Neuropharmacology 64 (2013) 185–190

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

The potential of nicotinic enhancement of cognitive remediation training in schizophrenia

Britta Hahn*, James M. Gold, Robert W. Buchanan

University of Maryland School of Medicine, Maryland Psychiatric Research Center, P.O. Box 21247, Baltimore, MD 21228, USA

ARTICLE INFO

Article history:
Received 25 January 2012
Received in revised form
29 May 2012
Accepted 31 May 2012

Keywords:
Schizophrenia
Cognition
Treatment
Cognitive remediation
Augmentation
Nicotinic

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.

* Corresponding author. Tel.: +1 410 402 6112; fax: +1 410 402 7198.
E-mail addresses: bhahn@mprc.umaryland.edu (B. Hahn), jgold@mprc.umaryland.edu (J.M. Gold), rwbuchanan@mprc.umaryland.edu (R.W. Buchanan).

0028-3908/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neuropharm.2012.05.050

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,