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Review article

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

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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

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.

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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

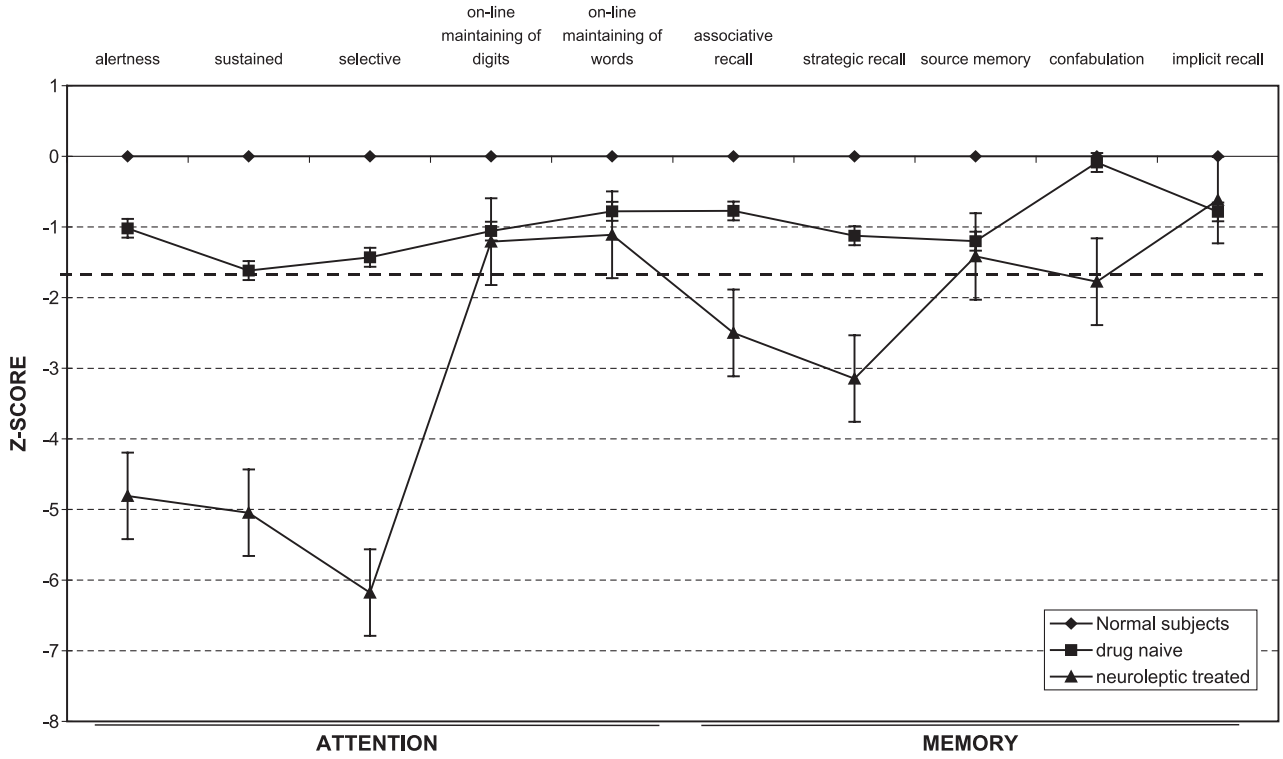

Fig. 1. Cognitive profile.

pharmaceutical industry regarding the US Food and Drug Administration's (FDA) approaches to drug approval for this indication; and issues in developing a research infrastructure that can carry out clinical trials of promising drugs. The MATRICS is a new US funded program bringing together representatives of academia, industry, and government in a consensus process for addressing all of these obstacles (Green et al., 2004).

The aim of this paper is to examine how an understanding of biochemical mechanisms underlying cognitive processes can lead to pro-cognitive drug treatments in schizophrenia.

2. Antipsychotic medication effects on neurocognition in schizophrenia

Table 1 lists the domains and instruments, which are typically used in research examining the effects of antipsychotic medications on neurocognition in schizophrenia. Knowing that antipsychotic medications influence the positive and negative symptoms of schizophrenia, what effect do they have on cognitive functioning? It is important to remember that neuroleptics were not synthesized and prescribed for the purpose of treating cognitive deficits. From the outset, 50 years ago, the goal of synthesis and prescription has primarily been to attenuate positive symptoms (and with the advent of atypical neuroleptics, negative symptoms as well) and possibly to protect against symptoms of depression (Stip, 2000a). Consequently, their potential to be recognized conceptually as cognitive enhancers is relatively artificial. Empirically, the questions regarding their impact on cognition flowed from the investigation of secondary effects. Above all, it was hoped that these drugs would not bring about deterioration in this area.

Table 2 provides a brief summary of results from trials examining the effects of antipsychotic medications in schizophrenia. Comprehensive reviews examining the effects of atypical medications have been presented elsewhere (Keefe et al., 1999; Purdon, 1999), therefore, a rehashing of this literature is beyond the scope of this paper. It is generally agreed that atypical medications are better for cognition when compared to conventional medications. This conclusion is based on studies that compared haloperidol at elevated doses. However, it must be noted that recent research using lower doses of haloperidol has demonstrated that there is very little difference between atypical and typical medications on cognitive functioning (Keefe et al., 2004).

3. On the trail of a hypothesis based on the psychopharmacologic profile

In terms of psychopharmacology, trials conducted over the past few years have shown that atypical neuroleptics such as olanzapine can improve skills related to explicit memory (Stip, 2000b). These results seemed odd to certain authors, given that olanzapine was supposed to have an anticholinergic psychopharmacological profile. Instead, few clinical anticholinergic effects were noted during the clinical trials, even when olanzapine was compared with drugs without an anticholinergic profile. Though early results were contradictory, recent controlled studies have shown that clozapine has a positive effect on various cognitive areas, especially verbal fluency and attention (Sharma and Mockler, 1998). It has also been suggested that a 5-HT_6 receptor antagonist effect may account for olanzapine's positive impact on memory. In this connection, a relationship has been demonstrated between 5-HT_6 receptors antagonism and both improvement in spatial learning in rats and increased cerebral acetylcholine (Fig. 2).

In addition, it has been suggested that clozapine and olanzapine are more effective than conventional neuroleptics in reducing negative symptoms (Kane et al., 1988; Beasley et al., 1997). Although other pharmacological mechanisms (5-HT_2 antagonism, selective mesolimbic dopamine blockade) have been proposed to explain the efficacy of clozapine and olanzapine against negative symptoms, their pronounced antimuscarinic activity may be one of the mechanisms involved (Tandon, 1997).

3.1. Dopamine

An optimum amount of dopamine activity in the prefrontal cortex is critical for cognitive functioning. From a neurochemical point of view, the "dopaminergic hypothesis" suggests that schizophrenic psychosis results from an increase in central dopaminergic transmission (Van Rossum, 1966). Conventional neuroleptics block postsynaptic dopamine D2 receptors (Farde et al., 1986). To see an improvement in positive symptoms, these receptors must be blocked 60% to 70% (Fitzgerald et al., 1999). When more than 80% blockade occurs, extrapyramidal symptoms appear (Farde et al., 1992). Atypical neuroleptics do not affect the same receptors, as do conventional neuroleptics. According to Meltzer (1990), their effectiveness in treating negative symptoms and their weak propensity for inducing extrapyramidal symptoms may be attributable to their greater affinity to serotonin 5-HT_2 receptors than for D2 receptors. Other authors (Kapur and Seeman, 2000) have suggested that it is more a question of differences in the ability to dissociate rapidly from dopaminergic receptors. In this regard, the affinity component that expresses the D2 receptor-unbinding rate (K_{off}) is faster for atypical neuroleptics such as clozapine and quetiapine, which may explain their atypical clinical properties.

Animal studies have demonstrated that clozapine increases dopamine efflux in the prefrontal cortex, with little or no effect on the limbic system. Ziprasidone, an investigational agent, was found to be more potent than

Table 1
Neurocognitive tests and descriptions

Domain	Description	Assessments
Psychomotor speed and dexterity	Psychomotor performance is typically assessed with motor tasks which place minimal demands on 'thinking' or cognition.	Grooved Peg Board; Finger Tapping Test; Pin Test (Lezak, 1983; Spreen and Strauss, 1991).
Visuoperceptual/ motor processing	Visuoperceptual and motor processing tasks require some higher-order cognitive functioning in addition to motor functioning	Trail Making Test Part A (Trails A) (Lezak, 1983) and Digit Symbol Substitution Test (Wechsler, 1981)
Verbal memory	Memory for lists of words and for verbatim recall of short paragraphs.	Rey Auditory–Verbal Learning Test (Spreen and Strauss, 1991); California Verbal Learning Test (Delis et al., 1987); Hopkins Verbal Learning Test (Brandt, 1991), Logical memory from the WMS-R; Verbal Paired Associates from the WMS-R; Digit Span Forward from WMS-R or WAIS-R.
Visual memory	Memory for nameable and non-nameable objects	Figural Memory (WAIS-III; Kaufman and Lichtenberger, 1998); Rey-Osterrieth Complex Figure Test [Rey-O] (Spreen and Strauss, 1991); (3) Visual Reproduction from the WMS-R; and (4) Visual Paired Associates from the WMS-R.
Executive functioning	Higher-order cognitive operations which require the concurrent processing of four principle elements: (1) motivation, (2) planning, (3) execution, and (4) the evaluation of performance	Wisconsin Card Sorting Test (Heaton, 1981); Trail Making Test Part B (Trails B) (Spreen and Strauss, 1991); Verbal Fluency; (Lezak, 1983); Mazes test; Design Fluency (the non-verbal counterpart to Verbal Fluency).
Attention	Attention can be divided according to types of attention: (1) selective: ability to attend to relevant or target stimuli over irrelevant stimuli; (2) sustained: ability to focus on a task for an extended period of time; (3) divided: ability to attend to two or more attentional tasks at the same time	Selective: Stroop Color Word Test (Golden, 1978); Petersen Consonant Trigram test (PCT) (Spreen and Strauss, 1991); Digit Span Distractibility Test (Oltmanns and Neale, 1975; Oltmanns, 1978); Span of Apprehension test (SoA) (Nuechterlein and Dawson, 1984) Sustained: Continuous Performance Test (CPT) Divided: Dichotic Listening
Working memory	Refers to the mental manipulation of either verbal or non-verbal information that is held in Short-Term Memory	Verbal Working Memory: Digit Span Backward; Letter Number Sequencing (WAIS-III; Kaufman and Lichtenberger, 1998) Non-Verbal Working Memory: Visual Memory Span Backward (WAIS-III; Kaufman and Lichtenberger, 1998)

clozapine in increasing dopamine efflux in the prefrontal cortex and also to have no effect on the limbic system. Both olanzapine and risperidone increase dopamine efflux in the prefrontal cortex as well. By contrast, haloperidol does not increase dopamine efflux in the prefrontal cortex, which may be part of the reason why older antipsychotic agents do not improve cognitive impairment.

Chakos et al. (1995) found that the caudate nuclei of patients treated with classical neuroleptics increased in volume, whereas the caudate nuclei volume of patients treated with clozapine diminished. For the first time, researchers demonstrated that neuroleptics had a direct effect on the brain's structures. Procedural memory requires intact basal ganglia to operate properly. Procedural learning refers to the process of learning either a cognitive or motor procedure in which the strategy of execution cannot be explicitly described (i.e., learning by doing). Procedures are then progressively learned over successive trials until there is an automation of the optimal performance. Studies of neurodegenerative disorders such as Huntington's and Parkinson's diseases show that a striatal dysfunction could affect procedural learning. In patients with schizophrenia treated with neuroleptics, some studies have reported that procedural learning is affected (Scherer et al., 2003). In normal volunteers, acute administration of chlorpromazine induces a deficit in procedural learning, which suggests a direct effect of neuroleptics, presumably via a D2 dopamine blockade in the striatum. Recently, we have shown that patients with schizophrenia who were treated with haloperidol showed deficits in procedural learning tasks, whereas clozapine- or risperidone-treated patients presented no such difficulties (Scherer et al., 2003). Purdon et al. (2003) observed differences between olanzapine, risperidone, and haloperidol on procedural learning in patients with schizophrenia. They concluded that risperidone and haloperidol negatively impacted procedural learning to a greater extent relative to olanzapine. Purdon et al. (2003) state that this difference is most likely due to differential D2 binding profiles in the dorsal striatum between medications. The differential effect of these substances on the striatal D2 receptors, irrespective of their classification as conventional or atypical neuroleptics, may explain these results. Data obtained in Montreal, in patients with schizophrenia treated

Table 2
Summary of studies examining the effects of atypical antipsychotic medications on neurocognitive functioning in schizophrenia

Author(s)	Design and trial duration	Study medication(s)	Motor	Visual perceptual	Verbal memory	Visual memory	Executive functioning	Reaction time	Attention	Working memory
Classen and Laux, 1988	Open-label, 7 days	Cozapine Haloperidol Fluphenazine (N=50)	cloz=hal						cloz=hal= fluphen	
Goldberg et al., 1993b	Open-label variable range: 3 to 24 months	Clozapine (N=13)		0 cloz	0 cloz	0 cloz - cloz (detected for immediate and delayed recall on visual reproduction)	0 cloz			0 cloz
Hagger et al., 1993	Open-label, 26 weeks	Clozapine (N=36)		0 cloz at 6 weeks +cloz at 6 months	+cloz		0 cloz (on WCST) +cloz (verbal fluency)		−cloz at 6 weeks back to baseline at 6 months	
Buchanan et al., 1994	Double-blind (1st 10 weeks) followed by open-label for 1 year	Clozapine Haloperidol (N=38)			0 cloz 0 hal	0 cloz 0 hal	0 cloz 0 hal +cloz (verbal fluency after 1 year)		0 cloz 0 hal	0 cloz 0 hal
Lee et al., 1994	Open-label 1 year	Clozapine various typicals (N=47)		cloz>typicals	+cloz +typicals		+cloz (WCST) +cloz (verbal fluency) 0 cloz (Trails B) 0 typicals (WCST) 0 typicals (Trails B) 0 typicals (verbal fluency)		+cloz 0 typicals cloz=typicals	
Zahn et al., 1994	Single-blind cross-over; 6 weeks on active medications and 20 days on placebo cross-over	Clozapine Fluphenazine Placebo (N=25)						cloz=fluphen= placebo		
Daniel et al., 1996	Single-blind cross-over 6 weeks per treatment	Clozapine Risperidone (N=20)			cloz=risp	cloz=risp	cloz=risp		cloz=risp	cloz=risp
Grace et al., 1996	Open-label, 3 years	Clozapine (N=31)		+cloz	+cloz	+cloz	+cloz			+cloz

(continued on next page)

Table 2 (*continued*)

Author(s)	Design and trial duration	Study medication(s)	Motor	Visual perceptual	Verbal memory	Visual memory	Executive functioning	Reaction time	Attention	Working memory
Stip and Lussier, 1996	Open-label average of 26 weeks	Risperidone (*N*=13			0 risp			+risp	0 risp (CPT) +risp (Span of Apprehension)	
Fujii et al., 1997	Open-label, 1 year	Clozapine (*N*=22)		0 cloz			0 cloz			
Galletly et al., 1997	Open-label, 32 weeks	Clozapine (*N*=19)		+cloz	+cloz		+cloz		+cloz	
Green et al., 1997	Double-blind 12 weeks	Risperidone Haloperidol (*N*=59)							+risp 0 hal risp>hal	
Rossi et al., 1997	Open-label 4 weeks	Risperidone (*N*=25)		+risp	0 risp		+risp			+risp
Lindenmayer et al., 1998	Open-label 12 weeks	Clozapine Risperidone (*N*=35)		0 cloz 0 risp cloz=risp	0 cloz 0 risp cloz>risp (list learning) cloz=risp (paragraphs)	0 cloz 0 risp cloz=risp	0 cloz 0 risp cloz=risp		0 cloz 0 risp cloz=risp	0 cloz 0 risp cloz=risp
Sax et al., 1998	Open-label, 9 weeks	Quettiapine (*N*=10) Normal Controls (*N*=12)							+*Q*; *Q*=NC at f/up	
Kern et al., 1998	Double-blind 12 weeks	Risperidone Haloperidol (*N*=56)	+risp 0 hal risp>hal		+rispl +hal risp>ha				risp > hal	
Manschreck et al., 1999	Open-label 12 months; comparison of patients who were discharged and inpatients	Clozapine (*N*=54)	+cloz (discharged patients only)	0 cloz	0 cloz	0 cloz	+cloz (discharged patients only on verbal fluency only)	0 cloz		
Liu et al., 2000	Double-blind 12 weeks	Risperidone Haloperidol (*N*=38)							0 risp 0 hal risp=hal	
Purdon et al., 2000	Double-blind 1 year	Olanzapine Risperidone Haloperidol (*N*=65)	+olan 0 risp 0 hal olan>hal risp=hal	0 olan 0 risp olan=risp olan>risp	0 risp	+olan +risp +hal olan=risp=hal	+olan 0 risp 0 hal olan=risp=hal			
Potkin, 2001	Double-blind during active treatment; single-blind during the placebo cross-over period; 6 weeks per treatment arm	Clozapine Haloperidol (*N*=27)		+cloz +hal	+cloz +hal cloz>hal (list learning) cloz=hal (WMS-R memory index)		WCST 0 cloz 0 hal cloz=hal Trails B +cloz 0 hal cloz>hal Verbal Fluency 0 cloz 0 hal cloz>hal			

Purdon et al., 2001a	Open-label, 6–8 weeks	Clozapine (*N*=18)		+cloz	+cloz (list learning; paragraphs; paired associates) 0 cloz (digit span forward)	+cloz	+cloz (Trails B and verbal fluency) 0 cloz (WCST)		0 cloz	0 cloz
Purdon et al., 2001b	Double-blind, 26 weeks	Quetiapine	0 quet	+quet	Verbal List Learning	Visual List Learning	WCST			
		Haloperidol (*N*=25)	0 hal	+hal	0 quet 0 hal Paragraph Memory (immediate recall) +quet +hal	+quet 0 hal Complex Figure +quet 0 hal Visual Reproduction 0 quet 0 hal	+quet 0 hal Trails B 0 quet +hal			
Smith, 2001	Double-blind for 8 weeks, then open-label olanzapine for 12 weeks	Olanzapine Haloperidol (*N*=34)			0 olan 0 hal olan=hal +olan during 3 month open label phase (verbal paired associates)	0 olan 0 hal olan=hal +olan during 3 month open label phase (visuospatial memory)	0 olan 0 hal olan=hal	0 olan 0 hal olan=hal		0 olan 0 hal olan=hal
Velligan et al., 2002	Double-blind, 24 weeks	Quetiapine	–	+quet	0 w/in analyses;				que>hal	
		Haloperidol (*N*=58)		+hal	quet=hal				at 24 weeks	
				quet>hal–	quet>hal					
Stip et al., 2003	Open-label, 8 weeks	Olanzapine (*N*=134)			+olan		+olan			
Bilder et al., 2002	Double-blind, 14 weeks	Clozapine Risperidone Olanzapine Haloperidol (*N*=101)	+cloz 0 risp 0 olan 0 hal				0 cloz +risp +olan 0 hal			

cloz—clozapine; hal—haloperidol; risp—risperidone; olan—olanzapine; quet—quetiapine; fluphen—fluphenazine; +, indicates improved performance; −, indicates reduced performance; >, indicates greater improvement of one medication over the other.

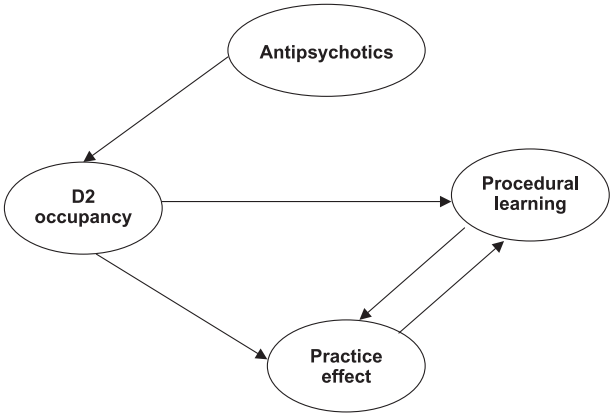

Fig. 2. Low and high D2 occupancy.

with Olanzapine and haloperidol using iodine 123-BZM with SPECT have shown that the melody of learning (or smoothness or learning consistency) in a visuomotor procedural task varies inversely with D2 receptor level saturation (Paquet et al., 2004). This line of research suggests that longitudinal studies examining the difference between atypical and typical (blocking a lot D2) agents requiring repeated measures with regard to cognitive performance can only be due a better preservation of the practice effect, i.e. the procedural learning. This is not due per se to the direct effect of the medication on the task but on the implicit learning of a task, which is related to a lower D2 blockade. In conclusion improvement related to new antipsychotics is related to a better side effect profile but not to a direct cognitive enhancing effect.

3.2. Cholinergic system

Cholinergic therapy (inhibition of cholinesterase) in Alzheimer's disease initially focused on inhibiting AChE, because AChE was the only enzyme known to be involved in inactivating acetylcholine in the healthy brain. However, it is now largely acknowledged that inhibition of AChE using specific inhibitors (donezepil) can elevate brain ACh levels, as evidenced in pre-clinical studies. AChE inhibitors divide into two main therapeutic classes based on their mode of action. Dual-action AChE inhibitors target both AChE and BuChE, whereas single-action AChE inhibitors target one of the two cholinesterase (AChE or BuChe) more specifically. Rivastigmine, which is CNS selective, is a dual-action AChE inhibitor (Kennedy et al., 1999). In placebo-controlled clinical trials lasting 6 months, rivastigmine had significant beneficial effects on the cognitive functions of patients with mild-to-moderate Alzheimer's disease (Giacobini, 2000). The cognitive functions of patients who received placebo deteriorated, while the mean variation in scores measuring the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-GOG) improved significantly among patients who received 3 to 6 mg of rivastigmine twice daily. In addition, the clinical trials demonstrated that rivastigmine provided benefits with respect to ADL, behaviour, and cognition across the entire disease continuum.

Diminished cholinergic activity has been associated with memory impairment (Karson et al., 1993, 1996). As is the case with dopamine, atypical antipsychotic agents also increase the efflux of acetylcholine in the prefrontal cortex. This is another quality that sets them apart from the typical antipsychotics. 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. Atypical antipsychotic drugs are not all the same, however; these have different effects on cognition, which is probably explained by the potency of their relative activity at different receptor sites. Compared with clozapine, olanzapine, quetiapine, and risperidone, ziprasidone is more potent at the following key receptor sites: D2, 5-HT2a, 5-HT1a, and 5-HT2c receptors (Schotte et al., 1995).

3.3. Cholinergic system and schizophrenia

Numerous studies have pointed to an anomaly of the cerebral (prefrontal) nicotinic and muscarinic receptors in schizophrenia (Breese et al., 2000; Freedman et al., 2000; George et al., 2000; Crook et al., 2001; Lai et al., 2001) or of the interneurons of the subcortical structures (Holt et al., 1999; German et al., 1999). Tandon et al. (1991) suggested that the cholinergic system played a key role in the pathophysiology of schizophrenia and that cholinergic–dopaminergic interactions were pertinent in the expression of positive and negative symptoms. More specifically, these authors suggested that muscarinic hyperactivity might be relevant in the production of negative symptoms and that reduced cholinergic activity might be associated with positive symptoms (Tandon and Greden, 1989). Finally, the Tandon group showed that biperiden, a relatively selective anticholinergic muscarinic M1 antagonist, reduced negative symptoms in unmedicated schizophrenic patients (Tandon et al., 1991, 1992a). Consequently, it would appear that the beneficial effects could not be attributed solely to improvement in extrapyramidal symptoms.

Another argument suggesting that cholinergic activity is involved in the negative symptoms of schizophrenia centers on its implication in sleep regulation (Tandon et al., 1992b; Riemann et al., 1994). According to Hobson (1988), PS appears when aminergic neurotransmission is low (REM-off system) and/or when cholinergic neurotransmission is elevated (REM-on system). Given that REM sleep regulation and the phasic and tonic aspects of dreaming are under cholinergic control, several groups have conducted sleep studies with a view to clarifying the role of the cholinergic system in schizophrenia. Increased cholinergic activity is associated with shortened REM latency and a reduction in SWS duration. Studies have shown that presence of negative symptoms correlates significantly with

shortened REM latency (Tandon et al., 1991) and increased SWS (Ganguli et al., 1987; Van Kammen et al., 1988; Tandon and Greden, 1989). In studies involving healthy subjects, administration of AChE inhibitors has at times shortened PS latency (Schredl et al., 2000; Holsboer-Trachsler et al., 1993). However, in populations where REM latency is already reduced, as is the case with schizophrenics, no effect was observed—possibly because the cholinergic system is hyperfunctional in this disease (Tandon and Greden, 1989; Keshavan et al., 1992).

Negative symptoms have also been linked to an increase in post-dexamethasone cortisol (Tandon et al., 1991; Saffer et al., 1985), in growth hormone response to TRH (Keshavan et al., 1989), and in pyridostigmine (O'keane et al., 1994), during the acute psychotic phase of schizophrenia. These data indirectly support the role of increased muscarinic activity in the production of negative symptoms, as cholinergic mechanisms are known to play a role in the release of corticotropin hormones (CRH) and in the regulation of growth hormone response to TRH stimulation.

It seems, then, that cholinergic hyperactivity may be involved in the production of negative symptoms in a subgroup of patients with schizophrenia and that cholinergic interaction with other transmitters may be important in the pathogenesis of negative symptoms during certain phases of the disease.

Atypical antipsychotics increase acetylcholine release in prefrontal cortex and hippocampus (Ichikawa et al., 2001). Olanzapine seems to be the most powerful on this mechanism as suggested by Shirazi-Southall'study (2002) on the acetylcholine efflux in rat hippocampus. Other drugs useful in psychiatry with indications other than schizophrenia could be of potential beneficial effect in schizophrenia.

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 of schizophrenia (Karson et al., 1993, 1996). These studies demonstrated that decreased choline acetyltransferase activity was related to deterioration in cognitive performance in schizophrenia. A recent study indicated that reduced anticholinergic activity played a role in the cognitive deficits of the schizophrenia spectrum (Kirrane et al., 2001). These authors showed that administration of cholinomimetics such as physostigmine improved cognitive performance in a visuospatial working memory task among patients with schizotypical personality disorder.

Similarly, a case study using an ABAB design which is a counterbalanced design to prevent the possibility of carry-over effects from trial to trial with donepezil as an add-on treatment to risperidone showed improvement in verbal fluency (MacEwan et al., 2001). However, a recent report by Friedman et al. (2002) failed to show any beneficial effect on cognition of donepezil added on to risperidone among 36 patients. In their discussion of these unexpected results, the authors raised methodological issues that remain to be analyzed more closely, including the effects of tobacco use on their series of patients (nicotinic tolerance was not evaluated). In this regard, it was recently demonstrated that, when given nicotine, patients with schizophrenia who smoked showed an improvement in episodic memory performance (Blaxton et al., 2001). Overall, these 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 (Hussain et al., 2001).

The presence of abnormal cholinergic function in schizophrenia provides the rationale to test the effectiveness of cholinesterase inhibitors in treating cognitive impairment in cognitively impaired patients with schizophrenia (Chouinard et al., 2004; Stip et al., 2004). Nineteen patients (age 28.6±6.7 years; M=11, F=2) stabilized with atypical neuroleptic underwent neurocognitive evaluations performed with Cambridge Neuropsychological Test Automated Battery (CANTAB) before and after 12 weeks of treatment with rivastigmine. Doses were adjusted depending on the tolerability of patients. Beginning at 3 mg/day reaching 6 mg the first month to progressively increase to 9 mg/day. Tasks used were "Stockings of Cambridge" (SOC) which evaluated executive functions and procedural memory and "Rapid Visual Processing" (RVP), which evaluated sustained attention, working memory, and visual detection. The results revealed that patients have improvements in executive functions such as planning after treatment with rivastigmine: they resolved more problems in a minimum of moves on the SOC. We also noted improvement in procedural memory: the patients proceed more rapidly on SOC after initial move. The patients show improvement in sustained attention: they made less error on RVP task in detecting stimuli. The PANSS score did not show a deterioration of the positive symptoms. Another recent study by Lenzi et al. (2003) found that rivastigmine resulted in significant improvements in quality of life, which were paralleled by significant improvements in cognitive function, learning, and memory, and trends for improvement in attention.

3.4. Glutamatergic system and cognitive deficits in schizophrenia

The glutamatergic neurons are the major excitatory pathways linking the cortex, limbic system, and thalamus, three regions believed to be involved in schizophrenia. A recent approach in the treatment of persistent negative symptoms and cognitive deficits has centered on the use of N-methyl-d-aspartate (NMDA) receptor agonists, such as glycine, D-serine and D-cycloserine. These drugs, when taken in conjunction with conventional or atypical antipsychotics, have brought about a significant reduction in both negative and cognitive symptoms. The importance of the glutamate NMDA receptor stems from the fact that

its blockade can induce behavioural and cognitive deficits in normal subjects which mimic schizophrenia (Krystal et al., 1999). Agents that indirectly enhance NMDA receptor function via the glycine modulatory site reduce negative symptoms and variably improve cognitive functioning in schizophrenic patients treated with typical antipsychotics (Goff and Coyle, 2001). Tsai et al. (1998) reported cognitive improvement in performance on the Wisconsin Card Sorting Test among schizophrenic patients who took D-serine together with antipsychotics. Following a comprehensive review of the literature addressing the role of glutamate in the pathophysiology of schizophrenia, these authors concluded that a dysfunction of glutamatergic neurotransmission could play a key role in the negative symptoms and cognitive deficits associated with schizophrenia.

3.5. Noradrenergic systems

The role of noradrenergic systems in cognition has been well studied. Animal as well as human research demonstrate that norepinephrin has a direct influence on prefrontal cortical functioning via postsynaptic α_{2a}-adrenoceptors (Friedman et al., 2004; Arnsten, 2004). Animal research has demonstrated that noradrenergic projections from the locus ceruleus to the prefrontal cortex can influence cognitive functioning, and more specifically, working memory and selective attention abilities. For instance, Coull (1994) demonstrated that agonism of the α_{1-2} receptors using clonidine and guanfacine can improve aged monkeys ability to attend to a delayed response task. Reducing noradrenergic activity has been shown to impair monkeys' attention abilities (Friedman et al., 2004). Friedman et al. (2004) reviewed the literature on potential noradrenergic targets which could influence cognitive functioning in schizophrenia. They concluded that an alpha 2a agonist such as guanfacine could improve cognitive functioning. Another target proposed was the inhibition of norepinephrin reuptake using atomoxetine.

In summary, the basis for the effectiveness of atypical antipsychotic agents on cognition rests on their ability to promote increased dopaminergic and cholinergic activity in the prefrontal cortex, antagonism at the 5-HT2a, 5-HT1a, 6, and 7 sites, and actions on other neurotransmitter systems. Numerous actions modulating the effects of atypical antipsychotics on DA and Ach release have been suggested: increasing prefrontal cortical dopamine and acetylcholine efflux (Kuroki et al., 1999); diminish the stimulation of AMPA/kainate glutamate receptors (Moghaddam et al., 1997) by 5-HT2a antagonism (Aghajanan and Marek, 2000) and 5-HT1a agonism (Ichikawa et al., 2001); blockade of neurotoxic effects of glutamate (Olney and Farber, 1995) changing pattern of gene expression in specific brain area (Robertson and Fibiger, 1996) or enhancing neurogenesis and connectivity (Gould, 1999). Some authors showed a contribution of 5-HT2a and D2 receptor antagonism to dopamine efflux in prefrontal cortex and N. Accumbens (Liegeois et al., 2002). In addition the role of 5-HT1a agonism in dopamine efflux in prefrontal cortex has been demonstrated (Yoshino et al., 2002).

4. New investigational agents

The discovery of atypical neuroleptics for the treatment of schizophrenia made it possible to improve the condition of patients. Meltzer (1990) defined atypical neuroleptics in terms of three characteristics: efficacy in treating negative symptoms and patients refractory to conventional therapies; few extrapyramidal effects; and mild prolactin elevation. There are several families of atypical neuroleptics: dibenzodiazepines (clozapine, olanzapine, quetiapine, zotepine, and amoxapine), benzamides (remoxipride and amisulpride), benzisoxazole (risperidone), ziprasidone, and sertindole.

Ziprasidone is the latest of the atypical antipsychotic agents. It presents a low incidence of side effects and an interesting and unique receptor profile. In one study, patients with schizophrenia who were stable on conventional antipsychotics, olanzapine, or risperidone were switched to ziprasidone on a flexible dosing schedule of 80 to 160 mg/day in an open-label fashion (Harvey et al., 1997). The switch to ziprasidone resulted in a statistically significant improvement in total learning and long-delay recall for patients originally taking conventional antipsychotics ($P<0.01$), olanzapine ($P<0.001$), or risperidone ($P<0.001$). A statistically significant improvement in the Digital Span Subtraction Test (a measure of attention/motor function) was observed in patients on ziprasidone who were switched from conventional antipsychotics or risperidone ($P<0.05$), but not in patients switched from olanzapine. Scores on the Continuous Performance Test significantly improved among patients switched from olanzapine ($P=0.01$) or risperidone ($P=0.038$), but they worsened among those switched from conventional antipsychotic medication. Significantly fewer errors were noted on the Wisconsin Card Sort Test (a measure of executive functioning) (Heaton, 1981) among patients switched from risperidone to ziprasidone ($P<0.001$), but not much effect was discerned among those switched from olanzapine to ziprasidone.

Ziprasidone treatment was associated with significant improvement across multiple areas of cognition when patients were switched from conventional antipsychotics, olanzapine, risperidone, or ziprasidone at doses used in the study. Cognitive improvements were noted for learning and memory, attention, and executive functions. The results suggested that ziprasidone had the potential to improve cognitive deficits. It also proposed that after a switch from other compounds to ziprasidone, the practice effect due to repetition of neuropsychological sessions with several tasks was facilitated.

Aripiprazole is a novel antipsychotic drug with a partial affinity to dopamine D2 receptors and a high affinity to 5-HT(1A) receptors. This stabilizing effect on the dopamine–serotonin system may contribute to the overall efficacy of aripiprazole against the anxiety, depression, negative symptoms, and cognitive deficits associated with schizophrenia (Jordan et al., 2002). Cornblatt et al. (2002) demonstrated aripiprazole's superiority over olanzapine in secondary verbal memory, but not in visual memory or executive functioning. Aripiprazole's neurocognitive benefits and the favorable side-effects profile may provide health advantages and facilitate psychosocial rehabilitation.

5. Conclusion

Cognitive impairment is now recognized as a major contributor to poor functional outcome among patients with schizophrenia. It is no longer sufficient to treat positive and negative symptoms; treatment should also be aimed at improving cognition in an attempt to help patients function better in the community. Typical antipsychotic agents do not improve cognition, and they induce a host of adverse effects. Anticholinergic drugs, which are used as adjuncts to antipsychotic agents, also have adverse effects. The newer antipsychotic agents appear to have a more favorable side-effects profile and to improve cognition. However, these drugs act differently across the cognitive domains (Harvey and Keefe, 2001).

Multiple avenues of research in neurotransmission suggest that neurotransmitters other than dopamine and serotonin are implicated in the clinical symptoms of schizophrenia, especially cognitive impairments. Consequently, the administration of drugs modulating cholinergic or glutamatergic neurotransmission holds the potential of a novel treatment for the cognitive deficits associated with schizophrenia. What remains to be clarified is the nature, extent, and mechanisms of these cognitive deficits as well as the link between the deficits and the effects of the medication. Also, further meta-analysis of this field is required to account for matters on the grounds of evidence-based medicine. Promising studies in which cognitive tasks involving working memory have been investigated using fMRI (Mendrek et al., 2004) may allow us to gain a better understanding of the mechanisms at play. If, as suggested by the evidenced-based literature, outcome is related to the cognitive spheres, then cognitive psychopharmacology is a discipline that cannot be overlooked. Where schizophrenia is concerned, we have taken but the first few steps on the road that will lead to the discovery of a cognitive enhancer.

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