Review

Nicotinic ACh Receptors in the Hippocampus: Role in Excitability and Plasticity

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Abstract

Introduction: The nicotinic ACh receptors (nAChRs) are in the cys-loop family of ligand-gated ion channels. They are widely expressed throughout the brain, including in the hippocampus where they are thought to be involved in regulating excitability, plasticity, and cognitive function. In addition, dysfunction in hippocampal nAChRs has been linked to a variety of neurological disorders and diseases, including Alzheimer's disease, schizophrenia, and epilepsy. In order to understand how to treat nAChR-related disorders and diseases, it is critical to understand how these receptors participate in normal brain function; this entails not only understanding the biophysical properties of ion channel function and their pattern of expression but also how these receptors are regulating excitability and circuit behavior.

Discussion: The primary cholinergic input to the hippocampus comes from the medial septum and diagonal band of Broca; however, the mechanistic details are unknown of how activation of cholinergic receptors, either through exogenous nAChR ligands or the activation of endogenous acetylcholine release, regulates hippocampal network activity. This entails direct study of the excitatory and inhibitory neuronal networks, as well as the role of nonneuronal cells, in regulating hippocampal function.

Conclusions: Here, I will review the latest work from my laboratory in which we have attempted to do just that, with the overall goal of learning more about the role of the hippocampal nAChR in synaptic plasticity.

Introduction

The nicotinic ACh receptors (nAChRs) are in the cys-loop family of ligand-gated ion channels. They are widely expressed throughout the brain, including in the hippocampus where various subtypes of nAChRs are thought to be involved in regulating excitability, plasticity, and cognitive function (Hasselmo, 1999; Jones, Sudweeks, & Yakel, 1999; Levin, 2002; Reis et al., 2009). Furthermore dysfunction in hippocampal nAChRs has been

linked to a variety of neurological disorders and diseases, including (but not limited to) Alzheimer's disease (AD), schizophrenia, and epilepsy (Dani, 2000; Eşkazan et al., 1999; Terry & Buccafusco, 2003; Tizabi, 2007). Thus far, six α (2–7) and three β (2–4) nAChR subunits have been found to be expressed in the mammalian brain, with the most prevalent subtypes of functional nAChRs in the hippocampus being comprised of the $\alpha 7$ and $\alpha 4\beta 2$ subtypes (Alkondon & Albuquerque, 1993, 2004; Jones & Yakel, 1997; Sargent, 1993; Sudweeks & Yakel, 2000; Wada et al., 1989).

Nicotine is the major compound in tobacco that affects memory and cognition (Dajas-Bailador & Wonnacott, 2004; Davis, Kenney, & Gould, 2007; McGehee & Role, 1996; Peeke & Peeke, 1984; Potter & Newhouse, 2008; Timmermann et al., 2007). Compounds acting on nAChRs are being developed for treating neurological diseases and disorders, including AD (Levin, McClernon, & Rezvani, 2006; Levin & Rezvani, 2002), Parkinson's disease (Park et al., 2007; Quik, Bordia, et al., 2007; Quik, Cox, et al., 2007; Villafane et al., 2007), attention-deficit hyperactivity disorder (Potter & Newhouse, 2008), schizophrenia (Tizabi, 2007), and epilepsy (Shin et al., 2007). In order to understand how to treat nAChR-related disorders and diseases, it is critical to understand how these receptors participate in normal brain function. This entails not only understanding the biophysical properties of ion channel function and their pattern of expression but also how these receptors are regulating excitability and circuit behavior.

The primary cholinergic input to the hippocampus comes from the medial septum and diagonal band of Broca (MSDB), and the activation of both nAChRs and muscarinic ACh receptors (mAChRs) can initiate and sustain network oscillations important for cognitive function (Cobb & Davies, 2005; Dutar et al., 1995; Frotscher & Léránth, 1985; Lawrence, Grinspan, Statland, & McBain, 2006; Lawrence, Statland, Grinspan, & McBain, 2006; Léránth & Frotscher, 1987). In addition to the primary cholinergic input from the MSDB, there is also a significant gamma-aminobutyric acid (GABA)-ergic input. Hippocampal GABAergic interneurons, which express both nAChRs and mAChRs, can coordinate the activity of large numbers of principal cells. The phasic GABAergic input, in concert with the tonic cholinergic excitation of interneurons, is thought to induce

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rhythmic inhibition of pyramidal cells (Buzsaki, 2002; Freund & Antal, 1988; Griguoli & Cherubini, 2011; Jones et al., 1999; Stewart & Fox, 1990; Tóth, Freund, & Miles, 1997). Additionally, inputs to the hippocampus from the entorhinal cortex (EC) are thought to regulate hippocampal theta rhythm (Buzsaki, 2002). Nevertheless, it is unclear precisely how both mAChRs and nAChRs, working in concert, can modulate the oscillatory properties of neurons within the hippocampus. Understanding how cholinergic receptor signaling regulates hippocampal network activity is critical since dysregulation of normal oscillations may induce hyperexcitability, leading to both seizures (Bertrand, Weiland, Berkovic, Steinlein, & Bertrand, 1998; Damaj, Glassco, Dukat, & Martin, 1999; Turski, Ikonomidou, Turski, Bortolotto, & Cavalheiro, 1989) and cognitive deficits linked with AD (Fodale, Quattrone, Trecroci, Caminiti, & Santamaria, 2006).

The nAChRs (in particular the $\alpha 7$ subtype) are thought to be participating in various mechanisms of neuroprotection (Dineley, 2007; Parri, Hernandez, & Dineley, 2011; Shen & Yakel, 2009). For example, the nicotine-mediated neuroprotection against either glutamate excitotoxicity or the β -amyloid (A β) peptide (associated with AD) is thought to be acting through the $\alpha 7$ nAChR (Dajas-Bailador, Lima, & Wonnacott, 2000; Jonnala & Buccafusco, 2001; Kihara et al., 1997; Stevens, Krueger, Fitzsimonds, & Picciotto, 2003; Svensson & Nordberg, 1999). Interestingly, there may also be a role for the $\alpha 7$ nAChR in inflammation in the brain as in the periphery (Shen & Yakel, 2009). In the brain (and in particular the hippocampus), nicotine or ACh activation of the $\alpha 7$ nAChR blocked the release of proinflammatory cytokines (Shytle et al., 2004; Tyagi, Agrawal, Nath, & Shukla, 2010), while in the periphery, ACh activation of the $\alpha 7$ nAChR inhibits cytokine synthesis (Wang et al., 2003). Nonneuronal cells in the nervous system have also been reported to express nAChRs. Astrocytes are the predominant glial cell in the mammalian brain (Agulhon et al., 2008). Glial cells express a wide variety of neurotransmitter receptors and ion channels, including the $\alpha 7$ nAChR subtype (Sharma & Vijayaraghavan, 2001; Shytle et al., 2004; Vélez-Fort, Audinat, & Angulo 2009). In addition, in the brain, astrocytes are also known to participate in synaptic signaling and plasticity (Agulhon et al., 2008; Araque et al., 2002; Fiocco, Agulhon, & McCarthy, 2009). Therefore, astrocytes may be playing a role in AD and/or neuroprotection that depend in part on the function of the $\alpha 7$ nAChRs. However, it should be noted that nicotine, particularly in developing fetuses and children, may be neurodevelopmentally harmful and produce AD-like symptoms (Swan & Lessov-Schlaggar, 2007).

It is critical that we understand in much more detail the relationships between the excitatory and inhibitory neuronal networks, as well as the role of nonneuronal cells, in regulating hippocampal function if we are to understand the role that the nAChRs are having in regulating hippocampal excitability, plasticity, and their role in disease.

Role of Nicotine in Regulating Hippocampal Excitability and Plasticity

Although nicotine has been known to enhance cognitive function for decades, the mechanisms whereby cholinergic receptor

activation can influence hippocampal neuronal networks are far from understood. To gain more insights into the role that nicotine (via activation of nAChRs) is playing in the intact hippocampal circuit, and to understand which regions in the hippocampal complex are responsible for the initiation and spreading of information involving cholinergic receptors during smoking, we have utilized voltage-sensitive dye imaging techniques in combination with patch-clamp and field recordings to investigate spatial-temporal aspects of cholinergic responses in the hippocampal complex (Tu, Gu, Shen, Lamb, & Yakel, 2009).

The hippocampal formation (HF), which is critical to memory and cognition and mediates the influences of nicotine on memory (Blozovski, 1983, 1985; Davis et al., 2007; Izquierdo et al., 2008), can be divided up into four main subregions (Amaral & Witter, 1995): the dentate gyrus, the hippocampal proper (including *Cornu Ammonis* [CA1], CA2, and CA3 regions), the subicular complex (including the subiculum [Sb]), and the EC (including Layers I–VI). Previously the main focus of investigation has centered on the hippocampal proper and dentate regions (Dani & Bertrand, 2007; Jones & Yakel, 1997) because of the known importance of these regions in learning and memory (Chen et al., 2006; Hasselmo, 2005; Hunsaker, Lee, & Kesner, 2008; Izquierdo et al., 2008; Lee, Hunsaker, & Kesner, 2005; Li & Chao, 2008) and the ability of nicotine to induce synaptic potentiation (Fujii, Ji, Morita, & Sumikawa, 1999; Gray, Rajan, Radcliffe, Yakehiro, & Dani, 1996; He, Deng, Zhu, Yu, & Chen, 2003; Hunter, de Fiebre, Papke, Kem, & Meyer, 1994; Matsuyama, Matsumoto, Enomoto, & Nishizaki, 2000; Sawada, Yamamoto, & Ohno-Shosaku, 1994). However, whether nAChRs were expressed in either the subicular complex or EC had been previously unknown, although both regions have critical roles in memory functions themselves (Blozovski, 1983, 1985; Burhans & Gabriel, 2007; Deadwyler & Hampson, 2004; Harich, Kinfe, Koch, & Schwabe, 2008; Izquierdo et al., 2008; Martin-Fardon, Ciccocioppo, Aujla, & Weiss, 2007; O'Mara, Commings, Anderson, & Gigg, 2001; Van Cauter, Poucet, & Save, 2008).

Therefore, we investigated how the slow bath application of nicotine (to emulate systematic administration occurring during smoking or while using nicotine patches) affected network activity in entorhino-hippocampal slices (Tu et al., 2009). We found that a concentration of nicotine comparable to that achieved through smoking (i.e., as low as 100 nM) depolarized neurons in the deep EC cortical layers (Layer VI) via activation of the $\alpha 4\beta 2$ subtype of non- $\alpha 7$ nAChRs. Subicular neurons, which project to the Layer VI of the EC, also contain functional non- $\alpha 7$ nAChRs that were activated by the bath-applied nicotine. Interestingly both of these nAChR-expressing excitatory postsynaptic current (ECVI) and Sb groups of neurons were primarily glutamatergic. Furthermore, when we recorded from ECVI neurons directly (utilizing patch-clamp techniques) and evoked glutamatergic EPSCs (eEPSCs) to the ECVI neurons by stimulating the Sb near the CA1 region, a low dose of nicotine (100 nM) enhanced synaptic transmission by enhancing the amplitude of these eEPSCs. This low dose of bath-applied nicotine also enhanced synaptic plasticity in the ECVI neurons since it was able to convert short-term potentiation (STP) that was induced by tetanus stimulation of the Sb to long-term potentiation (LTP). Since LTP is thought to be a cellular form of learning and memory, this nicotine-induced plasticity could help in understanding the procognitive effects of nicotine. In addition the ability of nicotine to enhance synaptic transmission and plasticity was through action

on both $\alpha 7$ and non- $\alpha 7$ nAChRs. Therefore, neurons in deep layers of the EC not only contain diverse subtypes of functional nAChRs, but that these neurons may also be important regulators of hippocampal excitability and plasticity during smoking.

In the HF, diverse nAChR subtypes are mainly expressed on GABAergic interneurons (Alkondon & Albuquerque, 2001; Fayuk & Yakel, 2004, 2005; Frazier, Buhler, et al., 1998; Frazier, Rollins, et al., 1998; Jones & Yakel, 1997; Khiroug, Giniatullin, Klein, Fayuk, & Yakel, 2003; Klein & Yakel, 2005; McQuiston & Madison, 1999; Sudweeks & Yakel, 2000; Welsby, Rowan, & Anwyl, 2007), although there is some evidence of expression by glutamatergic neurons (Fabian-Fine et al., 2001; Gray et al., 1996; Tu et al., 2009). It is notable, therefore, that we found that the neurons expressing the highest density of $\alpha 4\beta 2$ nAChRs in the HF that were depolarized by bath-applied nicotine were on the ECVI and Sb neurons and therefore, outside of the hippocampal proper and dentate regions. It should also be noted that while these neurons also express functional $\alpha 7$ receptors, these receptors were desensitized by the slow bath application of nicotine and thus did not contribute to the depolarizations observed in this study.

Role of Endogenous Cholinergic Inputs in Regulating Hippocampal Plasticity

Both the nAChRs and mAChRs have previously been associated with multiple forms of plasticity (Cobb & Davies, 2005; Fujii & Sumikawa, 2001; Ji, Lape, & Dani, 2001; Maylie & Adelman, 2010; McGehee, 2002). For example, for the $\alpha 7$ nAChR subtype, the activation of these receptors with exogenous ligands in the CA1 and dentate gyrus regions enhanced synaptic plasticity (Fujii et al., 1999; Mann & Greenfield, 2003; Welsby, Rowan, & Anwyl, 2006; Welsby et al., 2007). Furthermore, in the hippocampus, $\alpha 7$ nAChRs on presynaptic terminals can increase the probability of producing LTP and can block STP and LTP in the pyramidal cells (Ji et al., 2001). The non- $\alpha 7$ nAChRs (i.e., $\alpha 4$ -containing receptors) are also involved in regulating hippocampal plasticity as described above in the EC (Tu et al., 2009). These data were consistent with the report that $\alpha 4$ -containing nAChRs contribute to LTP facilitation in the hippocampal perforant path (Nashmi et al., 2007). The mAChRs are also involved in regulating many forms of plasticity (Maylie & Adelman, 2010). For example, the activation of either pre or postsynaptic mAChRs can either enhance or reduce LTP in the hippocampus (Buchanan, Petrovic, Chamberlain, Marrion, & Mellor, 2010; Cobb & Davies, 2005; Leung, Shen, Rajakumar, & Ma, 2003; Ovsepian, Anwyl, & Rowan, 2004; Seeger et al., 2004).

We wanted to understand how the endogenous activation of cholinergic inputs to the hippocampus regulated or induced synaptic plasticity in the hippocampus since the vast majority of prior knowledge is derived from the use of exogenously applied receptor agonists or blockers. Using exogenous ligands, information about the timing and context of neurotransmitter action is usually lacking, information which is critical however for information processing and computation (Dan & Poo, 2004; Gradinaru et al., 2010; Silberberg, Wu, & Markram, 2004). For example, small shifts in the timing of the same glutamatergic

input could result in either LTP or long-term depression in the case of spike-timing dependent plasticity (Zhang, Tao, Holt, Harris, & Poo, 1998). In addition previous studies have also shown that the timing of exogenously applied acetylcholine (ACh) is important in modulating high frequency stimulation (HFS)-induced hippocampal synaptic plasticity (Ge & Dani, 2005; Ji et al., 2001), suggesting the potential capability of ACh in executing physiological functions with high temporal precision.

Therefore, we investigated (Gu & Yakel, 2011) how the activation of the endogenous cholinergic input pathway from the septum to the hippocampus, either electrically or by using the recently developed optogenetic approach that allows precise control of specific cholinergic input with high temporal precision (Tsai et al., 2009; Witten et al., 2010), could regulate hippocampal synaptic plasticity. As opposed to the previous findings that ACh only has modulatory effects on existing HFS-induced synaptic plasticity (Dani & Bertrand, 2007; Jerusalinsky et al., 1997; Kenney & Gould, 2008; Power, Vazdarjanova, & McGaugh, 2003), we found that activation of the cholinergic input to the hippocampus with single electrical or light pulses can directly induce different forms of hippocampal synaptic plasticity after several trials, depending on the input context in the hippocampus, with a timing precision in the millisecond range. For example, when the cholinergic input to the CA1 hippocampal region was activated 100 ms prior to activation of the Schaffer collateral (SC) glutamatergic pathway, this resulted in an $\alpha 7$ nAChR-dependent LTP that was likely due to a postsynaptic effect that required the activation of the NMDA receptor (NMDAR), the prolongation of the NMDAR-mediated calcium transients in the CA1 pyramidal cell spines, and finally synaptic insertion of the GluR2-containing AMPA receptors into these spines. In contrast when the cholinergic input was activated only 10 ms prior to the SC pathway, this resulted in an $\alpha 7$ nAChR-dependent short-term depression (STD) that was likely mediated primarily through the presynaptic inhibition of glutamate release. Lastly, if the cholinergic input was activated 10 ms after the SC pathway, this induced LTP that was dependent on the activation of the mAChR and was mostly likely due to a postsynaptic mechanism. Therefore, altering the timing of activation of the septal cholinergic input to the hippocampus induces three different forms of plasticity that depended solely on the timing of the input relative to the SC stimulation.

Cholinergic dysfunction has long been hypothesized to be a major cause of the cognitive deficit in AD (Bartus, Dean, Beer, & Lippa, 1982; Terry & Buccafusco, 2003). Since hippocampal $\alpha 7$ nAChRs have previously been shown to have a critical role in working and reference memory (Levin, 2002; Levin et al., 2009), and the cognitive deficits associated with AD may be related to dysfunction of the $\alpha 7$ nAChRs (Dineley, 2007; Jonnala & Buccafusco, 2001; Kihara et al., 2001; Parri et al., 2011), we tested whether the various forms of plasticity mentioned above were sensitive to exposure to the soluble oligomeric (rather than the fibrillar) form of A β peptide; the soluble form of A β peptide has been proposed to cause the synaptic and cognitive dysfunction in AD (Haass & Selkoe, 2007; Hsieh et al., 2006; Lue et al., 1999; McLean et al., 1999; Selkoe, 2002). We found that the $\alpha 7$ nAChR-dependent LTP and STD were both completely blocked in slices preexposed to a low dose (100 nM) of oligomeric A β , whereas the mAChR-mediated LTP required higher doses (1 μ M) for complete blockage (Gu & Yakel, 2011). These results

thus provide a mechanism for A β to impair cholinergic-related synaptic plasticity and potentially cognitive functions.

These data show that a novel physiologically relevant neural activity pattern can induce different forms of synaptic plasticity in the hippocampus. Furthermore, we have shown that synaptic plasticity in the hippocampus can be induced by an extrinsic input, which provides a mechanism to integrate information from extrinsic pathways and store it in local hippocampal synapses. Therefore, this mechanism is likely relevant to understanding learning and memory, which usually involves the precise coordination among multiple brain regions. These results have revealed the striking temporal accuracy of cholinergic transmission and the physiological neural activity patterns that can induce dynamic synaptic plasticity as a result of interactions among neural networks, which is fundamental to understanding the information computation and storage in learning and memory.

Summary

Ongoing and future studies, taking advantage of new and more relevant animal models of disease, with new advances in cutting-edge biological methodologies (such as optogenetics), will allow further in-depth analysis of brain circuits and how they function in normal brains and in the diseased state. This guarantees that new and exciting advances should be just around the corner.

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Declaration of Interests

The author declares no competing conflicts.

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