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A cog in cognition: How the α7 nicotinic acetylcholine receptor is geared towards improving cognitive deficits

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ABSTRACT

Cognition, memory, and attention and arousal have been linked to nicotinic acetylcholine receptors (nAChRs). Thus it is not surprising that nAChRs have been strongly implicated as therapeutic targets for treating cognitive deficits in disorders such as schizophrenia and Alzheimer's disease (AD). In particular the alpha7 (α7) nAChR has been closely linked with normalization of P50 auditory evoked potential (AEP) gating deficits, and to a lesser extent improvements in pre-pulse inhibition (PPI) of the acoustic startle response. These two brain phenomena can be considered as pre-attentive, occurring while sensory information is being processed, and are important endophenotypes in schizophrenia with deficits likely contributing to the cognitive fragmentation associated with the disease. In addition α7 nAChRs have been implicated in attention, in particular under high attentional demand, and in more demanding working memory tasks such as long delays in delayed matching tasks. Efficacy of α7 nAChR agonists across a range of cognitive processes ranging from pre-attentive to attentive states and working and recognition memory provides a solid basis for their pro-cognitive effects. This review will focus on the recent work highlighting the role of α7 in cognition and cognitive processes.

Contents

1. Introduction

Cognition and its impairment or decline produced by a neurological disorder or neuropathological process has received considerable attention in the research and drug discovery communities. Strides have been made to delineate the etiology of cognitive deficits across therapeutic areas and to amend, enhance, or retain "Cognition". In so doing, perhaps paradoxically, the underlying neurophysiological mechanisms (the "cogs") and brain circuitry (the "cogwheels") that contribute to cognition and cognitive processes are being resolved.

Neurophysiological evidence, histological findings, and scores on a battery of clinical tests revealing impaired cognition and deficient sensory information processing have started to align two major disorders not typically associated with one another: schizophrenia and Alzheimer's disease. Schizophrenics and AD patients both demonstrate marked impairments in clinical tests of cognition with surprisingly similar profiles (McBride et al., 2002), exhibit overlapping regions in the brain that are affected, namely the cortex and hippocampus (McBride et al., 2002; Moxon et al., 2003a, 2003b; Thompson

Abbreviations: AD, Alzheimer's disease; AEP, auditory evoked potential; DAT, dementia of Alzheimer type; DHβE, dihydro-beta-erythroidine; EEG, electroencephalography; ERP, event-related potential; GABA, gamma-aminobutyric acid; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; MLA, methyllycaconitine; nAChR, nicotinic acetylcholine receptors; PAM, positive allosteric modulator; PPI, pre-pulse inhibition; S1, first or conditioning stimulus in a paired pulse paradigm; S2, second or test stimulus in a paired pulse paradigm; TC, test-to-conditioning; nRT, thalamic reticular nucleus.

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et al., 2004), have dysfunction of sensory pathways involved in orienting toward salient stimuli suggesting that a sensory deficit could contribute to cognitive deficits (Butler et al., 2001), including deficient P50 gating (Clementz et al., 1998; Jessen et al, 2001; Olichney & Hillert, 2004; Oranje et al., 2006; Thomas et al., 2008) and pre-pulse inhibition (Geyer et al., 2001; Ewers et al., 2006; Ueki et al., 2006). These factors implicate cholinergic dysfunction in disease progression and etiology and have revised the possibility of modulating α7 nAChR activation in the treatment of cognitive deficits seen in both patient populations.

The nAChRs have been implicated extensively in human and animal studies of attention, learning and memory. The alpha4beta2 (α4ß2) and alpha7 (α7) nicotinic receptors, which make up the majority of the nicotinic receptor subtypes within the brain, have been demonstrated to be involved in cognitive functioning. For example, nicotinic agonists including nicotine have improved memory function in multiple cognition assays while impairments have been observed following treatment with nicotinic antagonists. The pro-cognitive effects of nicotine have been established across multiple animal models and cognitive constructs ranging from improved performance of rats in the radial arm maze (Levin et al., 1995) and non-human primates in a delayed non-matching to sample task (Spinelli et al., 2006), delayed spatial alternation (Levin & Chin, 2004), aged-associated working memory deficits (Buccafusco & Jackson, 1991), sustained attention (Hoyle et al., 2006; Young et al., 2007), eye-blink classical conditioning (Woodruff-Pak & Santos, 2000), whereas nicotinic receptor antagonism has been demonstrated to produce deficits in reference and working memory in both rats and primates (Levin & Simon, 1998; Terry & Gearhart, 2007).

The nAChRs have also been genetically linked to cognitive deficits. For example, a genetic linkage between a region of chromosome 15 that encodes for the α7 nAChR and schizophrenia has been reported (Freedman et al., 1997; Riley et al., 2000). Additionally, significant reductions in α7 nAChR binding and levels have been observed in multiple brain regions of schizophrenics (Freedman et al., 1995; Guan et al., 1999; Martin-Ruiz et al., 2003), while mRNA levels of α7 nAChR are reduced in blood lymphocytes from patients (Perl et al., 2003).

The pro-cognitive findings, especially in the area of working memory, for α7 agonists provide support for the utility of compounds selectively targeting this mechanism in treating cognitive impairments. Towards this end, this review will focus on the role of the α7 nAChR in modulating cognitive processes important for treating cognitive deficits in neurodegenerative and psychiatric disorders with particular emphasis on in vivo preclinical models employed in supporting therapeutic utility.

2. Alpha7 nicotinic acetylcholinergic receptors

Neuronal nAChRs are widely expressed in the central nervous system where they mediate fast synaptic signalling and regulate the release of other neurotransmitters. They are involved in a variety of physiological processes, including specific cognitive functions such as attention and performance in working and associative memory, neuronal development, especially in the sensory cortex, and in reward mechanisms through the mesocorticolimbic system (Jones et al., 1999; Hogg et al., 2003; Gotti & Clementi, 2004; Gotti et al., 2006; Klein & Yakel, 2005; Dani & Bertrand, 2007). Cholinergic modulation plays a critical role in the functioning of many neuronal circuits. For example, GABAergic and glutamatergic synaptic inputs (i.e. ventral tegmental area dopaminergic neurons) are modulated by different nAChR subtypes with distinct desensitization properties and α7 and non-α7 receptors can have opposing effects within a single brain system (Mansvelder et al., 2002; Galindo-Charles et al., 2008; Papke et al., 2009).

Substantial evidence has suggested that nAChRs might contribute to their role in enhancement of cognitive functions by acting in local circuits of hippocampus and cerebral cortex. For example in the hippocampus, α7-containing nAChRs are located at postsynaptic sites on interneurones where they mediate fast cholinergic excitatory synaptic transmission (Alkondon et al., 1998; Frazier et al., 1998), and on presynaptic terminals where their activation increases intraterminal Ca2+ levels and facilitates glutamate release (Gray et al., 1996). Furthermore, they are known to participate in various forms of synaptic plasticity (Hunter et al., 1994; Fujii & Sumikawa, 2001a, 2001b; Ji et al., 2001; McGehee, 2002; Klein & Yakel, 2005). Thus α7 nAChR activation is primed to affect higher-order processes that likely underlie cognition. Furthermore, brain regions associated with cognitive deficits seen in schizophrenia and AD overlap with regions of α7 nAChR receptor expression. Just such a circuit – perhaps the major "cogwheel" in cognition – is the hippocampus.

The hippocampus receives afferent projections, is inundated with α7 nAChR receptors and has vast GABAergic interneuron distribution, and is thus a prime circuit in which to study the effects of α7 in "sensory gating", one means of assessing higher-order processing known to be involved in cognitive functioning (Adams et al., 2001; Court et al., 2001). In the hippocampus, cholinergic input mediated by α7 nAChR onto inhibitory interneurons in the CA3 region results in a reduction in the output of this region to repetitive stimuli. Specifically, cholinergic stimulation of GABAergic interneurons causes GABA to be released and subsequently bind to presynaptic GABA-B receptors on CA3 pyramidal neurons, thereby inhibiting their response (and their release of glutamate) to secondary stimuli (Luntz-Leybman et al., 1992; Adler et al., 1998; Freedman, 2003). This phenomenon is detectable as a relative change in postsynaptic potentials in response to the external stimuli and can be measured using electroencephalography (EEG). One way to elicit this phenomenon experimentally is to play two tonal stimuli in rapid succession. The EEG registers stereotypical changes in brain activity to each tone. These responses are auditory evoked potentials (AEP), which are described later in more detail. Normally there is a reduced response (smaller AEP) to the second stimulus, which is considered to be a result of "gating" of sensory information. This is commonly referred to as P50 auditory gating because the peak change (the P in P50 stands for positive) in the EEG occurs 50 ms after the stimulus in humans (Adler et al., 1982). This phenomenon has been extensively studied in preclinical animal models (i.e. Stevens et al., 1996) yet it was the most descriptive of these studies that demonstrated similar morphologies of the human P50, N100, P200, P300 and slow wave in relation to the mouse P20, N40, P80, P120 and slow wave (Siegel et al., 2003). In fact, Siegel et al. (Siegel et al., 1984, 2003; Connolly et al., 2003; Metzger et al., 2007; Ehrlichman et al., 2008) show the mouse P20 and N40 bear similarity to the human P50 and N100 in relative latency and orientation and that the mouse P20/N40 waveform is gated following repeated stimuli similar to the human P50 and N100 components.

The ability to inhibit neuronal activity to successive stimuli ("gate" information) is time dependent; As the interstimulus interval increases, the inhibitory current activated to the second stimulus decreases (Moxon et al., 1999; Moxon et al., 2003a, 2003b). The α7-pentameric receptor complex is known to desensitize and become inactive after it is bound by two molecules of acetylcholine (or agonist) (Adler et al., 1998; Papke et al., 2009). It is not yet known how extensive the desensitization is nor how long it persists in vivo (Sokolova et al., 2005), which suggests a role for the mechanics of the α7-pentameric receptor complex desensitization in the timing of sensory gating.

Impaired sensory gating in schizophrenics has been well characterized (see Adler et al., 1982; Baker et al., 1987; Boutros et al., 1999; Turetsky et al., 2009), however the culmination of studies over the past decade have documented abnormalities in the way information is processed across sensory modalities in schizophrenics that may in fact underlie the cognitive deficits commonly associated with the disorder. Moreover, a number of studies have shown a role of α7 nAChRs in modulating the processing of sensory information. The next section highlights these findings in studies employing in vivo electrophysiology.