Pharmacologic Strategies for Augmenting Cognitive Performance in Schizophrenia

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There is recognition that the cognitive symptoms of schizophrenia have the most substantial impact on illness outcome. Domains of cognition reported to be significantly affected include serial learning, executive function, vigilance, and distractibility, to name a few. Dopamine activity at D1 receptors mediates many cognitive processes subserved by the prefrontal cortex (PFC), particularly working memory. The number of D1 receptors in the PFC is decreased in schizophrenics and is unaffected by chronic administration of typical neuroleptics. Therefore, medications that increase dopamine in the PFC, such as atypical neuroleptics, or that directly activate the D1 receptor may prove useful in the remediation of prefrontal-dependent cognitive deficits in schizophrenia. Decreased levels of cortical norepinephrine (NE) are associated with impaired learning and working memory in animal models, and can be reversed by drugs that restore NE activity. More specifically, α-2 adrenergic receptor agonists have been particularly effective in improving delayed response performance in young monkeys with localized 6-hydroxydopamine lesions in the PFC. Furthermore, human postmortem studies have demonstrated decreased NE in the frontal cortex of demented schizophrenic patients. Therefore, α-2 receptor agonists hold promise as drugs to improve cognitive performance on tasks dependent upon PFC function in schizophrenics. Finally, the finding that cortical choline acetyl transferase activity correlates with Clinical Dementia Rating scores in schizophrenic patients and that cholinomimetic drugs enhance cognition in healthy subjects suggests that cholinergic drugs may also treat cognitive symptoms in schizophrenia. Two potential types of cholinomimetics for use in schizophrenics are the acetylcholinesterase inhibitors and M1/M4 muscarinic agonists, both of which increase cortical cholinergic activity. Biol Psychiatry 1999;45:1–16

Key Words: Cognitive, remediation, schizophrenia, dopamine, norepinephrine, acetylcholine

Introduction

The last few years have seen a recognition that cognitive symptoms have the most substantial impact upon illness outcome in schizophrenia, more so than either positive or negative symptoms (Breier et al 1991; Green 1996; Harvey and Keefe 1997). There are cognitive deficits that prevent a patient from retaining or relearning skills that are necessary for community functioning and reintegration that can be regarded as "rate limiting cognitive factors." Improvement of these deficits is hypothesized to lead to improved illness outcome.

Although typical neuroleptics are most effective in the management of positive symptoms, they do not remediate cognitive dysfunction (Verdoux et al 1995; Seidman et al 1993; Cleghorn et al 1990). Most patients experience cognitive deficits despite having achieved remission of positive symptom (Bilder et al 1992; Nuechterlein and Dawson 1984), which refutes the notion that cognitive dysfunction derives from positive symptoms. Therefore, cognitive symptoms have emerged as an independent feature of schizophrenia that needs to be targeted for remediation independent of positive symptoms.

There is a great deal of evidence implicating the prefrontal cortex (PFC) in cognitive functions relevant to schizophrenia (Goldman-Rakic 1987). The PFC has rich catecholaminergic innervation (Lewis 1992) so that dysfunction of this brain region could likely involve disruption of normal catecholaminergic functioning including dopaminergic (DA) and noradrenergic (NE) functioning. Therefore, pharmacologic remediation of cognitive symptoms through manipulations of these neurotransmitter systems merits investigation. In addition, evidence implicating the involvement of acetylcholine (ACh) in cognitive processes relevant to schizophrenia provides potential for remediation strategies by manipulations of acetylcholine as well.

This review will be limited in scope to the DA, NE, and ACh neurotransmitter systems for a few reasons. First, animal models demonstrate that enhancement of these neurotransmitter systems improves cognitive function, especially those relevant to schizophrenia. Second, there is direct evidence from human studies that dysfunction of these neurotransmitter systems correlates with the cognitive dysfunction in schizophrenia. Lastly, drugs targeting

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these neurotransmitter systems are available for clinical trials in schizophrenic patients and have already demonstrated cognitive enhancing potential in human subjects.

Given the evidence supporting risperidone's ability to improve the performance of schizophrenic patients on tasks of verbal working memory (Green et al 1997) and executive function (McGurk et al 1997), there is a growing interest in examining the potential of atypical neuroleptics as drugs that can remediate the cognitive dysfunction of schizophrenia. The proposed mechanism of this beneficial effect on cognition is antagonism of serotonin $(5\text{-HT})_{2A}$ receptors, which in turn activates dopaminergic neurons that project to the PFC, thereby increasing DA neurotransmission in the PFC; however, pharmacologic studies of 5-HT_2 receptor antagonists administered alone have demonstrated these drugs either impair or have no effect on the performance of animals and humans on tests of learning, memory, or attention (Welsh et al 1998; Routsalainen et al 1997; Vitiello et al 1997; Harvey et al 1996; Danjou et al 1992). Therefore, references to the effects of atypical neuroleptics on cognition in relation to 5-HT_2 receptors will be reviewed in the section on dopamine given that these effects are mediated through cortical dopaminergic neurotransmission.

There is also growing interest in the *N*-methyl-D-aspartate (NMDA) type of glutamate receptor as a pharmacologic target in the treatment of schizophrenia based on a proposed glutamatergic deficiency in schizophrenia. The evidence implicating the NMDA receptor in learning and memory in animals has prompted clinical trials of agents that facilitate NMDA receptor activity in schizophrenic patients to enhance cognitive function; however, trials of NMDA receptor agonists, such as D-cycloserine and milacemide, have not convincingly proven their therapeutic utility in schizophrenia. A few studies have demonstrated a positive effect of NMDA agonists (Golf et al 1995), whereas other studies have demonstrated no effect (Rosse et al 1991, 1996) or a deleterious effect on schizophrenic symptoms (Golf et al 1996;Cascella et al 1994). More recently, a new class of glutamatergic drugs, referred to as AMPAkines, have been developed that activate the AMPA-type glutamate receptor. Behavioral studies indicate that one such AMPAkine, CX516, improves encoding of memory in rats (Hampson et al 1998a, 1998b) and some aspects of memory in humans as well (Ingvar et al 1997; Lynch et al 1997). These data offer some promise for this class of drug to be used as an augmentation agent to enhance cognitive performance of schizophrenic patients; however, safety trials of CX516 have not utilized doses given as successive daily administrations, which would be required for studies evaluating its therapeutic utility in schizophrenia. Therefore, any recommendations for use of these drugs in schizophrenia will have to wait until adequate safety data are available. A more thorough review of the role of glutamate in the cognitive dysfunction of schizophrenia is beyond the scope of this paper.

Ultimately, the review will offer testable hypotheses for manipulating the DA, NE, and ACh neurotransmitter systems with the goal of enhancing the therapeutics of schizophrenia by remediating some of the cognitive deficits.

Dopamine

Role of Dopamine in Cognition

PFC dopamine plays an important role in cognition. The spatial delayed response task in animals is particularly sensitive to PFC lesions. During this task animals have to retain a spatial item, whether it is food location or the position of a visual target, over a specific period of time and recall that location. This test is considered a specific test of frontal function and working memory. Working memory refers to a process by means of which an item of information can be maintained "in mind" to allow operations conducive to comprehension and planning (Goldman-Rakic 1996).

The cellular basis of working memory appears to involve a group of neurons found in the PFC that exhibit "memory fields" in the delayed response task. Memory fields are defined as the maximal firing of a neuron to the internal representation of a visual target in one or a few neighbor locations of the visual field. These cells are characterized by increased firing when the animals must retain the location of the target during a delay period between target presentation and time of response. Different neurons encode different target locations. When these neurons fail to maintain their activity during the delay period performance on the task worsens (Williams and Goldman-Rakic 1995).

Working memory can be improved or worsened by manipulating dopamine in the PFC. When dopaminergic neurons projecting to the PFC from the ventral tegmental area in the rat are destroyed by injection of 6-hydroxydopamine (6-OHDA), dopamine concentration in the PFC falls to levels significantly below baseline, and performance in the delayed response task becomes severely impaired (Simon et al 1980). The same impairment in delayed alternation tasks is observed when the 6-OHDA injection is directly applied to the PFC.

Pharmacologic Manipulations of the Dopaminergic System

The destruction of the dopaminergic projections to the PFC is not the only means of inducing working memory

deficits in the rat. The use of dopaminergic antagonists, especially those more selective for the D1 receptor such as SCH2330, worsens performance in the delayed response paradigm (Didriksen 1995). This is consistent with anatomical data indicating that the D1 receptor is the most abundant dopaminergic receptor in the mammalian PFC (Goldman-Rakic et al 1990; Cortes et al 1989), and therefore most likely to be involved in the cognitive processes mediated by dopamine in the PFC.

Comparative analysis of the neuroanatomy of the PFC of both humans and primates shows that the organization of the cortical dopamine system is similar (Goldman-Rakic et al 1992), allowing extrapolation of information generated in monkeys to humans. A clear link between PFC dopamine and working memory is apparent in monkeys. As in the rodent, near-total depletion of dopamine in the monkey PFC, induced by selective destruction of dopaminergic terminals via 6-OHDA injection, produces a performance deficit in the delayed alternation task that is equivalent to the deficit seen in that task after total PFC ablation. This deficit can be reversed to predepletion performance by intraperitoneal administration of either levodopa (L-DOPA) or apomorphine (Brozoski et al 1979). Specifically, iontophoretic application of dopamine to the PFC of animals performing a delayed response task induces an increase in neuronal firing during the delay period (Sawaguchi et al 1988), which constitutes the basis for the previously described task improvements observed after L-DOPA and apomorphine administration. Furthermore, measurement of dopamine concentration in the PFC of monkeys before and during performance of a delayed response task shows a significant increase in the dopamine levels while the animals are engaged in the working memory test (Watanabe et al 1997).

Injection of selective D1 receptor antagonists, such as SCH39166 or SCH23390, and nonselective D1 antagonists, such as haloperidol, to the monkey's PFC induces deficits in the delayed response task that are dose dependent. The higher the dose that the animal receives, the worse its performance. These working memory impairments do not occur after application of the D2-selective antagonist sulpiride, nor the D2/D3 antagonist raclopride, suggesting that the observed defects are specific to D1 receptor blockade (Sawaguchi and Goldman-Rakic 1991, 1994); however, dopaminergic blockade does not invariably worsen performance in working memory tasks. Iontophoretic application of the selective D1 antagonist SCH39166 during the delayed response task increases neuronal firing during the delay period. This enhancing effect disappears if the applied dose is further increased, resulting in a decrease in neuronal activity (Williams and Goldman-Rakic 1995). When the D1 antagonists are applied iontophoretically at effectively low doses there is an increase in firing frequency during the delay period. When the dose is further increased there is a decrease in the activity of the memory cells, which correlates with the behavioral deficits.

An increase in extracellular dopamine concentration in the PFC can be detrimental for working memory if it is above basal levels. Such an increase, equivalent to the one seen under mild stress (Thierry et al 1976), can be achieved experimentally via administration of the anxiogenic β-carboline FG7142 (Tam and Roth 1985), producing performance deficits in working memory tasks in both rats and monkeys. This impairment is positively correlated with dopamine turnover (i.e., more dopamine induces more impairment) and can be reversed by SCH23390, haloperidol, or the atypical neuroleptic clozapine (Murphy et al 1996). An equivalent result can be seen with administration of the D1-selective agonists A77636 and SKF81297. At low doses there is improved performance in working memory tasks, but, when the dose is increased the result can be impairment (Cai and Arnsten 1997). These data are taken as indicating that dopamine enhances working memory only within a certain limited concentration range beyond which it can become excessive for optimal working memory function, and below which deficits are also encountered.

Chronic administration of phencyclidine (PCP), a noncompetitive NMDA receptor antagonist, induces a decrease in basal and stress-related dopamine levels in the prefrontal cortex of mammals that continues after cessation of PCP administration. Consistent with the dopaminergic model of frontal cognitive dysfunction, this decrease translates as behavioral deficits in working memory tasks in the monkey (Jentsch et al 1997b). This impairment can be corrected by administration of the atypical neuroleptic clozapine, which increases extracellular dopamine in the PFC of monkeys (Youngren et al 1994). The effect of clozapine in the control animals is the opposite, worsening performance in the working memory task. This is consistent with the hypothesis that an increase in dopamine beyond the baseline level is detrimental for working memory.

Relevance to Schizophrenia

The revised dopaminergic hypothesis of schizophrenia proposes the coexistence of a hyperdopaminergic state in the mesolimbic pathway along with hypodopaminergia in the mesocortical tract. Positive symptoms are induced by elevation of dopamine in the limbic system, whereas negative and cognitive symptoms are due to decreased dopamine prefrontal function (Davis et al 1992). The degree to which decreased cortical dopamine is related to the cognitive impairment of schizophrenia (Kahn et al 1994) is worth investigating because of the potential

strategies for improving the cognitive deficits of schizophrenia this work uncovers.

Both animal and human studies have demonstrated that PFC concentrations of homovanillic acid (HVA) show a direct correlation with cerebrospinal fluid (CSF) HVA concentrations (Elsworth et al 1987; Wester et al 1990). Consequently, changes in mesocortical dopamine in schizophrenia can be measured via CSF levels of the dopamine metabolite HVA, which is considered a reflection of cortical dopamine metabolism (Pickar et al 1992). It is not surprising, therefore, that CSF HVA correlates with performance on neuropsychological measures in schizophrenic patients. Low CSF concentration of HVA predicts poor performance in visuospatial recall tasks and attention in verbal tasks and executive function measured by the Wisconsin Card Sorting Test (WCST), in schizophrenic patients (Berman et al 1988; Kahn et al 1994).

A consistent pattern of decreased PFC blood flow in schizophrenia has been demonstrated by functional imaging studies (Ingvar and Franzen 1974; Berman and Weinberger 1991). Moreover, tasks that normally produce increases in blood flow to the PFC, such as the WCST, fail to have such an effect in schizophrenic patients (Weinberger et al 1986, 1988). It is well recognized that schizophrenics perform poorly on the WCST (Goldberg et al 1987; Elliott et al 1995). This impairment is due to a primary deficit in working memory. WCST performance is also significantly correlated with performance in an auditory working memory task (Gold et al 1997) and an oculomotor delayed response task, which measures visuospatial working memory (Park 1997). Based on these data it can be hypothesized that enhancing working memory via manipulation of dopamine in the PFC should result in improved WCST performance. Indeed, administration of amphetamine during the WCST induces an increase in PFC blood flow, which correlates with the improvement seen in task performance after drug administration (Daniel et al 1991).

A correlation exists between the number of PFC D1 receptors and WCST performance in schizophrenia. The number of prefrontal D1 receptors is decreased in schizophrenic patients, irrespective of medication status. There is a direct correlation between D1 receptor number in the PFC and WCST performance and Brief Psychiatry Rating Scale negative symptom scores (Okubo et al 1997), suggesting that decreased number of PFC D1 receptors along with decreased dopaminergic turnover in the PFC are the basis of the impairments in executive function seen in schizophrenia.

Poor visuospatial working memory performance in schizophrenics has been reported using a human analogue of the monkey's delayed response task (Park and Holtzman 1992). This deficit is independent of medication (Carter et al 1996; Fleming et al 1997a). There is evidence that this working memory deficit is already present at the time of the first episode (Gur et al). Verbal working memory, measured by a Brown–Peterson paradigm or the digit span test, is also defective in schizophrenia (Fleming et al 1995; Green et al 1997).

Therapeutic Implications

Typical neuroleptics have little or no effect on measures of executive function and working memory in schizophrenia. Haloperidol, a D2 and D1 antagonist drug, induces decreases in neuronal firing in the delay period of the delayed response task; however, this decrease does not translate into a behavioral deficit in humans (Sawaguchi and Goldman-Rakic 1991). In addition, short-term (2 weeks) administration of neuroleptics induces an increase in the number of D1 receptors in the PFC (Damask et al 1996), whereas chronic administration (6 months) decreases the amount of D1 receptors in the PFC of monkeys (Lidow et al 1997; Lidow and Goldman-Rakic 1994). Perhaps neuroleptics do not worsen executive performance in schizophrenia, as could be expected by the reduction in D1 receptors, because there is a deficit prior to treatment, and chronic treatment induces little further decreases in PFC D1 receptor density of schizophrenic patients.

Drugs That Increase PFC Dopamine

All atypical neuroleptics antagonize 5-HT_{2A} receptors, which in turn activates dopaminergic neurons in the ventral tegmental area (VTA), which project to the PFC, nucleus accumbens, and the substantia nigra (SN). This inhibition is mediated by 5-HT_{2A} receptors located on the soma of the dopaminergic neurons. Systemic administration of low doses of 5-HT_{2A} blockers, such as ritanserin, or atypical neuroleptics with 5-HT_{2A} blocking properties, like risperidone or ziprasodone, selectively increase firing of VTA neurons, with a consequent increase in PFC dopamine turnover. Furthermore, if the 5-HT_{2A} blockers are applied to the PFC via local injection, the same increase in extracellular DA turnover is not observed.

This increase in PFC dopamine after atypical neuroleptic administration may be beneficial in the remediation of PFC-dependent cognitive deficits, such as working memory. There is evidence that risperidone can improve verbal working memory as measured by the Digit Span Distractibility Test (Green et al 1997), and executive function measured by the Trails B test (McGurk et al 1997). In both cases the subjects were tested pre- and post-drug treatment, and the control group was constituted by schizophrenic patients receiving haloperidol; however, despite showing improvement after administration of risperidone,

the performance rates in both tests continued to be subnormal. Long-term follow-up studies are necessary to detect whether the observed improvements in executive function and working memory correlate with improvements in illness outcome.

Clozapine also induces an increase in extracellular concentration of dopamine in the PFC. This increase is seen both as a response to a challenge dose, and as an increase in basal dopamine turnover after subchronic (21 day) administration (Youngren et al 1984), and is sufficient to acutely ameliorate the cognitive deficits induced by chronic PCP administration in the monkey; however, long-term (12–15 months) administration of clozapine to schizophrenic patients does not appear to improve executive function (Goldberg et al 1993; Hagger et al 1993; Buchanan et al 1994; Hoff et al 1996) despite improvement in other areas of cognition such as verbal fluency or digit coding. One possible explanation is clozapine's interaction with other transmitter systems, such as its potent anticholinergic effects. Another possibility is the development of tolerance to the actions of clozapine on PFC dopamine; however, there are no data on basal dopamine measures after long-term clozapine administration. It is also possible that the induced increase in PFC dopamine is beyond the optimal range that would improve working memory.

Drugs That Stimulate PFC D1 Receptors

Given the above data it is also reasonable to approach the therapeutics of cognitive dysfunction in schizophrenia by directly stimulating the D1 receptor in the PFC. Although D1 receptor agonists are in experimental phases, one clinical trial has taken place in schizophrenic patients using the selective partial D1 agonist SKF-38393 (Davidson et al 1990). This trial had modest results on the WCST, but the study used acute doses of drug within a narrow dose range.

Another promising drug is dihydrexidine, a selective and full D1 agonist that is being developed for the treatment of Parkinson's disease. Animal studies have demonstrated cognitive enhancing properties of this drug (Steele et al 1996), which appear mediated by D1 activation and by interaction with the cholinergic system. This compound would be of considerable interest in the remediation of the cognitive deficits of schizophrenia, and could be combined with a selective D2 antagonist treating the positive symptoms of schizophrenia.

Norepinephrine

NE has been implicated in the etiology of symptoms of schizophrenia. The unique clinical properties of clozapine are believed by some to be related to its potent effects on the noradrenergic system (Pickar et al 1992). There is ample evidence, as elaborated below, that pharmacologic manipulations of the noradrenergic system, specifically the potentiation of α-2 noradrenergic receptor activity, may be beneficial in treating some of the cognitive deficits associated with schizophrenia. Areas of cognition that may be enhanced in schizophrenic patients by drugs that potentiate α-2 receptor activity include: serial learning, vigilance, distractibility, visuomotor skills, and spatial working memory.

Role of Norepinephrine in Cognition

An understanding of the role of noradrenergic neurotransmission in the execution of cognitive functions has evolved from the accumulation of data from animal models (Leslie et al 1985; Carli et al 1983; Oke and Adams 1978; Stein et al 1975). The central noradrenergic system has two distinct projections: those originating from the ventrolateral tegmental noradrenergic cells, which are associated mainly with sexual and feeding behaviors, and those originating from the locus ceruleus (LC) cells, which are associated with certain cognitive functions (Crow 1968; Mason and Iversen 1979), including those dependent upon an intact PFC, to which it projects (Arnsten and Goldman-Rakic 1985). It is hypothesized that the LC is activated with the presentation of novel stimuli, which then attenuates the influence of distracting stimuli, thereby focusing attention on task-relevant behaviors (Coull 1994). By modulating distractibility in response to novel stimuli, LC functioning can influence diverse cognitive tasks associated with the presentation of novel stimuli, such as new learning, distractibility, and vigilance — cognitive functions severely impaired in schizophrenic patients (Harvey and Keefe 1997). Also, since the PFC is rich in noradrenergic terminal fields from the LC, and the PFC is involved in cognitive functions relevant to schizophrenia (Goldman-Rakic 1987), dysfunction of noradrenergic receptors in the PFC could contribute significantly to the cognitive dysfunction of schizophrenia.

A variety of cognitive deficits, relevant to patients with schizophrenia, can be produced in animals with lesions of the LC noradrenergic system. These include deficits in sustained attention (Carli et al 1983; Cole and Robbins 1992) and shifting attention (Devauges and Sara 1990). In addition, rats with lesions of the LC demonstrate impaired learning directly associated with decreased levels of cortical norepinephrine (Anlezark et al 1973).

Pharmacologic Manipulation of the Noradrenergic System

Animal models demonstrate that cognitive deficits induced by various lesions to the LC are reversible by the

administration of drugs that enhance noradrenergic neurotransmission. For example, the administration of diethyldithiocarbamate (DDC), an inhibitor of the enzyme dopamine-beta-hydroxylase (DBH), to rats, depletes norepinephrine stores in the brain, and produces complete retention failure of passive avoidance learning (Stein et al 1985; Hamburg and Cohen 1973). Subsequently, normal learning of the passive avoidance task is restored in DDC-treated rats with a single intraventricular dose of norepinephrine (Stein et al 1975). Puromycin also induces amnesia of maze learning in rats through reductions of NE (Roberts et al 1970). Subsequently, this amnesia is reversed by the administration of drugs increasing noradrenergic activity, such as imipramine, tranylcypromine, and D-amphetamine (Roberts et al 1970).

Although many studies have focused on the significance of dopaminergic inputs to the PFC (Arnsten et al 1994; Goldman-Rakic et al 1992; Brozoski et al 1979), noradrenergic inputs from the LC have an important influence on the PFC as well (Arnsten et al 1996). In addition, this projection may be reciprocal, such that the PFC may supply the only cortical afferents to the LC (Arnsten and Goldman-Rakic 1984; Sara and Herve-Minvielle 1995). Therefore, PFC dysfunction may impair regulation of the LC, a notion that is supported by direct evidence from rodent studies, where lesions of the PFC disinhibit firing of the LC (Sara and Herve-Minvielle 1995). Consequently, schizophrenic patients may experience cognitive dysfunction related to LC dysregulation in addition to the cognitive impairments associated with PFC dysfunction.

α-2 receptor activity may be the most important mechanism of noradrenergic neurotransmission in the PFC. In vivo microdialysis experiments to evaluate the regulation of norepinephrine release in the frontal cortex and hippocampus in rats demonstrate that norepinephrine reuptake is the principal mechanism of norepinephrine regulation in the hippocampus, and α-2 receptor activation is the principal mechanism in the frontal cortex (Thomas et al 1992). In addition, a high density of α-2 receptors has been observed in the area of the principal sulcus of the PFC (Goldman-Rakic et al 1990). Therefore, pharmacologic studies of the noradrenergic system in relation to cognition in nonhuman primates have utilized drugs selective for the α-2 receptor. α-2 agonists, such as the antihypertensive drug clonidine, have been the drugs of choice in studies of nonhuman primates. The delayed response task has been extensively utilized in these investigations because performance on this task is known to depend on the integrity of frontal lobe function. This is relevant to the understanding of PFC-dependent cognitive dysfunction in schizophrenia because poor performance on a delayed response task is characteristic of the working memory abnormality of schizophrenia.

Young monkeys with localized 6-OHDA (hydroxy dopamine) lesions to the PFC are rendered unable to perform a delayed response task. Subsequently, the α-2 adrenergic agonist clonidine improves performance on the spatially delayed response task (Arnsten and Goldman-Rakic 1985), presumably at postsynaptic sites in the prefrontal cortex. Also, improvements in spatial delay response tasks in aged nonhuman primates is achieved with clonidine and another α-2 agonist, guanfacine (Arnsten et al 1988). Guanfacine was found to be approximately 25 times more potent than clonidine in enhancing delayed response performance, 10 times less potent in lowering blood pressure, and much less likely to cause sedation (Arnsten et al 1988). This differential response profile produced by these two α-2 agonists can be attributed to the existence of α-2 receptor subtypes, each of which demonstrates different affinities for these two drugs. Binding experiments have revealed the existence of two distinct subtypes of α-2 receptors: a rauwolscine-sensitive (R_s) site, which binds both rauwolscine and idazoxan, and a rauwolscine-insensitive (R_I) site, which binds idazoxan only (Boyajian and Leslie 1987). These two sites demonstrate different affinities such that guanfacine has a greater affinity for the R_I site and clonidine for the R_S site (Arnsten et al 1988). A link is hypothesized between enhancement of delayed response performance and the putative R_I receptor located postsynaptically in the cortex (Arnsten et al 1988).

Relevance to Schizophrenia

The animal models presented thus far provide relevant information for cognitive enhancement strategies for schizophrenic patients utilizing a noradrenergic augmentation approach. More specifically, studies presented below, which correlate central noradrenergic function with cognitive function in schizophrenia, particularly in the frontal cortex, further support a noradrenergic approach to augment cognitive performance of patients with schizophrenia. Indeed, hypotheses implicating dysregulation of norepinephrine in the pathophysiology of symptoms of schizophrenia have been circulating for almost three decades since Stein and Wise (1971) first proposed that schizophrenia was due to a "progressive deterioration of central noradrenergic pathways leading to anhedonia and loss of drive." Subsequently, an increasing number of studies have reported abnormal findings in different aspects of noradrenergic systems in schizophrenia.

IN VIVO CSF STUDIES. CSF studies of norepinephrine initially identified generalized NE increases in chronic schizophrenic patients compared with aged matched normal control subjects (Lake et al 1980; Kemali et al 1982).

When medication and symptom status was factored into the analysis, medication-free relapsing patients demonstrated significantly higher levels of NE and 3-methoxy-4-hydroxyphenylglycol (MHPG) in CSF (van Kammen et al 1989a, 1990). These data implicate a role for norepinephrine in the mediation of acute psychoses, and appear contrary to the model we are proposing for decreased cortical noradrenergic functioning mediating the cognitive symptoms of schizophrenia (see Postmortem Studies); however, a relationship was not sought between cognitive status and NE parameters in these studies. Furthermore, the nature of noradrenergic dysregulation in schizophrenia may not be homogenous throughout the central nervous system (CNS). A preferential role of the α-2 receptor in schizophrenia may provide an explanation for the coexistence of low and high NE states mediating different symptom clusters in schizophrenia. As mentioned previously, presynaptic activation of α-2 receptors will attenuate NE activity, whereas postsynaptic activation of α-2 receptor will enhance NE activity. Therefore, disruption of normal presynaptic, site-specific, α-2 adrenergic inhibition of CNS noradrenergic activity could contribute to the observed increase in CSF norepinephrine associated with psychotic relapse, whereas disruption of normal postsynaptic activation in the PFC could contribute to the cognitive dysfunction observed in schizophrenia. Support for this hypothesis is demonstrated by clonidine-induced reductions in CSF norepinephrine and MHPG being associated with better antipsychotic response (van Kammen et al 1989b) and clonidine's ability to reverse impaired cognitive performance induced by NE-depleting lesions in the frontal cortex (Arnsten and Goldman-Rakic 1985). A similar pattern is demonstrated in patients with Alzheimer's disease (AD), where cognitive impairment is the hallmark feature. Postmortem findings demonstrate measures of decreased NE function in AD (see Postmortem Studies), whereas in vivo CSF measures of NE are elevated in AD (Raskind et al 1984). Furthermore, CSF NE is further increased in patients with AD when given yohimbine (an α-2 antagonist) and is associated with increased incidence of behavioral disturbances (Peskind et al 1995).

POSTMORTEM STUDIES. Postmortem studies of patients with Alzheimer's disease have provided the best direct evidence for the association of diminished noradrenergic function and cognitive impairment in humans. For example, studies have demonstrated decreased counts of noradrenergic neurons in the LC (Bondareff et al 1981; Mann et al 1980; Mann and Yates 1981), some decreased levels of norepinephrine in the cortex (Adolfsson et al 1979), and others decreased dopamine beta hydroxylase activity in the cortex of patients with AD (Cross et al 1981). Furthermore, there is also direct evidence for the involvement of α-2 receptors in AD from binding studies of [^{3}H]*p*-aminoclonidine, which demonstrated decreased binding to α-2 receptors in the prefrontal cortex of AD patients by 50% of age-matched control subjects (Kalaria et al 1989).

Initially, increases in norepinephrine levels in the nucleus accumbens of patients with paranoid schizophrenia were reported (Crow et al 1979; Farley et al 1978; Bird et al 1974). MHPG levels in the nucleus accumbens and hypothalamus were also found to be elevated in schizophrenic patients (Kleinman et al 1985); however, ante mortem cognitive functioning was not factored into the analysis of NE levels in these studies. When antemortem cognitive functioning was correlated with central catecholamine function in schizophrenic patients, Bridge et al (1985) demonstrated significant decreases in noradrenergic function. A total of 19 subjects over the age of 60 (13 patients and 6 control subjects) had their records assessed for antemortem cognitive function using the Modified Mini-Mental Status Exam (MMSE) (Folstein et al 1975). The schizophrenic group was classified as demented (MMSE $\leq$ 20, $n = 6$) or nondemented (MMSE $>$ 20, $n = 7$). Data for samples from both nucleus accumbens and hypothalamus demonstrated significant decrements of NE in the demented compared to the nondemented group of schizophrenic subjects.

Since 1989, our group has been collecting cognitive data on chronically institutionalized patients. These patients have ranged in age from 25 to 104 years. More than 800 patients have been assessed, 508 of whom met DSM-III-R and/or DSM-IV criteria for schizophrenia. Of these 508 patients 308 have had detailed cognitive and symptomatic assessments as well. Among the 308 cases, 178 of these patients have had yearly follow-up examinations. What is clear from these evaluations is that many elderly institutionalized schizophrenic patients in our sample suffer with cognitive impairment severe enough to warrant a secondary diagnosis of dementia, but have no postmortem neuropathological findings to account for the severity of the dementia. As part of an ongoing survey of neurochemical characteristics of postmortem brain tissue from schizophrenic subjects, cortical NE, MHPG, 5-HT, and 5-hydoxyindoleacetic acid (5-HIAA) was assayed in six cortical regions derived from elderly chronic schizophrenic subjects (Powchik et al in press). All schizophrenic subjects in this study had antemortem evaluation of cognitive functioning within 1 year of death.

Norepinephrine was found to be significantly reduced in frontal cortex of the cognitively impaired [i.e., Clinical Dementia Rating (CDR) $\geq$ 1] schizophrenic subjects in Brodmann areas 8 and 32 [$p < .002$ by Tukey honest significant difference (HSD)] and 44 ($p < .03$ by Tukey

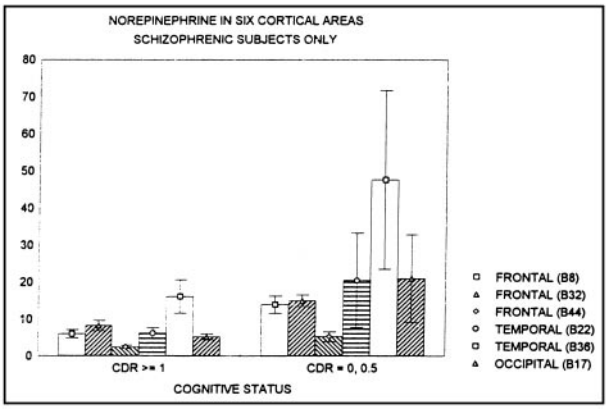

Figure 1. NE deficits in cortex in demented schizophrenics.

HSD) compared to the schizophrenic subjects with CDRs of 0 or 0.5 (Figure 1). There were trend level reductions in temporal cortical NE. Similar, but less pronounced deficits of MHPG were also found. The data for NE are shown in Figure 1 and are consistent with the report of Bridge et al (1985). Since noradrenergic deficits can be age-related, it is important to note that age was not significantly different in the two groups.

These data are crucial in supporting recommendations to improve cognitive impairment associated with cortical NE deficits that extrapolate treatments employed in animal models to humans with schizophrenia (see Therapeutic Implications).

Therapeutic Implications

The ability of α-2 agonists to improve working memory in monkeys with lesions of the PFC is of great importance in the search for pharmacologic therapies for psychiatric disorders with PFC dysfunction and its associated cognitive impairment. Symptoms of PFC dysfunction accompany several psychiatric disorders, including attention-deficit hyperactivity disorder and Korsakoff's syndrome in addition to schizophrenia (Arnsten et al 1996). Studies of α-2 agonists in these clinical populations has demonstrated that these drugs can improve PFC-mediated cognitive functions in humans as well as they have in animals. For example, clonidine improves PFC-mediated cognitive tasks, such as verbal fluency and Stroop test, in patients with Korsakoff's syndrome (Moffoot et al 1994; Mair and McEntee 1986). To support a PFC mechanism mediating clonidine's beneficial effects on verbal fluency test performance, Moffoot et al (1994) demonstrated that improved performance correlated with increased frontal cortical function by single photon emission computed tomography imaging. Extrapolating these findings to patients with schizophrenia, Fields et al (1988) demonstrated clonidine's ability to significantly improve performance of schizophrenic patients on the Trails B task, a task linked, in part, to the PFC. In addition, performance of schizophrenic patients on tests of learning and delayed recall is significantly improved by clonidine (Fields et al 1988).

CHOICE OF α-2 ADRENERGIC AGONIST. Even though clonidine has demonstrated cognitive enhancing ability in schizophrenic patients, it may not be the optimal choice for this purpose. The successful cloning and sequencing of the α-2 receptor has provided evidence for the existence of α-2 receptor subtypes in humans (Kobilka et al 1987). Therefore, it is reasonable to expect guanfacine to have more beneficial effects on cognition in schizophrenic patients while producing fewer undesirable effects because of its selectivity for the putative R_I site. In a double-blinded comparison of the differences in performance produced by guanfacine and clonidine in healthy subjects, Kugler et al (1980) demonstrated guanfacine's superiority as a cognitive enhancing agent, consistent with the findings of Arnsten et al (1988) in aged nonhuman primates. Mental activity was less suppressed on electroencephalogram with guanfacine than clonidine and performance on tests of information processing and reaction time was better with guanfacine than clonidine (Kugler et al 1980).

ALTERNATIVE NORADRENERGIC DRUGS. Direct-acting β-adrenergic agonists represent an alternative to the α-2 agonists. For example, isoproterenol has demonstrated memory-enhancing capacity in challenge studies with rats (Levin et al 1996); however, isoproterenol's significant side effect profile, including reflex tachycardia, other arrhythmias, and angina, limits its use as a cognitive enhancing agent in humans. Finally, other drugs that will nonspecifically increase noradrenergic activity, such as tricyclic antidepressants, monoamine oxidase inhibitors, amphetamines, etc., are another possibility as implicated by the animal data of Roberts et al (1970); however, these drugs lack specificity for the noradrenergic system and have actions at other receptors, including muscarinic, histaminergic, and direct α-1 antagonism, which may produce deleterious effects on cognition in addition to other unwanted effects.

Acetylcholine

Central cholinergic function is impaired in a number of diseases associated with cognitive dysfunction, such as dementia of the Alzheimer's type and Parkinson's disease. These patients experience cognitive deficits that include disturbances of mnemonic function and language usage. Schizophrenic patients also show impairments of mnemonic function that affect both verbal and episodic long-

term memory and language use (Saykin et al 1992; Goldberg et al 1989; Tamlyn et al 1992; Davidson et al 1996), and therefore may be cholinergically mediated as well. Although postmortem studies of schizophrenic patients have not identified gross abnormalities of the cholinergic system, as is found in patients with AD, subtle changes in cholinergic function in the more cognitively impaired schizophrenic patients may provide a rationale for enhancing cholinergic neurotransmission to improve cognitive performance in these patients.

Role of Acetylcholine in Cognition

The relationship between memory and ACh has been studied in animals using directed lesions and behavioral pharmacology. The basal cholinergic complex sends afferents to the entire nonstriatal telencephalon with two projections: the septohippocampal and the nucleus basalis of Meynart (NbM)-cortical pathways (Woolf and Butcher 1989). The correlation between lesions in these pathways and subsequent memory deficits indicates the involvement of these pathways in memory processes (Miyamoto et al 1987). Lesions of the septohippocampal pathway decrease performance in the delayed nonmatch to position paradigm in rats (Aggleton et al 1992; McAlonan et al 1995), whereas lesions of the nucleus basalis produce deficits in passive avoidance conditioned responses, and radial arm maze and water maze performance (Page et al 1991; Winkler et al 1995). Taken together, these findings demonstrate that the septohippocampal pathway is associated with working memory processes through hippocampal storage of intermediate-term memory (Brito et al 1983; Eichenbaum et al 1994; Fadda et al 1996), and that the NbM-cortical pathway is involved in reference memory through long-term information storage in the neocortex (Dunnett 1985; Meek et al 1987). The memory deficits caused by the above lesions are ameliorated by administration of acetylcholinesterase (AChE) inhibitors, such as physostigmine (Mandel et al 1989). Also, the grafting of ACh-producing cells into the brains of lesioned rats improves performance levels on memory tasks, such as the water maze (Dunnett 1990; Winkler et al 1995).

Pharmacologic Manipulations of the Cholinergic System

Further insight into the importance of acetylcholine in memory and learning comes from pharmacologic studies of behavior. Administration of scopolamine or atropine induces memory dysfunction in rats, primates, and humans (Blozovski et al 1977; Aigner and Mishkin 1986; Drachman 1977). This drug-induced impairment is subsequently reversed after displacement of the blocking agent (Dawson et al 1992), and by the use of AChE inhibitors. These drugs act by preventing the breakdown of acetylcholine in the synaptic cleft. The administration of physostigmine to both young and aged monkeys produces an overall improvement of mnemonic processes in both groups (Bartus and Uehara 1979). Tacrine and donepezil, two AChE inhibitors, can reverse the deficits induced by scopolamine in T-maze and passive avoidance tests in rats (Nielsen et al 1989; Wanibuchi et al 1994) and induced deficits in memory in monkeys (Rupniak et al 1997). This supports the notion that memory function can be improved by increasing synaptic acetylcholine, and specifically by AChE inhibition.

A role for acetylcholine in the processes of attention has been demonstrated in rats. Performance on the five-choice serial reaction task is impaired following basal forebrain lesions (Robbins et al 1989). Furthermore, both the systemic administration of physostigmine and the transplant of cholinergic embryonic cells into the brains of rats with basal forebrain lesions improve the visual attentional impairments (Muir et al 1992). The role of acetylcholine in attentional processes has also been described in monkeys. Continuous intraventricular injections of scopolamine during a continuous performance task requiring localization of briefly presented visual stimuli result in a decrease in the number of responses. This effect becomes more apparent when the stimulus presentation is shortened and toward the end of the testing session (Callahan et al 1993).

Relevance to Schizophrenia

Although the size and number of cells in the NbM of schizophrenic patients is not significantly different from that of normal control subjects (El-Mallack et al 1991), a correlation does exist between the degree of cognitive impairment in schizophrenic patients and measures of cortical choline acetyl transferase (ChAT) activity (Haroutunian et al in press). The activity of ChAT, a marker of cholinergic function, was compared in the parietal cortex of 20 normal elderly control subjects, 95 elderly schizophrenics, and 135 AD cases. The activity of ChAT was not significantly reduced in the parietal cortex of the schizophrenic cases; nevertheless, ChAT activity did significantly correlate with CDR scores in the schizophrenic cohort ($r = -.29$, $p < .005$) (Haroutunian et al in press). These findings suggest that although the activity of ChAT in the parietal cortex of schizophrenic patients is not significantly reduced in comparison to normal elderly control subjects, its relative activity may nevertheless contribute to cognitive dysfunction. Indeed, normal subjects, presumably with an intact cholinergic system, who recall a smaller number of words during a serial learning task under drug-free conditions are most sensitive to the enhancing or impairing properties of cholinomimetics

(Sitaram et al 1978). This finding is particularly relevant to schizophrenic patients with cognitive impairment given that impairments in mnemonic function are possibly the most salient deficits (Saykin et al 1992).

Therapeutic Implications

Physostigmine, when given intravenously to normal volunteers, significantly improves new learning (Davis et al 1978); however, intravenous physostigmine is quite short acting and would not be a viable long-term treatment strategy. Other agents, such as the cholinesterase inhibitors donepezil and tacrine, represent additional choices for the purpose of cognitive enhancement. Donepezil use is associated with a lower incidence of gastrointestinal and hepatotoxic effects than tacrine, making donepezil the better choice of AChE inhibitor for use to enhance cognition in patients with schizophrenia (Summers et al 1986, Rogers et al 1996). In addition, administration to patients is considerably easier with donepezil than tacrine given that donepezil is administered only once daily. A daily dose 5 mg has an incidence of side effects similar to that of placebo. As well, its ability to improve cognitive function has been demonstrated in controlled trials (Rogers et al 1996). Patients with Alzheimer's disease demonstrate enhanced cognition, as measured by improvement on the the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), with the use of donepezil (Rogers et al 1996).

Another approach is the use of selective muscarinic agonists. From the five muscarinic receptors, M1 has been identified as a potential site for cognitive enhancing drugs because of its postsynaptic localization and dense distribution in the hippocampus and cerebral cortex (Levey et al 1991; Flynn et al 1995). M4 receptors have a similar anatomic distribution, in addition to sites in the substantia nigra and striatum (Yasuda et al 1993). Since a high density of M1 and M4 receptors are located in the cortex, where cholinergic activity correlates with CDR scores in schizophrenic patients (Haroutunian et al in press), use of an M1/M4 agonist, like xanomeline, may also improve deficits in mnemonic functioning associated with schizophrenia. Xanomeline has been developed as a potential treatment for cognitive dysfunction associated with Alzheimer's disease (Bymaster et al 1994). Clinical trials in Alzheimer's disease have demonstrated treatment with xanomaline to improve scores on the ADAS-cog. Specific improvements were noted on tests of constructional praxis, orientation, spoken language ability, and word-finding difficulty in spontaneous speech (Bodick et al 1997). Since schizophrenic patients perform even more poorly than AD patients on tests of naming and constructional praxis (Davidson et al 1996), xanomeline may be particularly useful in schizophrenia given its ability to specifically improve these two cognitive measures in AD patients; however, xanomeline, orally administered, has a dose-dependent side effect profile, which includes nausea, dyspepsia, and diaphoresis, and leads to a high rate of drug discontinuation. Cognitive improvements are also dose dependent and are observed predominately in the high-dose group, limiting the use of this particular muscarinic agonist for cognitive remediation in schizophrenics. Therefore, development of a muscarinic agonist that can produce improvements in cognitive performance without producing side effects is warranted, and may prove useful in treating the cognitive deficits associated with schizophrenia.

Conclusions

The data implicating dopamine, norepinephrine, and acetylcholine in the core cognitive deficits of schizophrenia have been reviewed. These data provide the basis for the following testable hypotheses for manipulating these neurotransmitter systems with the goal of enhancing the therapeutics of schizophrenia by remediating some of the cognitive deficits.

1. Drugs that increase dopamine in the PFC, within a limited concentration range, such as atypical neuroleptics, may improve prefrontal cognitive deficits, such as working memory and executive functions, in schizophrenic patients.
2. Drugs that activate D1 receptors in the PFC, within a limited concentration range, may improve prefrontal cognitive deficits, such as working memory and executive functions, in schizophrenic patients.
3. Drugs that activate postsynaptic α-2 adrenergic receptors in the frontal cortex may improve serial learning, working memory, and attention in schizophrenic patients.
4. Drugs that increase cortical cholinergic activity, such as AChE inhibitors and M1/M4 muscarinic agonists, may improve memory, language use, and constructional praxis in schizophrenic patients.

Controlled clinical trials to test the therapeutic legitimacy of these approaches are eagerly anticipated.

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