Published in final edited form as:
Eur J Pharmacol. 2014 March 15; 727: 181–185. doi:10.1016/j.ejphar.2014.01.072.

The therapeutic promise of positive allosteric modulation of nicotinic receptors

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Abstract

In the central nervous system, deficits in cholinergic neurotransmission correlate with decreased attention and cognitive impairment, while stimulation of neuronal nicotinic acetylcholine receptors improves attention, cognitive performance and neuronal resistance to injury as well as produces robust analgesic and anti-inflammatory effects. The rational basis for the therapeutic use of orthosteric agonists and positive allosteric modulators (PAMs) of nicotinic receptors arises from the finding that functional nicotinic receptors are ubiquitously expressed in neuronal and non-neuronal tissues including brain regions highly vulnerable to traumatic and ischemic types of injury (e.g., cortex and hippocampus). Moreover, functional nicotinic receptors do not vanish in age-, disease- and trauma-related neuropathologies, but their expression and/or activation levels decline in a subunit- and brain region-specific manner. Therefore, augmenting the endogenous cholinergic tone by nicotinic agents is possible and may offset neurological impairments associated with cholinergic hypofunction. Importantly, because neuronal damage elevates extracellular levels of choline (a selective agonist of α7 nicotinic acetylcholine receptors) near the site of injury, α7-PAM-based treatments may augment pathology-activated α7-dependent auto-therapies where and when they are most needed (i.e., in the penumbra, post-injury). Thus, the nicotinic-PAM-based treatments are expected to be highly efficacious with fewer side effects as compared to a more indiscriminate action of exogenous orthosteric agonists. In this review, I will summarize the existing trends in therapeutic applications of nicotinic PAMs.

Keywords

positive allosteric modulator; nicotinic acetylcholine receptor; PNU-120596; choline; cerebral ischemia; analgesia

1. Positive Allosteric Modulation of Nicotinic Acetylcholine Receptors

Neuronal nicotinic acetylcholine receptors play critical roles in maintaining cognitive, autonomic and immune homeostasis as summarized in recent comprehensive reviews

Chemical compounds discussed in this article: 1-(5-chloro-2,4-dimethoxyphenyl)-3-(5-methylisoxazol-3-yl)urea; i.e., PNU-120596 (PubChem CID: 311434); choline chloride (PubChem CID: 6209); epibatidine (PubChem CID: 854023); (R)-5-(2-azetidinylmethoxy)-2-chloropyridine; i.e., ABT-594 (PubChem CID: 3075702); 3-(2,4-dimethoxybenzylidene)-anabaseine); i.e., DMXB-A (PubChem CID: 6438361).

(Bencherif et al., 2011; Lendvai et al., 2013; Olincy et al., 2006; Wallace and Porter, 2011). In the central nervous system, deficits in cholinergic neurotransmission correlate with reduced attention and cognitive impairment (Bartus et al., 1982; Cabrera et al., 2006), while cholinergic hyperactivity correlates with depression (Janowsky et al., 1974). Although the muscarinic acetylcholine receptor component of cholinergic activity is essential for healthy cognition (Petersen, 1977), pro-cognitive effects of nicotinic agonists are evident and treatments that support activation of central nicotinic acetylcholine receptors can offset neurological impairments associated with cholinergic hypofunction (Kitagawa et al., 2003; Levin et al., 2006; Newhouse et al., 2004). In addition, nicotinic receptors modulate nociceptive neurotransmission and have been viewed as promising targets of non-opioid analgesics (Damaj et al., 2000; Lee et al., 2011; Rode et al., 2012; Umana et al., 2013; Zhu et al., 2011).

As an alternative to somewhat indiscriminate action of exogenous orthosteric nicotinic agonists, positive allosteric modulators (PAMs) of nicotinic receptors have been proposed as a novel promising approach to counteracting neurocognitive deficits (Callahan et al., 2013; Hurst et al., 2005; McLean et al., 2012; Thomsen et al., 2011), acute and chronic nociception (Freitas et al., 2012; Freitas et al., 2013; Lee et al., 2011; Munro et al., 2012; Zhu et al., 2011) and cerebral ischemia (Kalappa et al., 2013; Sun et al., 2013). Nicotinic PAMs offer at least three important advantages over exogenous orthosteric nicotinic agonists. First, PAMs alone do not activate nicotinic receptors, but they increase the activation efficacy/potency of endogenous nicotinic agonists (i.e., choline and acetylcholine) which are released naturally as needed. Thus, the native spatiotemporal patterns of nicotinic receptor activation may remain largely intact. One possible exception is α7-PAMs that inhibit α7 desensitization, e.g., 1-(5-chloro-2,4-dimethoxyphenyl)-3-(5-methylisoxazol-3-yl)urea (i.e., PNU-120596). These PAMs (known as Type-II) can recruit endogenous choline (a selective agonist of α7 nicotinic acetylcholine receptors) and produce persistent α7 receptor activation (Freitas et al., 2013; Gusev and Uteshev, 2010; Kalappa et al., 2010; Munro et al., 2012). Therefore, certain spatiotemporal patterns of α7 activation mediated by endogenous choline may exist only in the presence, but not absence of α7-PAMs. Secondly, allosteric binding sites are evolutionary less conserved than orthosteric sites (Yang et al., 2012) and thus, allosteric sites exhibit greater structural diversity than orthosteric sites. Therefore, allosteric sites are more likely to allow selective targeting by synthetic compounds than orthosteric sites. This property may have arisen from an apparent delay in the evolutionary development of allostery relative to orthosteric activity of ligand-gated receptors (Yang et al., 2012). Finally, activation of nicotinic receptors by nicotinic agonists is reduced by desensitization. As a result, neurocognitive, behavioral and analgesic effects of nicotinic agonists are expected to develop tolerance (Harris et al., 2004; Lendvai et al., 2013; Umana et al., 2013). Some α7-PAMs inhibit α7 receptor desensitization (Dinklo et al., 2011; Faghih et al., 2009; Hurst et al., 2005) and thus, may reduce tolerance to make nicotinic treatments more efficacious (Freitas et al., 2012).

Desensitization also serves as a cytoprotective mechanism against potentially toxic receptor overstimulation and theoretically, PAMs that inhibit α7 desensitization may cause cytotoxicity. However, the existing experimental data argue that PAMs that inhibit α7 desensitization are therapeutically efficacious (Freitas et al., 2012; Freitas et al., 2013; Hu et al., 2009; Hurst et al., 2005; Kalappa et al., 2013; McLean et al., 2012; Munro et al., 2012; Sun et al., 2013). Moreover, in addition to potentiating α7 activation, α7-PAMs may also potentiate α7 open channel block (Kalappa and Uteshev, 2013) further raising the threshold for cytotoxicity.

The rational basis for the therapeutic use of orthosteric agonists and PAMs of nicotinic receptors arises from the finding that functional nicotinic receptors are ubiquitously

expressed in neuronal and non-neuronal tissues including brain regions highly vulnerable to traumatic and ischemic types of injury (e.g., cortex and hippocampus). Moreover, functional nicotinic receptors do not vanish in age-, disease- and trauma-related neuropathologies, but their expression and/or activation levels decline in a subunit- and brain region-specific manner (Kelso and Oestreich, 2012; Leonard et al., 2000; Nordberg and Winblad, 1986). Therefore, augmenting the endogenous cholinergic tone by PAMs is possible and may offset neurological impairments associated with cholinergic hypofunction.

2. Exploring nicotinic-PAMs as therapeutic alternatives to orthosteric nicotinic agonists

Neurodegenerative, sensorimotor and psychiatric disorders associated with cognitive decline and decreased attention have been linked to deficits in the expression and function of nicotinic acetylcholine receptors (Freedman et al., 1995; Guan et al., 2000; Leonard et al., 2000; Nordberg and Winblad, 1986; Perry et al., 1995). By contrast, activation of nicotinic receptors by endogenous and exogenous nicotinic agents is generally pro-cognitive and can be therapeutic in patients and animal models of age-, disease- and trauma-related neurocognitive dysfunctions (Arendash et al., 1995; Bencherif et al., 2011; Guseva et al., 2008; Kelso and Oestreich, 2012; Lendvai et al., 2013; Olincy et al., 2006; Thomsen et al., 2011; Verbois et al., 2003; Wallace and Porter, 2011). Therefore, there is a clear rationale for exploring nicotinic-PAM-based treatments as alternatives to orthosteric nicotinic agonists. In fact, PNU-120596, the first α7-PAM with an *in vivo* efficacy, improved the auditory gating deficits in rats (Hurst et al., 2005), a major functional biomarker in schizophrenia research. Other α7-PAMs have since been synthesized and showed similar efficacies in restoration of auditory gating in rodents (Dinklo et al., 2011; Faghih et al., 2009; Ng et al., 2007).

Functional α7 nicotinic receptors expression is beneficial to the nervous system, as moderate activation of these receptors enhances cellular resistance to brain injury, which has been demonstrated in both *in vivo* and *ex vivo* experimental models of dementias, cerebral ischemic stroke and traumatic brain injury (Akaike et al., 2010; Del Barrio et al., 2011; Egea et al., 2007; Guseva et al., 2008; Kaneko et al., 1997; Li et al., 1999; Parada et al., 2013; Roncarati et al., 2009; Shimohama et al., 1998; Takeuchi et al., 2009). For example, neuroprotection by nicotine was lost in α7 knock-out mice exposed to oxygen-glucose deprivation (Egea et al., 2007); while activation of α7 nicotinic receptors by low concentrations of a partial selective agonist protected pheochromocytoma-12 (PC12) cells from death in a nerve growth factor (NGF)/serum deprivation toxicity model (Li et al., 1999). The mechanisms underlying α7-mediated neuroprotection may involve activation of the serine/threonine-specific protein kinase and B-cell lymphoma protein (i.e., AKT/Bcl-2)-dependent pathways (Akaike et al., 2010; Shimohama, 2009). These likely mechanisms would allow neurons meet the energy demand of ischemic/hypoglycemic conditions and delay the ultimate failure of the Na^+/K^+-ATPase pumps by delaying mitochondrial dysfunction. Such a failure would cause a rapid loss of the neuronal trans-membrane electrochemical gradient leading to terminal anoxic depolarization and spreading depression (Kalappa et al., 2013; White et al., 2012).

Choline, a ubiquitous cell membrane building material and a precursor/metabolite of acetylcholine, is a selective endogenous agonist of α7 nicotinic receptors (Alkondon et al., 1997; Papke et al., 1996). The endogenous levels of extracellular choline (<10 μM) are sub-threshold for α7 activation (Uteshev et al., 2003) due to choline's low potency for α7 activation (EC_{50}~0.5 mM) (Papke and Papke, 2002) and tendency to induce α7 desensitization (IC_{50}~40 μM) (Uteshev et al., 2003). However, under conditions of energy deprivation, cellular dysfunction and injury/death, the extracellular concentration of choline

can be considerably elevated (Djuricic et al., 1991; Gasull et al., 2000; Kiewert et al., 2010; Rao et al., 2000) providing a large source of this endogenous α7 agonist. Significantly elevated levels of choline have been recently demonstrated by direct measurements in the ischemic core and penumbra in the middle cerebral artery occlusion (MCAO) model of ischemic stroke in rats (Kiewert et al., 2010). In this regard, the hypothesis that MCAO-induced focal elevations in the extracellular levels of choline near the site of injury act as a form of ischemia-activated penumbral auto-therapy is very intriguing. While these elevated levels of choline may be neuroprotective even in the absence of α7-PAMs, it would be expected that α7-PAM-based treatments will significantly augment the injury-induced α7-dependent neuroprotection by endogenous choline where and when it is most needed (i.e., in the ischemic penumbra, post-injury) (Kalappa et al., 2013; Sun et al., 2013). Furthermore, α7-PAMs would be expected to expand the range of ischemic penumbra that falls under significant injury-induced α7-dependent neuroprotection by endogenous choline, because α7-PAMs increase the α7 activation efficacy/potency of choline and appear to convert sub-neuroprotective levels of choline into neuroprotective. Conversely, because of the elevated levels of choline in ischemic penumbra, α7-PAMs may not require co-application of exogenous α7 agonists to produce significant neuroprotection in focal cerebral ischemia (Kalappa et al., 2013; Sun et al., 2013). While not necessary in ischemic injury, co-administration of nicotinic agonists and nicotinic-PAMs appears to be critical in treatments of acute, chronic and neuropathic pain (Umana et al., 2013) (Fig. 1), conditions that are not expected to elevate the levels of extracellular choline and acetylcholine.

In the MCAO model of cerebral ischemic stroke in rats, PNU-120596 has significantly reduced cerebral infarct volume and neurological deficits when the drug was administered up to 6 hours post-MCAO (Kalappa et al., 2013; Sun et al., 2013). Such a remarkable post-MCAO effectiveness of PNU-120596 invites additional pre-clinical studies of α7-PAMs as a conceptually novel family of treatments that are based on a substantively different mechanism, i.e., recruiting and enhancing injury-induced α7-dependent auto-therapy by endogenous cholinergic pathways. Treatments that incorporate endogenous mechanisms are expected to be highly efficacious and cause fewer adverse reactions as compared to treatments utilizing exogenous orthosteric agonists. Moreover, as functional α7 nicotinic receptors are ubiquitously expressed in both neuronal and non-neuronal tissues, the presence of neurovascular and/or immune components in the therapeutic effects of α7-PAMs would not be surprising, as we have recently discussed (Sun et al., 2013). A possible contribution of the immune system in the therapeutic effects of α7-PAMs would be consistent with the ubiquitous expression of functional α7 nicotinic receptors in many immune cells (Wang et al., 2003) and the anti-inflammatory efficacy of PNU-120596 (Munro et al., 2012; Parada et al., 2013). Potential non-neuronal sources of nicotinic-PAM-mediated brain protection are not well understood and present a great interest.

3. Analgesic effects of nicotinic-PAMs

Serious adverse reactions and a high potential for addiction reduce clinical enthusiasm for the use of opioids as analgesics (Umana et al., 2013). Moreover, opioids may not always be effective against neuropathic pain. Therefore, there is a critical need in developing non-opioid compounds with analgesic potency comparable to that produced by opioids. Nicotinic receptors have been viewed as promising targets of non-opioid analgesics (Badio and Daly, 1994; Nirogi et al., 2013; Qian et al., 1993; Umana et al., 2013). For example, epibatidine, a compound isolated from the skin of South African frogs *Epipedobates tricolor*, is a highly potent non-opioid analgesic with a potency for neuropathic pain (Badio and Daly, 1994). As an analgesic, epibatidine is ~100-fold more potent than morphine and its analgesic action is derived from direct binding and activation of α4β2 and α7 nicotinic receptors (Gerzanich et al., 1995). However, the initial optimism for the use of epibatidine and (R)-5-(2-

azetidinylmethoxy)-2-chloropyridine (i.e., ABT-594), an epibatidine-based selective agonist of α4β2 nicotinic receptors) as potent analgesics has declined because of serious autonomic adverse reactions (Rowbotham et al., 2009). The recent development of α4β2-PAMs (e.g., 3-(3-(pyridine-3-yl)-1,2,4-oxadiazol-5-yl)benzonitrile; (i.e., NS9283) revived the interest in developing nicotinic receptor-based analgesic tools because of the distinct therapeutic qualities of PAMs discussed above. For example, while NS9283 alone does not produce significant analgesic effects in animal models of acute, persistent, neuropathic and inflammatory pain, a combination of NS9283 with ABT-594 (Lee et al., 2011; Zhu et al., 2011) or 1-(5-chloropyridin-3-yl)-[1,4]diazepane fumarate (i.e., NS3956; another potent orthosteric α4β2 agonists) (Rode et al., 2012), significantly enhances the analgesic efficacy/potency of these treatments. Importantly, the autonomic adverse reactions of ABT-594 (e.g., emesis, heart rate, body temperature likely caused by activation of α3β4 nicotinic receptors) and sensorimotor performance (e.g., locomotion, rotarod performance, exploratory behavior) are not potentiated by NS9283 indicating that PAM-based approaches can increase the therapeutic index of α4β2 agonists in treating pain (Lee et al., 2011; Zhu et al., 2011).

In addition to α4β2 nicotinic receptors, α7 nicotinic receptors act as another potential target of analgesic drugs (Damaj et al., 2000; Feuerbach et al., 2009; Medhurst et al., 2008). Not surprisingly, α7-PAMs have been demonstrated to produce robust anti-nociceptive effects by enhancing the efficacy/potency of endogenous choline (Freitas et al., 2012; Freitas et al., 2013; Munro et al., 2012). The analgesic effects of nicotinic-PAMs can be further enhanced by combining PAMs with exogenous orthosteric nicotinic agonists as discussed previously (Freitas et al., 2013; Umana et al., 2013). Together these results demonstrate that nicotinic-PAMs hold significant promise as potent analgesics targeting α4β2 and α7 nicotinic receptors.

4. Conclusions

Activation of nicotinic receptors produces robust pro-cognitive, neuroprotective, analgesic and anti-inflammatory effects (Fig. 1). Nicotinic PAMs may act as a powerful alternative to exogenous orthosteric nicotinic receptor agonists, such as 3-(2,4-dimethoxybenzylidene)-anabaseine (i.e., DMXB-A, the code name, GTS-21 (Kem, 2000)) to help counteract neurocognitive deficits, nociception and brain injury. As a novel therapeutic opportunity, nicotinic-PAMs that could recruit endogenous cholinergic pathways and enhance pathology-activated auto-therapies would hold significant translational potential. Because of the ubiquitous expression of nicotinic receptors in neuronal and non-neuronal tissues, developing highly selective nicotinic-PAMs which, ideally, could target only a single player, i.e., the nicotinic receptors, would allow nicotinic-PAM-based interventions to target and recruit multiple endogenous neuronal and non-neuronal therapeutic cholinergic pathways. Although a lot remains to be learned about nicotinic-PAMs, recent pre-clinical findings create a strong sense of optimism and further extend the therapeutic promise of this novel class of compounds.

Acknowledgments

I thank Dr. John Dani and Dr. Daniel McGehee for productive discussions and criticism. I thank Dr. Imad Damaj for helpful suggestions. This study was supported by the NIH grant DK082625 and a grant from the Rainwater Charitable Foundation to VU.

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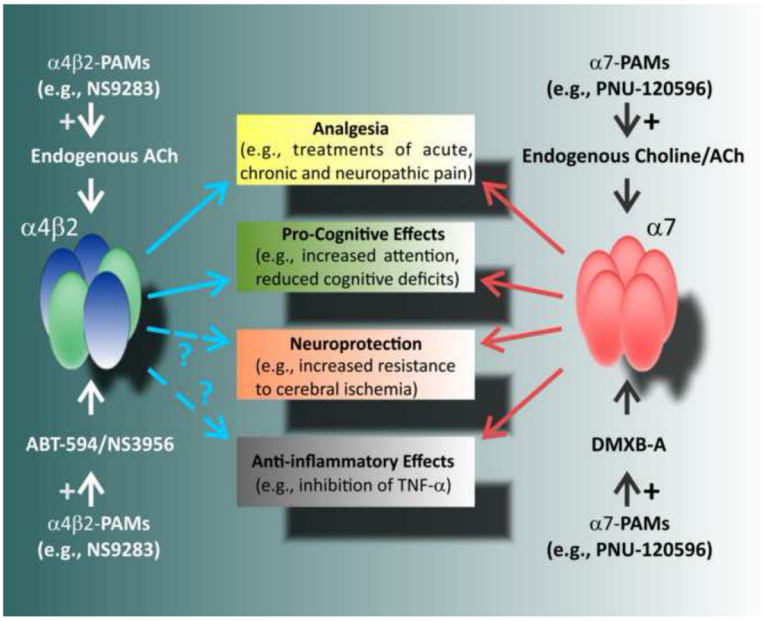

Fig. 1. A schematic representation of potential therapeutic contributions of α4β2- and α7-PAMs

α4β2 and α7 nicotinic-PAMs enhance the activation efficacy/potency of endogenous (i.e., choline and acetylcholine) and exogenous (e.g., DMXB-A, the code name GTS-21 (Kem, 2000)) orthosteric nicotinic receptor agonists. However, α7-PAMs appear to have a broader spectrum of therapeutic activity as compared to α4β2-PAMs, possibly, because they appear to be able to convert endogenous choline into a potent therapeutic agent. DMXB-A is a selective α7 nicotinic receptor agonist that has been extensively tested at various phases of pre-clinical and clinical trials as a potential therapy for a number of neurological conditions, including Alzheimer's disease (Kem, 2000) and most recently, schizophrenia (Freedman et al., 2008; Olincy et al., 2006) (see http://clinicaltrials.gov/). As a novel therapeutic opportunity, nicotinic-PAMs that could recruit endogenous cholinergic pathways and enhance pathology-activated auto-therapies would hold significant translational potential. Because of the ubiquitous expression of nicotinic receptors in neuronal and non-neuronal tissues, developing highly selective nicotinic-PAMs which, ideally, could target only a single player, i.e., the nicotinic receptors, would allow nicotinic-PAM-based interventions to target and recruit multiple endogenous neuronal and non-neuronal therapeutic cholinergic pathways.