Invited review

The potential of nicotinic enhancement of cognitive remediation training in schizophrenia

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ABSTRACT

Cognitive deficits in schizophrenia are critically important predictors of long-term psychosocial outcome and are not significantly ameliorated by currently available medications. Cognitive remediation training has shown promise for alleviating cognitive symptoms of schizophrenia, but the clinical significance has often been limited by small effect sizes. Approaches that achieve larger improvement involve time requirements that can be cost-prohibitive within the current clinical care system. This mini-review evaluates the theoretical potential of a pharmacological enhancement strategy of cognitive remediation training with nicotinic acetylcholine receptor (nAChR) agonists. nAChR agonists can facilitate sensory processing, alertness, attention, learning and memory. While these effects may be too subtle and short-lasting to be of clinical relevance as a primary treatment of cognitive deficits, they constitute an ideal effects profile for enhancing training benefits. Several mechanisms are described through which repeated coupling of cognitive training challenges with nAChR stimulation may enhance and accelerate cognitive remediation training effects, advancing such interventions into more effective and practicable treatments of some of the most debilitating symptoms of schizophrenia.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.

1. The treatment of cognitive dysfunction in schizophrenia

Schizophrenia is marked by pervasive neurocognitive deficits, such as impairments in perceptual processing, vigilance/alertness, attention, episodic and working memory, executive function, and social cognition. These deficits are key predictors of long-term community outcome, predicting the ability to live independently and maintain employment (70–80% of patients are un- or under-employed; (Lehman, 1999)) better than psychotic symptoms (Green, 1996; Green et al., 2004; Tan, 2009).

Unlike hallucinations and delusions, these symptoms are not significantly ameliorated by currently available medications. First- and second-generation antipsychotics are minimally effective in improving cognition in schizophrenia (Tandon et al., 2010). Initial research on second-generation antipsychotics generated hope for therapeutic effects to extend into the cognitive domain, but yielded no consistent evidence thereof (Beninger et al., 2010). Other drug classes have been investigated as possible augmentation therapies, such as nicotinic and muscarinic acetylcholine receptor agonists (Martin and Freedman, 2007; Radek et al., 2010; Sellin et al., 2008; Hong et al., 2011), cholinesterase inhibitors (Chouinard et al., 2007; Stip et al., 2007), NMDA and AMPA receptor ligands (Goff et al., 2008a, 2008b; Lieberman et al., 2009), a D1 agonist (George et al., 2007), a 5-HT3 antagonist (Akhondzadeh et al., 2009), and the analeptic drug Modafinil (Saavedra-Velez et al., 2009). Despite reports of small benefits, no pharmacological add-on strategy has obtained convincing clinical support (Zink et al., 2010). There are to date no FDA-approved treatments targeting these symptoms.

By investigating direct drug effects on cognitive deficits, the above studies applied the standard medical approach of attempting to medicate symptoms. However, cognitive abilities and their underlying neural substrates depend largely on their frequency of engagement (Maguire et al., 2000; Woollett et al., 2009). Thus, an expectation of substantial improvement by acutely enhancing neuropharmacological parameters may be overly optimistic. In chronic disease conditions marked by cognitive dysfunction such as schizophrenia, cognitive faculties have often suffered from years or decades of neglect and disuse. Disease-related neurochemical factors may have triggered or contributed to this state; yet, the resulting scarcity of cognitive engagement likely exacerbated, consolidated, and perpetuated it.

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As an alternative way of tackling chronic cognitive impairment, several training approaches have been tested in people with schizophrenia (PSZ). Interventions ranged from environmental aids, compensation strategies, and techniques to enhance executive function and social cognition, to repetitive drill-like exercises that challenge sensory information processing, attention and memory. Training-related improvements in neurocognitive tests varied greatly between studies but tended to reflect low to medium effect sizes, with some occasional generalization to psychosocial functioning, employment, and clinical symptoms (Twamley et al., 2003; Velligan et al., 2006; McGurk et al., 2007; Medalia and Choi, 2009). There is indication that cognitive remediation training can induce structural and functional brain changes (Haut et al., 2010; Keller and Just, 2009; Temple et al., 2003; Subramaniam et al., 2012; Eack et al., 2010), indicating that such programs may indeed be able to reverse neurocognitive deficits amenable to use-dependent plasticity.

In PSZ, deficits in different stages of auditory stimulus and speech processing have been described (Kugler and Caudrey, 1983; Javitt, 2000; Vercammen et al., 2008; Naatanen and Kahkonen, 2009), which appear to contribute to higher-order cognitive deficits (Javitt et al., 1999; Kawakubo et al., 2006; Leitman et al., 2010). A computerized training approach that places particular emphasis on early sensory processing (Posit Science, Duncan, SC) and that improved auditory processing and oral language abilities in dyslexia (Temple et al., 2003) has been adapted for use in PSZ. The program originally targeted auditory processing, and effect sizes on verbal learning, memory and working memory subscales of the MATRICS Consensus Cognitive Battery were moderate to large (Fisher et al., 2009). The addition of an analogous visual processing training enhanced and broadened outcome (Fisher et al., 2010b). Effects persisted at 6 months follow-up and were associated with positive changes in the Quality of Life Scale (Fisher et al., 2010b). This intervention involves 50—100 h of training over 10—20 weeks.

Another computerized cognitive training approach, Cognitive Enhancement Therapy (CET), was similarly intensive, combining 60—75 h of progressive attention, memory and problem solving training with weekly social cognitive group exercises over a 2-year period. CET has been shown to produce moderate to large effect sizes on neurocognition, processing speed, as well as social cognition and adjustment in PSZ (Hogarty et al., 2004; Eack et al., 2009). Robust and sustained improvements in executive function and working memory were also reported by Bell and colleagues (Bell et al., 2001, 2007), who added 26 weeks, up to 5 h/week, of performance-adaptive computerized exercises of attention, memory, executive function, and dichotic listening, as well as weekly social processing group meetings to vocational rehabilitation programs. Thus, sufficient dosage and intensity appear to be critical for the success of cognitive remediation training in schizophrenia. However, the time demands and costs of such lengthy interventions may limit their broad clinical applicability.

A pharmacological means of enhancing and speeding the effects of cognitive remediation training could improve the feasibility of this technique into a broadly applicable treatment of the cognitive symptoms of schizophrenia. The basic idea is to acutely induce a neuropharmacological state during the training sessions that creates a fertile soil for the training exercises. This approach is fundamentally different from pharmacologically treating cognitive deficits directly, as treatment success would manifest itself in enhanced training-induced neurocognitive benefits long after the drug has cleared out of the system. The search for drugs that modulate experience-dependent changes would constitute a new approach, and below we review the evidence that nicotinic acetylcholine receptor (nAChR) agonists are ideal candidates for such a purpose.

2. The potential of nicotinic enhancement of cognitive remediation training

Most behavioral studies of nAChR stimulation have been conducted with the prototypical non-selective nAChR agonist nicotine. Nicotine and other nAChR agonists have been shown to acutely enhance sensory, alerting/attentional and mnemonic processes in schizophrenia (Depatie et al., 2002; Larrison-Faucher et al., 2004; Myers et al., 2004; Smith et al., 2006; Barr et al., 2008; Jubelt et al., 2008; AhnAllen et al., 2008; Freedman et al., 2008; Woznica et al., 2009), mimicking effects in healthy subjects (Heishman et al., 1994, 2010; Knott et al., 2010; Fisher et al., 2010a) and laboratory animals (Kenney and Gould, 2008; Hahn et al., 2003; Acri et al., 1994). These effects tend to be short-lasting (depending on the compound's half-life), but by repeatedly coupling the window during which they unfold with the intense information processing challenges of a cognitive remediation training session, nAChR stimulation could optimize the training benefits and produce long-lasting cognitive benefits. There are several potential mechanisms:

2.1. Several (mainly event-related potential) studies suggest that nicotine facilitates early sensory processing (Phillips et al., 2007; Knott et al., 2010; Fisher et al., 2010a). In PSZ, research has primarily focused on nAChR agonist (in particular of the α7 subtype) effects on sensory gating (Martin and Freedman, 2007; Leiser et al., 2009). However, for an enhancement of cognitive training benefits, and in particular for training challenges integrating a bottom-up approach such as the Posit Science programs, sensory processing facilitation of all types may be important, allowing training challenges to be met at a higher level of difficulty. The premise is that more accurate and efficient sensory representations form better building blocks for higher-order functions and create less resources competition with such functions (Adcock et al., 2009).

2.2. Acute facilitation of alertness and attention during the training sessions is another mechanism via which nAChR agonists could increase training effects. Among the beneficial performance effects of nicotine, attentional enhancement is reported with the greatest consistency (Stolerman et al., 1995; Newhouse et al., 2004). Given that inattention and low levels of alertness can limit other cognitive processes, these effects may enable a deeper engagement in all functions challenged by the training exercises. Furthermore, nAChR agonists may strengthen participants' endurance during training sessions, enabling them to stay on task longer and complete more exercises. Indeed, nicotine has consistently been shown to improve sustained attention (Koelega, 1993). This mechanism may be of particular importance for trainees with schizophrenia, who display sustained attention deficits (Pigache, 1999; Nestor et al., 1990; Mass et al., 2000).

2.3. Evidence that some performance benefits of nAChR agonists can extend beyond their (and their metabolites') presence in the body has also been explained by nAChR activation inducing cellular signaling events that lead to long-lasting plastic changes in the brain (Buccafusco et al., 2005; Castner et al., 2011). Such events include changes in enzyme activity, protein phosphorylation, immediate early gene expression (demonstrated up to 72 h after nicotine administration), gene transcription, and neurotransmitter and neurotrophic factor release. Notably, nicotine can promote the induction of long-term potentiation (LTP), which is then maintained without continued nAChR activation (Kenney and Gould, 2008; Hamid et al., 1997; Matsuyama et al., 2000). Hasselmo (2006) summarized further cellular mechanisms through which cholinergic neurotransmission, which is potentiated by nAChR activation, modulates the encoding of new memories. Enhanced neuronal plasticity is also in line with findings implicating acetylcholine release in skill learning that requires cortical reorganization (Conner et al., 2003). Thus,

through modulation of activity-dependent cellular events and neural plasticity, nAChR agonists may promote learning and cognitive skill development stimulated by the training exercises.

In summary, facilitation of sensory information processing, alertness, attention, and mnemonic processes confers an ideal effects profile for enhancing behavioral training effects. Via all three mechanisms, nAChR agonists might be expected to acutely enhance information processing and cognitive skill acquisition during training, thereby augmenting long-lasting training benefits. Support for this notion comes from the finding that training outcome in schizophrenia is negatively associated with the anti-cholinergic burden of psychiatric medication (Vinogradov et al., 2009). The presence of a nAChR agonist during the cognitive exercises may shorten the training period necessary to induce significant and clinically relevant improvement, and potentiate the improvement seen after a training period of specified length. This may be especially true in conditions marked by nAChR hypo-function, such as schizophrenia (Dalack et al., 1998; Adams and Stevens, 2007).

3. Considerations when applying nAChR agonists therapeutically: lessons from nicotine

3.1. nAChR subtypes

nAChRs are pentameric ligand-gated cation channels composed of α2-7 and β2-4 subunits in the mammalian CNS. Different combinations of these subunits form functional receptors with distinct pharmacological properties, channel conductances and response kinetics, and distinct neuroanatomical distributions (Gotti et al., 2009).

In recent years, research on nAChR agonists effects in schizophrenia has largely focused on the homomeric α7 subtype, based on evidence that sensory gating deficits in PSZ and unaffected relatives, and the diagnosis of schizophrenia itself, are associated with polymorphisms in or near the α7 subunit gene and promoter region (Freedman et al., 1997; Leonard et al., 2002; Martin et al., 2004). Furthermore, a partial α7-selective agonist was found to acutely alleviate sensory gating deficits and produce small additional cognitive improvements in PSZ (Freedman et al., 2008; Olincy et al., 2006). Unfortunately, these findings appear to have created the unfounded impression that other nAChR subtypes are irrelevant in schizophrenia. The cognitive benefits of nAChR agonists are, in fact, not restricted to α7 nAChRs (Dunbar et al., 2007; Grottick et al., 2003; Levin, 2002; Radek et al., 2010; Hahn et al., 2003), and both α7 and α4β2 nAChR binding is decreased in postmortem brains of PSZ (Martin et al., 2004), suggesting abnormalities in the regulation of both of these most abundantly expressed subtypes.

At present, it is unknown which nAChR subtype(s) would be the most relevant for mediating enhancement of cognitive training benefits. Several different mechanisms (sensory processing, attention, neural plasticity) qualify as potential mediators, which contributes to the uncertainty. Thus, an initial proof of principle could be best accomplished with a non-selective nAChR agonist whose behavioral profile is mediated by a wide range of nAChR subtypes. Nicotine is an example of such a compound, making it a convenient tool for a first characterization of nAChR agonist effects on training-induced benefits. There is no evidence that nicotine spares any of the nAChRs expressed in the CNS, with its behavioral effects mediated not just by α4β2* ("high-affinity"), but also by α7 ("low-affinity") (Hahn et al., 2011; Tucci et al., 2003), and other nAChR subtypes such as α6β2*(no α4) (Gotti et al., 2010) and α3β4 (Glick et al., 2011). Newer compounds with similar non-

selectiveness and a somewhat longer duration of action may be preferential if available.

The verdict is also out on which secondary neurotransmitter system(s) would be critical. Nicotine, for example, interacts with every major neurotransmitter system in the brain (Wonnacott et al., 2006). There is indication that noradrenergic (Hahn and Stolerman, 2005) and glutamatergic (Quarta et al., 2007), but not dopaminergic (Hahn et al., 2002a, 2003) neurotransmission is involved in its attention-enhancing effects; muscarinic cholinergic and sero-tonergic neurotransmission in the effects on working memory (Levin et al., 2006); and GABAergic interneurons in the effects on sensory gating (Martin et al., 2004). However, more work remains to be done before there is a rationale for attempting to target specific systems with subtype-selective agonists.

3.2. Choice of dose

The cognitive-enhancing effects of nAChR agonists often display an inverted U-shaped dose–response curve, with the most beneficial effects observed at relatively small doses (Hahn et al., 2002b, 2003; Olincy et al., 2006). Judging from the nicotine literature, this may be explained, in part, by aversive side-effects at larger doses that interfere with beneficial effects, especially in organisms not chronically exposed to the drug (Stolerman, 1999; Perkins et al., 1994; Hahn and Stolerman, 2002). Additional reasons for greater efficacy at lower doses may be related to the pharmacological properties of nAChRs. Cholinergic projections generally provide diffuse and sparse cortical innervation, often not terminating at synapses. Accordingly, non-synaptic diffuse volume transmission appears to be a predominant ACh signaling mechanism in cortex and hippocampus, with nAChRs responding to low and sustained rises in agonist concentration (Dani and Bertrand, 2007).

The EC_{50} (half maximal effective concentration) of nAChR agonists usually does not take full consideration of the receptor desensitization dose–response curve, with slow desensitization at low concentrations and increasingly fast and persistent desensitization at higher concentrations. Thus, the relative maximum response can occur at agonist concentrations below their EC_{50} (Mike et al., 2000). For example, based on nicotine's low affinity and high EC_{50} at α7 nAChRs, the role of this subtype for the behavioral effects of nicotine is easily underestimated if we do not consider that it is less readily desensitized than the "high-affinity" α4β2* nAChR at sustained physiological concentrations seen after systemic administration (Wooltorton et al., 2003; Mansvelder et al., 2002). Under sustained equilibrium conditions, steady-state nAChR activation can be seen at low but not high agonist concentrations (Papke et al., 2011).

Thus, there is a good rationale for picking relatively small doses of nAChR agonist for enhancement of cognitive remediation training. The added benefit is, of course, that smaller doses produce fewer side effects, and less neuroadaptation with repeated exposure.

3.3. Chronic dosing

The clinical significance of nAChR agonists as a direct medication of cognitive deficits is limited not only because effects are small relative to the magnitude of the impairment, but also because continued effectiveness would require continuous exposure, which may be associated with neuroadaptive changes. Although the nicotine literature suggests that tolerance does not develop to the performance-enhancing effects of nAChR agonists (White and Levin, 1999; Grottick and Higgins, 2000; Nelsen and Goldstein, 1972, 1973; Hahn and Stolerman, 2002), there are adverse cognitive effects upon withdrawal (Hughes, 2007), and acute nicotine

withdrawal in PSZ causes greater deficits in the very functions it enhances acutely (George et al., 2002; Sacco et al., 2005; AhnAllen et al., 2008). It remains to be shown whether newer nAChR agonists share this property.

Augmenting the effects of a cognitive remediation program would require exposure to a nAChR agonist only during training sessions, with the idea that persistent training effects are enhanced after the drug has cleared out of the system. To further limit drug exposure and prevent persistent nAChR inactivation and other neuroadaptive changes, an intermittent dosing regime may be advantageous. In the context of daily training sessions, such a schedule could consist of drug co-administration with two to three intervening non-drug training days. A further advantage is that this allows for any performance and learning boosts on drug days, and any newly acquired skills, to be consolidated on subsequent non-drug training days and to generalize to a non-drug state.

3.4. Smoking status

Just as acute performance-enhancing effects of nicotine can be shown in smokers and non-smokers (LeHouezec et al., 1994; Foulds et al., 1996; Levin et al., 1998; Phillips and Fox, 1998; Min et al., 2001), both smokers and non-smokers may benefit from nAChR agonist augmentation of cognitive remediation training. However, at least in the case of nicotine, a smaller dose may have to be chosen for nicotine-naïve individuals to minimize aversive side effects (most commonly palpitations and nausea) and low tolerability, which may overshadow any cognitive benefits and disrupt the training procedures. Because rapid tolerance develops to these adverse effects with repeated administration (Perkins et al., 1994; Heishman and Henningfield, 2000; Stolerman, 1999), it may be advantageous to administer one or two doses, in a controlled setting, prior to the training schedule. More selective nAChR agonists may have a more favorable side effects profile.

For former smokers, there are concerns that exposure to a nAChR agonist may act as a priming cue and trigger relapse. This argues for refraining from administering a nAChR agonist with subjective stimulus properties similar to nicotine to this population, at least until there is evidence that the compound does not increase the risk of relapse to nicotine dependence. Administration via a route through which nicotine has not been consumed recreationally may minimize such priming mechanisms. In never-smokers, exposure to nAChR agonists is not expected to facilitate the initiation of smoking because their effects have never been associated with dependent smoking, and the protracted absorption from a tablet, gum, lozenge or patch, as opposed to the rapid delivery via inhalation, works against any reinforcing effects and abuse liability (Johanson and Fischman, 1989; Wakasa et al., 1995; Houtsmuller et al., 2003).

The argument can be made that, because smokers are chronically exposed to nicotine, there would be little added benefit from a clinician-administered nAChR agonist. However, cigarette-derived nicotine is unlikely to be optimally timed in relation to the training session. Furthermore, because of its rapid rise and metabolism (Henningfield and Keenan, 1993), cigarette-derived nicotine would not cover the entire training period.

4. Conclusions

Given the limited success of the direct medication approach to the cognitive deficits of schizophrenia, it may be time to consider alternative drug development strategies for this symptom group. Rather than seeking pharmacological agents capable of improving cognitive functions per se, redirecting efforts onto agents capable of

enhancing the effects of cognitive remediation training may offer new and different therapeutic opportunities. The effects profile of nAChR agonists makes them strong candidates for such endeavor. Acute facilitation of learning and skill acquisition via enhanced sensory processing, alertness, attention, and neural plasticity is likely to enable larger training effects, which can be expected to persist beyond the presence of nicotine in the body.

Clearly, not all cognitive training approaches would be expected to profit equally from nicotinic enhancement, with neuroplasticity-based restorative strategies targeting impaired basic brain functions through repetitive exercises likely to show greater benefit than compensatory strategies largely based on knowledge transfer. Furthermore, the benefits of nicotinic enhancement of cognitive remediation training may vary with participant characteristics such as medication status (Vinogradov et al., 2009).

In summary, synergistic effects of nAChR agonists with training-induced neurocognitive challenges may alleviate some of the most debilitating symptoms of schizophrenia. Given early in the disease course, such intervention may slow or prevent the development of psychosocial problems. Later on it may alleviate problems that have developed, in part by enhancing the effectiveness of other rehabilitative interventions.

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