021). Thus, Aβ may disrupt hippocampal synapses by modulating nAChRs function.

For modeling certain aspects of AD, Cai et al (2022) used intracerebroventricular administration of Aβ peptide to produce deposits in the hippocampus within 14 days of injection. These authors studied the effects of a Ras GTPase inhibitor on the impaired spatial memory and synaptic plasticity which is present in that rodent model. In addition to beneficial effects on spatial memory, they found an enhanced α7 nAChRs cell surface expression. Moreover, Ras GTPase inhibitor enhanced hippocampal brain-derived neurotrophic factor (BDNF) concentration, which was reversed by the antagonism of α7 nAChRs (Cai et al., 2022). In line with this research, a mice model of perioperative cognitive disorder was used for assessing the effects of α7 nAChRs modulation on a hippocampal-dependent spatial learning task (Wei et al., 2022). Following an aseptic laparotomy, these authors found a decrease of BDNF protein expression in the hippocampus, which was reversed by α7 nAChRs activation and promoted by their inhibition. Additionally, in a mice model of chronic hypoxia-induced cognitive dysfunction, systemic activation of α7 nAChRs improved cognitive impairment and increased BDNF protein expression in the hippocampus (Shen et al., 2021). These findings suggest that α7 nAChR-induced increase in BDNF may be linked to pro-cognitive effects of α7 nAChR activation. In summary, although cognitive improvement promoted by α7 nAChRs might be an indirect effect following the decrease on inflammation or the increase on neurotrophic factors, the evidence supports that α7 nAChRs are promising pharmacological targets for neurological disorders such as AD (Greenfield et al., 2022). Moreover, the role of α7 nAChRs in impaired cognition may be related to their involvement in attention and not only in memory processing (Ballinger et al., 2016). Even though attention is required for memory encoding (Muzzio et al, 2009), rodent studies analyzed in this review did not rule out attentional effects of drugs used for targeting α7 nAChRs.

Another neurological disorder where cognitive impairment is a core clinical symptom is schizophrenia (Green et al., 2019). Preclinical studies have shown that α7 nAChR agonists, partial agonists, and positive allosteric modulators have pro-cognitive effects in a variety of animal models (Terry and Callahan, 2020; Unal et al., 2021; Potasiewicz et al., 2021). Despite extensive preclinical and clinical research assessing the role of nAChRs as key elements on the pathophysiology of cognitive deficits in schizophrenia, it seems that there is no strong evidence to consider α7 nAChR agonists as add-on treatment to antipsychotics to improve cognition in schizophrenia (reviewed by Koola, 2021; Recio-Barbero et al, 2021; Letsinger et al, 2022). A combination of several factors has been put forward to explain why α7 nAChR agents have pro-cognitive effects in preclinical studies but fail to improve cognition in clinical trials. For instance, polypharmacy and drug exposure history are not properly addressed and chronicity of the illness is not considered in preclinical rodent models (Bertrand and Terry, 2018; Terry and Callahan, 2020).

6. Concluding remarks and future perspectives

The study of mPFC, hippocampus and amygdala have dominated the assessment of several neurotransmission systems and their role in different types of memories. α7 nAChRs are known players in plasticity processes which are essential for learning and memory. However, from the information reviewed here, it is evident the paucity of information about the role of α7 nAChRs in specific brain regions involved in memory processing. More studies are needed to clarify the involvement of these receptors in different stages and types of memories. For instance, assessing brain overlapping regions which may be involved in different aspects of cognition, mapping their activation by the assessment of c-fos

expression, by calcium imaging or miniscope techniques, and exploring what are the pre- and postsynaptic signaling pathways and targets that calcium influx via α7 nAChRs activates or modulates would add valuable information about the cellular and molecular mechanisms associated with α7 nAChRs activation. Additionally, a deep knowledge about the crosstalk between α7 nAChRs and other neurotransmission systems is still lacking. It is important to note that nAChRs are highly expressed in presynaptic terminals, modulating other neurotransmitter release, such as dopamine or glutamate (Cheng and Yakel, 2015; Figure 2) For example, in the mPFC α7 nAChRs activation increases dopamine release (Livingstone et al., 2009). Moreover, a new mechanism of cholinergic modulation of dopamine release has been recently described in the striatum (Liu et al., 2022), where the activation of nAChRs in dopaminergic axons promotes action potentials independently of somatodendritic integration. Thus, studying different mechanisms of interaction between cholinergic and other neurotransmission systems would be of interest for deeper understanding on nAChRs function in memory processing and cognition, and improve therapy strategies for cognitive deficits.

Conflict of Interest

The authors declare no conflict of interest. The funders had no role in data collection and interpretation, or the decision to submit the work for publication.

Data Availability Statement

Data sharing is not applicable as no original data were created or analyzed in this study.

CRediT authorship contribution statement

Verónica Pastor: Conceptualization, Writing - original draft, Writing - review & editing.

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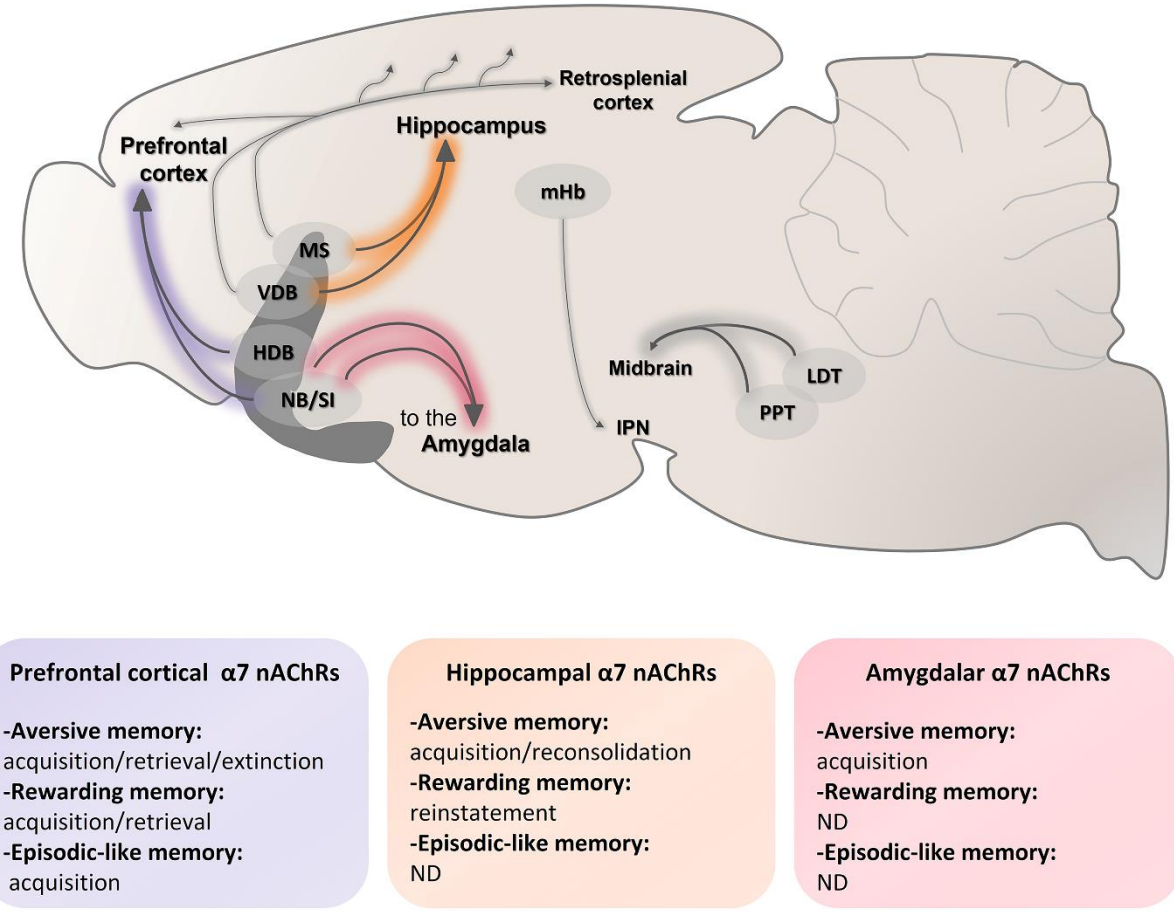

Figure 1: Schematic representation of cholinergic pathways in the rodent brain and α7 nAChRs involvement in memory processing. This figure depicts a simplified scheme of cholinergic pathways in the rodent brain, where wider arrows represent principal connections (see the text for details). The lower panel summarizes the studied role of α7 nAChRs in the medial prefrontal cortex, the hippocampus and the amygdala, highlighting the memory types and stages which were described in the literature. HDB: horizontal limb of the diagonal band of Broca; IPN: interpeduncular nucleus; LDT: laterodorsal tegmental nucleus; mHb: medial habenula; MS: medial septum; NB: nucleus basalis magnocellularis; ND: non determined; PPT: pedunculopontine nucleus; SI: substantia innominata; VDB: vertical limb of the diagonal band of Broca.

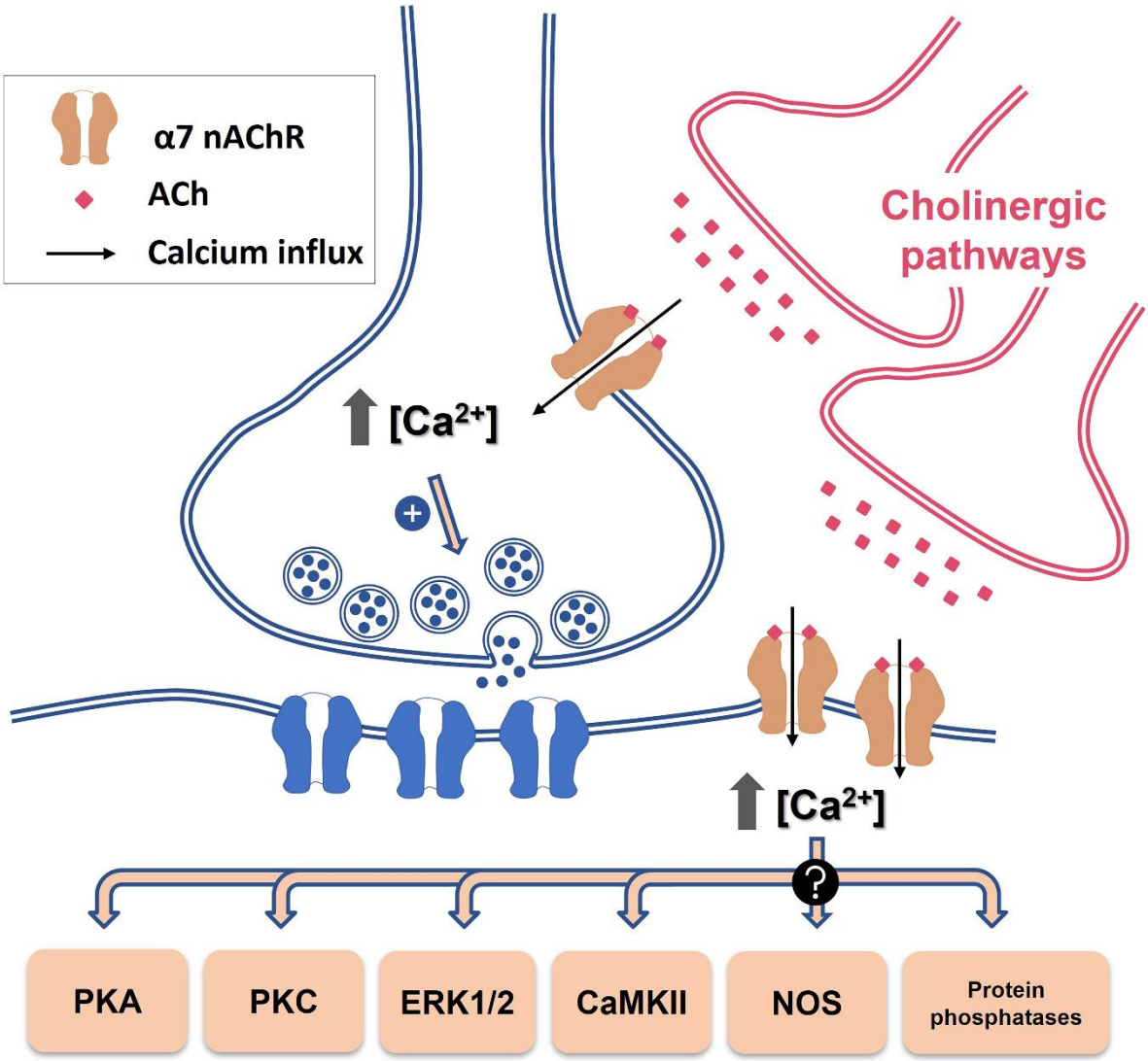

Figure 2: Schematic representation of potential mechanisms underlying α7 nAChR-induced modulation of synaptic function. Presynaptic α7 nAChRs are highly permeable to calcium and thus facilitate the calcium-dependent release of many neurotransmitters (e.g., dopamine or glutamate). Postsynaptic nAChRs may mediate the calcium-dependent activation of different signaling pathways, including -but not limited to- those involving protein kinase A (PKA), protein kinase C (PKC), extracellular signal-regulated kinase (ERK), calcium/calmodulin-dependent kinase II (CaMKII); nitric oxide synthase (NOS); or protein phosphatases.

Table 1: Behavioral effects of α7 nAChRs modulation on different memory types and stages in adult rodents. CeA: central nucleus of the amygdala, CPA: conditioning place aversion, CPP: conditioning place preference, dHipp: dorsal hippocampus, mPFC: medial prefrontal cortex, vHipp: ventral hippocampus.

	Rodent model	Memory stage assessed						Brain area	α7 nAChRs modulation	Behavioral effect
		Acquisition	Consolidation	Retrieval	Extinction	Reconsolidation	Reinstatement			
Raybuck and Gould, 2010	Male C57BL/6J mice	Cued-Trace fear conditioning						mPFC	antagonist	increase
Raybuck and Gould, 2010	Male C57BL/6J mice			Cued-Trace fear conditioning				mPFC	antagonist	decrease
Raybuck and Gould, 2010	Male C57BL/6J mice			Context-Trace fear conditioning				mPFC	antagonist	decrease
Wright et al, 2019	*Male Wistar rats*						*Reinstatement of morphine CPP*	*mPFC*	*antagonist*	*no effect*
Miguelez-Fernandez et al, 2021	Male SD rats	Trace fear conditioning						mPFC	antagonist	decreased freezing during conditioning
Miguelez-Fernandez et al, 2021	*Male SD rats*			*Trace fear conditioning*				*mPFC*	*antagonist*	*no effect*

Miguelez-Fernandez et al, 2021	Male SD rats				Trace fear conditioning			mPFC	antagonist	increased freezing during extinction
Pastor et al, 2021	Male Wistar rats	Cocaine CPP		Cocaine CPP				mPFC	antagonist	decrease
Pastor et al, 2021	*Male Wistar rats*		*Cocaine CPP*					*mPFC*	*antagonist*	*no effect*
Esaki et al, 2021	Male C57BL/6J mice	Novel object recognition						mPFC	antagonist	decrease of nicotine-induced enhancement
Boccia et al, 2010	Male CF-1 mice					Inhibitory avoidance		dHipp	antagonist	decrease
Kenney et al, 2012	Male C57BL/6J mice	Contextual fear conditioning						vHipp	antagonist + systemic nicotine	increase
Kenney et al, 2012	*Male C57BL/6J mice*	*Contextual fear conditioning*						*vHipp*	*antagonist*	*no effect*
Kenney et al, 2012	*Male C57BL/6J mice*			*Contextual fear conditioning*				*vHipp*	*antagonist*	*no effect*
Wright et al, 2019	Male Wistar rats						Reinstatement of morphine CPP	vHipp	antagonist	increase

Wright et al, 2019	*Male Wistar rats*		*Reinstatement of morphine CPP*	*dHipp*	*antagonist*	*no effect*
Ishida et al, 2011	Male SD rats	Naloxone-precipitated morphine CPA		CeA	agonist	decrease

Table 1: Behavioral effects of α7 nAChRs modulation on different memory types and stages in adult rodents. CeA: central nucleus of the amygdala, CPA: conditioning place aversion, CPP: conditioning place preference, dHipp: dorsal hippocampus, mPFC: medial prefrontal cortex, vHipp: ventral hippocampus.

Graphical abstract text

Cholinergic pathways through acetylcholine receptors actively participate on memory modulation. α7 nicotinic acetylcholine receptors are involved in different memory types and stages. They may be promising pharmacological targets for some neurological disorders where memory deficits are present.