Available online at www.sciencedirect.com

SCIENCE DIRECT®

Progress in Neuro-Psychopharmacology & Biological Psychiatry 29 (2005) 219–232

Progress In Neuro-Psychopharmacology & Biological Psychiatry

www.elsevier.com/locate/pnpbp

Review article

On the trail of a cognitive enhancer for the treatment of schizophrenia

Emmanuel Stip[a,*], Sylvie Chouinard[a], Luc Jean Boulay[a,b]

[a]*Department of Psychiatry, Centre de Recherche Fernand-Seguin, Hôpital Louis-Hippolyte Lafontaine, Université de Montréal, 7331, rue Hochelaga Montréal (Québec), Canada, H1N 3V2*

[b]*Department of Psychiatry, University of Ottawa Institute of Mental Health Research, Royal Ottawa Hospital, 1145 Carling Ave, Ottawa Ontario, Canada, K1Z 7K4*

Accepted 19 November 2004
Available online 16 January 2005

Abstract

The aim of this critical review is to address that the study of cognition and antipsychotics is not always driven by logic and that research into real pro-cognitive drug treatments must be guided by a better understanding of the biochemical mechanisms underlying cognitive processes and deficits. Many studies have established that typical neuroleptic drugs do not improve cognitive impairment. Atypical antipsychotics improve cognition, but the pattern of improvement differs from drug to drug. Diminished cholinergic activity has been associated with memory impairments. Why atypical drugs improve aspects of cognition might lie in their ability to increase dopamine and acetylcholine in the prefrontal cortex. An optimum amount of dopamine activity in the prefrontal cortex is critical for cognitive functioning. Another mechanism is related to procedural learning, and would explain the quality of the practice during repeated evaluations with atypical antipsychotics due to a more balanced blockage of D2 receptors. Laboratory studies have shown that clozapine, ziprasidone, olanzapine, and risperidone all selectively increase acetylcholine release in the prefrontal cortex, whereas this is not true for haloperidol and thioridazine. A few studies have suggested that cholinomimetics or AChE inhibitors can improve memory functions not only in Alzheimer's disease but also in other pathologies. Some studies support the role of decreased cholinergic activity in the cognitive deficits while others demonstrate that decreased choline acetyltransferase activity is related to deterioration in cognitive performance in schizophrenia. Overall, results suggest the hypothesis that the cholinergic system is involved in the cognitive dysfunctions observed in schizophrenia and that increased cholinergic activity may improve these impairments. Furthermore, a dysfunction of glutamatergic neurotransmission could play a key role in cognitive deficits associated with schizophrenia. Further meta-analysis of various clinical trials in this field is required to account for matters on the grounds of evidence-based medicine.

Keywords: Cognition; Cognitive enhancer; Cholinergic system; Neuroleptic; Schizophrenia

Contents

1. Background . . . 220
2. Antipsychotic medication effects on neurocognition in schizophrenia . . . 221
3. On the trail of a hypothesis based on the psychopharmacologic profile . . . 221
   3.1. Dopamine . . . 221
   3.2. Cholinergic system . . . 226

Abbreviations: AchE, Acetylcholinesterase; ABAB, Counter Balance Design; ADAS-GOG, cognitive portion of the Alzheimer's Disease Assessment Scale; BuChE, Butyrylcholinesterase; CANTAB, Cambridge Neuropsychological Test Automated Battery; CRH, Corticotropin hormones; EPS, Extrapyramidal symptoms; FDA, US Food and Drug Administration's; LTM, Long-term memory; NMDA, N-methyl-d-aspartate; PRE-A, Conflict reaction time; REM, Rapid eye movement; RVP, Rapid Visual Processing; PS, Paradoxal Sleep; SOC, Stockings of Cambridge; STM, Short-term memory; SWS, Slow wave sleep.

* Corresponding author. Tel.: +1 514 251 4015x2345; fax: +1 514 251 2617.
E-mail address: emmanuel.stip@umontreal.ca (E. Stip).
URLs: http://www.hlhl.qc.ca, http://www.rohcg.on.ca/roh-internet/webpage.cfm.

0278-5846/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2004.11.004

3.3. Cholinergic system and schizophrenia . . . 226
3.4. Glutamatergic system and cognitive deficits in schizophrenia . . . 227
3.5. Noradrenergic systems . . . 228
4. New investigational agents . . . 228
5. Conclusion . . . 229
Acknowledgment . . . 229
References . . . 229

1. Background

It is very well documented that persons with schizophrenia show neurocognitive impairments across multiple domains (Green, 1998). These include impairments in motor functioning (King, 1994; Voruganti et al., 1997), in various aspects of attentional abilities (Green and Walker, 1986; Raine et al., 1997; Addington et al., 1997; Chen et al., 1998), in executive functions (Tollefson, 1996; Heinrichs and Zakzanis, 1998), and in memory functioning (Goldberg et al., 1993a,b) (Fig. 1). For a more complete review of the cognitive deficits present in schizophrenia, the reader is referred to Sharma and Harvey (2000a,b) and Green (1996).

Cognition can grow increasingly impaired with each episode of schizophrenia, and most patients remain in the fifth percentile below normal in neuropsychological functioning (Green, 1998). Furthermore, vocational functioning is impaired in patients with schizophrenia. Approximately 85% of these patients are unemployment irrespective of treatment. Cognitive deficits are thought to account in large part for this poor functional outcome (Green, 1996; Green et al., 2000). McGurk and Meltzer (2000), demonstrated that a relationship exists between cognitive deficits and work status among schizophrenic patients. As such, there is recognition that improving cognitive functioning is crucial in this patient population. However, we must determine which cognitive domains should be targeted and which psychopharmacological treatments are promising candidates for improving functioning.

Much research has taken place attempting to determine if psychopharmacological interventions can ameliorate cognitive impairments in schizophrenia. However, this area of research requires methodological refinement (Harvey and Keefe, 2001). Recently, the NIMH has identified obstacles that are likely to interfere with the development of pharmacological agents for treating cognition in schizophrenia. These include: a lack of a consensus as to how cognition in schizophrenia should be measured; differing opinions as to the pharmacological approaches that are most promising; challenges in clinical trial design; concerns in the

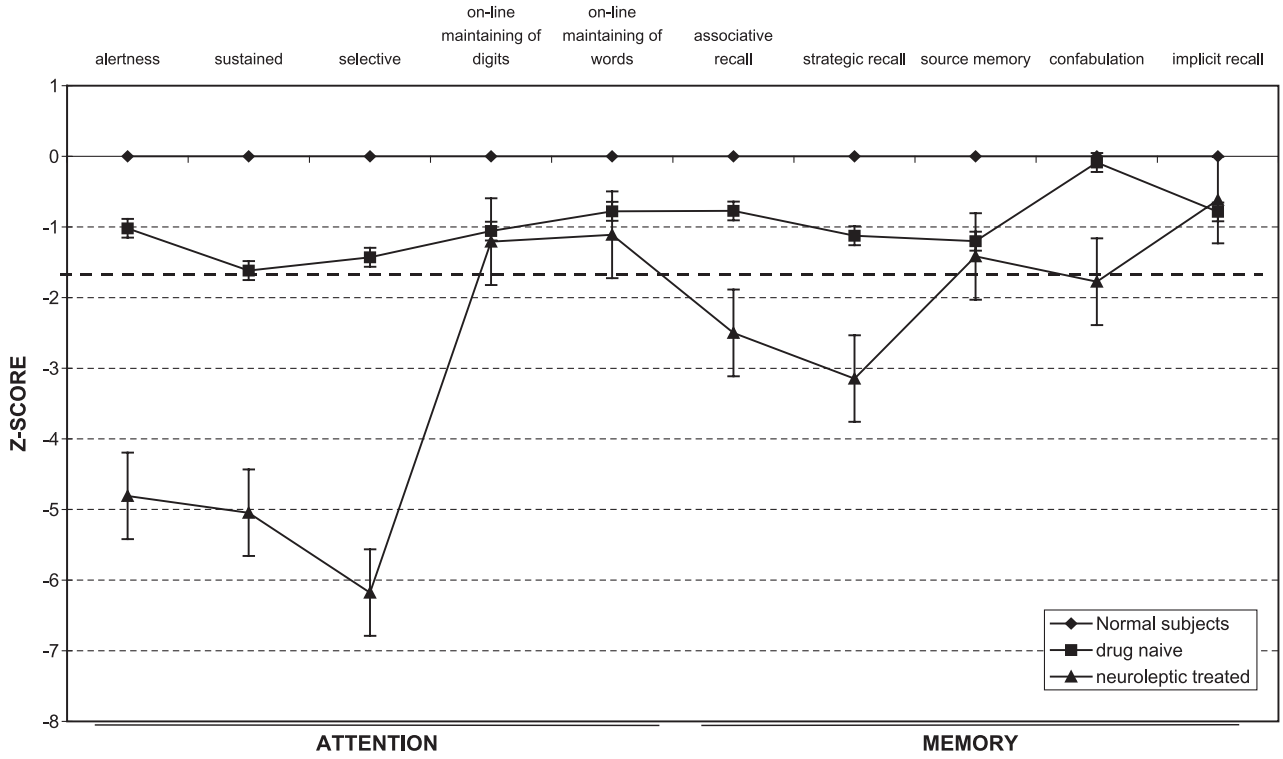

Fig. 1. Cognitive profile.