ABSTRACT

Although cognitive dysfunction is considered one of the more debilitating symptoms of schizophrenia, there is a fundamental gap in our knowledge of how the primary pharmacologic treatments of this disease, first- and second-generation antipsychotics (FGAs and SGAs, respectively), affect cognition, particularly over extended periods of time. Moreover, it has been known for decades that chronic treatment with FGAs can lead to imbalances in cholinergic function in the striatum that result in movement disorders; however, there is a growing body of evidence to suggest that both FGAs and SGAs can lead to cholinergic alterations in brain areas more traditionally considered as memory-related, such as cortical and hippocampal regions. Data from our laboratories in rodents indicate that some SGAs (if administered for sufficient periods of time) can be associated with impairments in memory-related task performance as well as alterations in the cholinergic enzyme choline acetyltransferase, the vesicular acetylcholine transporter, and nicotinic (α7) and muscarinic (M2) acetylcholine receptors. Given the well documented importance of central cholinergic function to information processing and cognitive function, it is important that the mechanisms for such chronic antipsychotic effects be identified. In this review, two potential mechanisms for long-term antipsychotic-related cholinergic alterations in the central nervous system are discussed: 1) antipsychotic antagonist activity at dopaminergic-D2 receptors on cholinergic neurons and 2) antipsychotic effects on neurotrophins that support cholinergic neurons, such as nerve growth factor and brain derived growth factor. Novel strategies to optimize the therapeutics of schizophrenia and maintain cognitive function via adjunctive cholinergic compounds and antipsychotic crossover approaches are also discussed.

Schizophrenia is a chronic and disabling illness characterized by severe behavioral symptoms that commonly require life-long therapeutic intervention. Fortunately, the pharmacologic treatments for schizophrenia, which include first- and second-generation antipsychotics (FGAs and SGAs, respectively), have been demonstrated in numerous clinical trials to improve the behavioral symptoms in most schizophrenic patients. It has been widely held since their advent in the late 1980s that SGAs (as a class of compounds) have many advantages over FGAs, including greater improvements in negative symptoms, prevention of relapse, increased functional capacity, fewer movement-related side effects, and superior effects on cognition (reviewed in Miyamoto et al., 2005). Accordingly, SGAs presently account for nearly all of the new treatments for schizophrenia.
prescriptions written for neuroleptics in the United States. Whereas only specifically United States Food and Drug Administration approved for treating psychotic symptoms in schizophrenia and bipolar disease, SGAs are now routinely used “off-label” for the behavioral symptoms of other illnesses in patients ranging in age from the very young (e.g., in autism and attention deficit hyperactivity disorder) to the very old (e.g., Alzheimer’s disease). This widespread off-label drug use is beginning to cause controversy now that several long-term side effects have emerged with SGAs, such as abnormal weight gain, development of diabetes mellitus, hyperlipidemias, etc. (reviewed in Gardner et al., 2005). Further concern has been fueled by the first phase of results (Lieberman et al., 2005) of the Clinical Antipsychotic Trials of Intervention Effectiveness. In this large prospective clinical study, the SGAs, olanzapine, quetiapine, risperidone, and ziprasidone, seemed to offer few significant advantages over the FGA perphenazine when dropout rates (ostensibly due to intolerable side effects, lack of efficacy, etc.) were considered. Given the well documented challenges associated with non-compliance to therapeutic regimens in schizophrenia, there could be several possible interpretations of the Clinical Antipsychotic Trials of Intervention Effectiveness study; however, collectively, the information summarized above would strongly support the conclusion that a more critical look at SGAs is warranted, particularly because they are markedly more expensive than conventional antipsychotics.

Antipsychotics and Cognitive Function

If SGAs (compared with FGAs) indeed have superior effects on cognition as has been reported (see Keefe et al., 2006), the continued preference for SGAs in the treatment of schizophrenia would be warranted. Neuropsychological evaluations of schizophrenic patients consistently indicate cognitive impairments approaching two standard deviations below the mean of control subjects (Wilk et al., 2004). Such deficits are evident at the onset of the illness, and in contrast to the positive and negative symptoms (which tend to be episodic), cognitive decrements in schizophrenia generally persist throughout the illness (Nuechterlein et al., 1992). In addition, compared with other symptom domains, cognitive dysfunction in schizophrenia (particularly in the domains of memory, executive function, and vigilance) appears to have the greatest impact on key indicators of functional outcome, which include the acquisition of social skills, success in rehabilitation programs, and vocational achievements (reviewed in Green et al., 2000).

As noted above, studies focused on the cognitive effects of antipsychotics have commonly reported superior effects of SGAs over FGAs, and several studies have further suggested that SGAs improve cognitive function (reviewed in Harvey et al., 2004). However, a parsimonious interpretation of the currently available literature on this subject would have to take into consideration methodological weaknesses and other limitations of many of the studies. For example, in earlier studies, confounding variables included relatively wide study group heterogeneity, cognitive testing while florid psychotic symptoms were present, and extensive prior antipsychotic exposure by the study subjects. Other limitations included polypharmacy at the time of cognitive testing and the concomitant use of anticholinergic drugs (i.e., drugs known to impair cognition) by those treated with FGAs to control extrapyramidal symptoms (Sharma and Mockler, 1998). A common limitation of both older and newer studies is the large, potentially inappropriate doses of the FGAs used in the comparisons (Carpenter and Gold, 2002). Although some of the aforementioned study design flaws have been addressed in more recent investigations, many of the newer studies have been retrospective or open label in design, and virtually all the studies have been of relatively short duration (i.e., they have rarely exceeded a few months to a year in length, even though most schizophrenic patients require decades of antipsychotic therapy).

Although there are a few exceptions (e.g., Wolff and Leander, 2003), the results of most animal studies conducted to date suggest that SGAs and FGAs are either inactive or that they exert negative effects on cognition. In acute studies, the FGA haloperidol (Ploeger et al., 1992) and the SGAs clozapine, olanzapine, and risperidone impaired place navigation in the Morris Water Maze (Skarsfeldt, 1996). Haloperidol (Beaty and Rush, 1983), clozapine (Addy and Levin 2002), and olanzapine (Levin et al., 2005) impaired spatial working memory in radial arm maze tests, and haloperidol, clozapine, and risperidone impaired performance of a delayed non-match to position task (Didriksen, 1995). In chronic studies (which are much more relevant to the more common clinical use of antipsychotics in schizophrenia), haloperidol, clozapine, and risperidone impaired acquisition in a radial arm maze task in rats whereas olanzapine had no measurable adverse effects (Rosengarten and Quartermain, 2002). In another chronic study, haloperidol was found to disrupt radial arm maze choice accuracy in rats, but only during the first week of administration (Levin et al., 1987). Most recently, Didriksen et al. (Didriksen et al., 2006) found that acute administration of clozapine and olanzapine impaired water maze performance in rats (replicating earlier studies), whereas in chronically treated animals, the impairments abated in the clozapine-treated animals but were exacerbated in the olanzapine-treated animals. Interestingly, the SGA sertindole remained without effect on water maze performance following acute or chronic treatment in these studies.

The results of studies in our laboratories to date also indicate that, like FGAs, representative SGAs (e.g., olanzapine, risperidone, ziprasidone) can impair some cognitive tasks if they are administered for sufficiently long periods of time. Figure 1 provides a summary of six different chronic studies conducted in our laboratory that support such a conclusion. Rats were administered either vehicle alone (very dilute acetic acid in distilled water), 2.0 mg/kg/day haloperidol, 2.5 mg/kg/day risperidone, 10.0 mg/kg/day chlorpromazine, or 10.0 mg/kg/day olanzapine in drinking water for periods ranging from 45 to 180 days. After the treatment period, they were given a drug-free washout period and then tested in a water maze task. To assess the effects of the length of time of drug administration across the studies, the area under the latency learning curve for each animal was calculated, and then group performances were compared across the studies statistically (two-way ANOVA for effects of treatment and time of administration). This method of comparing latency area under the curve (AUC) in water maze studies to provide a more simple comparison between groups has been published previously (Youngblood et al., 1997). As shown in Fig.
There were no detectable antipsychotic effects on AUC at the 45-day time period; however, by 90 days of treatment, haloperidol, risperidone, and olanzapine were associated with impairments that were also present (or a significant trend toward impairment was observed) at the 180-day time period. It is also important to note that, under vehicle conditions, those treated for 180 days were impaired compared with the 45-day time point. The basis for this finding is unclear but could reflect an age-related effect because the rats were approximately 9 to 10 months old by the 180-day time point. We have observed, for example, some evidence of water maze learning impairments in 12-month-old rats in previous studies. The chlorpromazine data for the 90- and 180-day time points are included in the figure (for illustration purposes) but were not included in the statistical analysis because we have not yet conducted a 45-day study with this compound.

Collectively, when interpreting the studies described in the preceding paragraphs, there are some limitations that should be considered. For example, in several of the studies, there was no clear justification for the doses selected or the method of drug delivery used; therefore, logical questions regarding clinical relevance of the results arise (see Kapur et al., 2003). In addition, the experiments described above (and most studies to date) were conducted in normal animals (i.e., not in animal models derived to express symptoms of schizophrenia or other psychiatric disorders). In the studies conducted in our laboratories (e.g., Terry et al., 2005a), dosing levels were chosen based on the plasma antipsychotic levels that were achieved and the predicted D2 occupancy values associated with the specific doses. Furthermore, given the wide use of antipsychotics in conditions as diverse as attention deficit hyperactivity disorder, autism, schizophrenia, and Alzheimer's disease, conducting experiments in normal animals is a logical initial approach to understanding chronic antipsychotic effects on the mammalian brain that could be relevant to a variety of diseases. Nevertheless, a comprehensive (and therapeutically relevant) understanding of the effects of chronic antipsychotic treatments on cognitive function will require experiments in animal models of psychiatric illness.

**Antipsychotics and the Central Cholinergic System**

Whereas the therapeutic agents used to treat schizophrenia should ideally target the actual pathophysiological causes of the illness, to date, such mechanisms have not been unequivocally established. Unfortunately, this lack of knowledge applies to the underlying neurobiological substrates of the behavioral symptoms as well as the cognitive deficits in schizophrenia. Abnormalities in the neurotransmitters dopamine, serotonin, and glutamate have commonly been implicated in many aspects of the neuropathology of schizophrenia; however, there is some (albeit limited) evidence that alterations in acetylcholine neurotransmission are present as well (see Sarter et al., 2005). Such data may be especially significant to the cognitive deficits, because cholinergic neurons, particularly those originating in the basal forebrain, influence many components of information processing, including attention, encoding, memory consolidation, and retrieval (see review in Gold 2003). The evidence includes significant correlations between reduced choline acetyltransferase (i.e., ChAT, the acetylcholine-synthesizing enzyme) levels and impaired cognition in schizophrenia and decreases in both nicotinic acetylcholine receptors (nAChRs) and muscarinic acetylcholine receptors (mAChRs) in post mortem brains of schizophrenics; the latter finding has been verified by single photon emission-computed tomography in living, unmedicated schizophrenic patients (see review in Friedman, 2004).
In light of the information provided above, an interesting question arises to what extent antipsychotics affect the central cholinergic system. The FGAs thioridazine and chlorpromazine and the SGAs clozapine and olanzapine have been shown to bind all of the known muscarinic acetylcholine receptor subtypes, with relatively high affinity (reviewed in Bymaster et al., 2003), although the significance of this binding to the therapeutics and adverse effects is unknown. Interestingly, although both FGAs and SGAs have been observed to increase acetylcholine levels in the hippocampus of rats (Shirazi-Southall et al., 2002), the effects of the SGAs, clozapine and olanzapine, were considerably more robust. Furthermore, the SGAs, clozapine, olanzapine, risperidone, and ziprasidone, significantly increased acetylcholine release in rat medial prefrontal cortex, whereas the FGAs haloperidol and thioridazine did not (Ichikawa et al., 2002). Such differential effects on acetylcholine release were hypothesized (in the studies cited above) to possibly underlie the reported superiority of SGAs on cognitive function compared with FGAs. However, given that these studies evaluated acute drug effects on basal efflux of acetylcholine in the brains of animals that were not behaviorally tested, several questions are left unanswered such as 1) whether such effects would persist for extended periods of time (i.e., the more clinically relevant question regarding antipsychotics) and 2) how such antipsychotic effects on basal release of acetylcholine might be expected to influence cognitive processes that may require periodic fluctuations (i.e., increases or decreases) in cholinergic activity.

To date, most of the data regarding the chronic effects of antipsychotic drugs on central cholinergic neurons have come from studies designed to investigate the basis of their adverse motor reactions. For example, an increase in the activity of cholinergic interneurons in the striatum in response to FGAs has been reported to initially parallel adverse extra-pyramidal effects in humans, whereas longer treatment periods have been associated with decreases in cholinergic activity below baseline [i.e., effects that correspond with the emergence of tardive dyskinesia (TD)] (see Miller and Chouinard, 1993). Such temporal effects may account for the ability of anticholinergic drugs (e.g., benztpine) to ameliorate extra-pyramidal side effects of FGAs during early use and their lack of efficacy (or even tendency to exacerbate symptoms) in TD. Whereas SGAs are commonly reported to be associated with fewer extra-pyramidal symptoms and a lower risk of TD than FGAs, such reports should not be construed to suggest that SGAs are free of these adverse effects. In fact, a brief perusal of the manufacturer’s package insert will clearly indicate that such adverse effects can be associated with virtually any of these agents, with the possible exception of clozapine. Although the currently available evidence also suggests that the risks of TD are probably lower with most SGAs compared with FGAs of high potency, this may not necessarily be the case with FGAs of low potency (e.g., chlorpromazine) taken at moderate doses (Gardner et al., 2005).

Given the evidence of a possible cholinergic basis for antipsychotic related extra-pyramidal effects and TD, another logical question arises whether such cholinergic effects might influence information processing and cognition as well, particularly since cholinergic interneurons in the striatum have been shown to exhibit long-term potentiation (Suzuki et al., 2001) and to play an important role procedural learning (Kitabatake et al., 2003). In addition, several years ago, the FGA haloperidol (administered chronically to rats) was observed to decrease ChAT immunoreactivity as well as ChAT enzyme activity in the hippocampus (Mahadik et al., 1988), a structure well known for its role in encoding, consolidation and episodic memory (Squire 1994). More recently, we have detected time-dependent effects of both representative FGAs and SGAs on ChAT, the vesicular acetylcholine transporter (VACHT), as well as nicotinic (\(\alpha_7\)) and muscarinic (\(M_1\)) acetylcholine receptors (Terry et al., 2005, 2006a,b) in other memory-related brain regions. Figure 2 provides a summary of some of these experiments where the cholinergic marker proteins, ChAT and VACHT, were quantified in rat brain after 90 days of treatment. Figure 2A illustrates immunostaining results, whereas Fig. 2B illustrates the effects of ELISA experiments that were conducted to measure levels of the cholinergic marker protein VACHT. Thus, 90 days of chronic treatment with several antipsychotics (i.e., both FGAs and SGAs) was associated with significant decreases in cholinergic marker proteins in the striatum, as well as in brain regions, more traditionally though, to support cognition (e.g., basal forebrain, cortex).

Antipsychotics, Dopamine-Acetylcholine Interactions

The mechanism of the chronic effects of antipsychotic drugs on the levels of central cholinergic markers and cognitive function described above is presently unknown. All of the agents evaluated in the aforementioned experiments have significant antagonist activity at \(D_2\) receptors, and furthermore, \(D_2\) receptors have been localized on cell somata as well as axonal and dendritic processes of striatal cholinergic interneurons in the dorsal striatum and nucleus accumbens (Alcantara et al., 2003). These receptors are well known to inhibit acetylcholine release when bound by dopamine, and in the context of TD, the \(D_2\) receptor antagonist effects of FGAs in animals have been reported to result in excessive neuronal activity, intracellular accumulation of calcium, and subsequent cell damage (see Miller and Chouinard, 1993). It is interesting to hypothesize that such negative effects could affect mnemonic function given the reported role of cholinergic interneurons in the striatum in long-term potentiation and learning noted above. Furthermore, our detection of sustained antipsychotic-related decreases in cholinergic markers in the cortex may reflect the involvement of dopamine-acetylcholine interactions in the nucleus accumbens. It has been hypothesized that dopamine in the nucleus accumbens inhibits the activity of GABAergic projections to the basal forebrain, thus modulating the excitability of cholinergic neurons that project to the cortex (see Sarter and Bruno, 1999). Accordingly, chronic exposure to drugs that antagonize mesolimbic dopamine receptors could indirectly lead to imbalances in cholinergic activity in basal forebrain neurons (and thus projection areas such as the cortex). Our findings of antipsychotic-related decreases in cholinergic markers in the hippocampus may be even more difficult to interpret because \(D_3\) receptors are relatively sparse in the septohippocampal pathway. However, it should be noted that dopamine regulation of septohippocampal cholinergic activity via the \(D_1\) receptor has been described previously (Day and Fibiger, 1994) and that several FGAs and SGAs (including those we
evaluated) have significant antagonist activity at D₁ receptors (see Miyamoto et al., 2005).

**Antipsychotics and Neurotrophins**

The effects of antipsychotics on the neurotrophins, nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), may be particularly germane to this review because both proteins are known to support cholinergic neurons in the adult mammalian brain and cognitive function (reviewed in Fahnestock et al., 2002; Counts and Mufson 2005). Interestingly, both acute (3 days) and subchronic (21 days) exposure to haloperidol in rats decreased the levels of BDNF in the prefrontal cortex, hippocampus, and amygdala. Decreased BDNF concentrations (Angelucci et al., 2000) and decreased expression of BDNF mRNA (Lipska et al., 2001) have also been observed after risperidone and clozapine administration. Another report indicated that subchronic (29-day) treatment with haloperidol or risperidone in rats increased NGF immunoreactivity in the hypothalamus but decreased NGF levels in the striatum and hippocampus. The same investigators (Angelucci et al., 2005) more recently found that 29 days of oral olanzapine treatment increased NGF in the hippocampus, occipital cortex, and hypothalamus but decreased BDNF in the hippocampus and frontal cortex. The results of studies in our laboratories over the last several years indicate that the effects of both SGAs and FGAs on NGF are temporally dependent; specifically, they can be very different depending on the length of time of administration. Thus, whereas NGF levels in the hippocampus were either unchanged or up-regulated in rats in response to several antipsychotics during short periods of treatment (7, 14, and 45 days), they were significantly decreased by haloperidol, chlorpromazine, olanzapine, and risperidone when continuously administered orally for 90 or 180 days (Pillai et al., 2006; Terry et al., 2006b). Figure 3 provides a summary of some of the results in the hippocampus obtained by our laboratories to date. In Fig. 3A, the representative immunohistochemical images are shown, whereas in Fig. 3B, representative data from ELISA experiments illustrating the effects of several antipsychotics on NGF over time are shown. Thus, at the early time points (e.g., 45 days), SGAs did not seem to decrease NGF (in fact, olanzapine even increased NGF substantially), whereas after longer periods of treatment (90 days and beyond), all of the antipsychotics tested to date were associated with decreases in NGF in the hippocampus.

Notwithstanding the potentially important therapeutic ramifications of the studies cited above, the role of neurotrophins in brain function is a very complex, rapidly evolving, and poorly understood subject, and the study of neurotrophins in schizophrenia and other psychiatric disorders is in its infancy. The fields of neurodevelopment, aging, and Alzheimer's disease research clearly indicate that a more comprehensive understanding of such issues is likely to require many years of diligent research. Future studies in both normal and pathophysiologic states designed to characterize the

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**Fig. 2.** First- and second-generation antipsychotics are associated with persistent decreases in cholinergic marker proteins in the rat brain. Rats were treated orally with antipsychotics for 90 days, given a 2-week washout period, and sacrificed for measurements of cholinergic marker proteins in the brain. A, ChAT immunostaining of 40-μm coronal sections of cortex (CTX) or caudate-putamen (CP). Diagram (bregma 1.68 mm) is adapted from Paxinos and Watson (2005). The bar represents approximately 5 μm in the cortex and 10 μm in CP. B, results of ELISA measurements of the VAcHT protein in homogenates of basal forebrain and prefrontal cortex. Each bar (expressed as a percentage of vehicle control) represents the mean ± S.E.M. for each test group. *, significantly different from vehicle control, p < 0.05. The statistical test used was a one-way ANOVA. V or VEH, vehicle controls; H or HAL, haloperidol; R or RISP, risperidone; ZIP, ziprasidone; CPZ, chlorpromazine; OLZ, olanzapine. n = 5–6 for all groups.
distinct and possibly opposing actions of proneurotrophin and mature neurotrophins in regulating neuron survival and synaptic plasticity, as well efforts to further define the role of low- and high-affinity neurotrophin receptors (and their interactions), will be required.

**Antipsychotics and Central Cholinergic Function: Therapeutic Implications**

Given the reported cholinergic deficits in schizophrenia (described above), it has been hypothesized that a cholinergic strategy for ameliorating cognitive deficits using compounds, such as acetylcholinesterase inhibitors (AChEIs), mAChR agonists, nAChR agonists, or allosteric potentiators of nAChR function might be viable (reviewed in Friedman, 2004). To date, however, the only approach that has been evaluated clinically to any significant extent has been the adjunctive administration of AChEIs with antipsychotics. The data from such studies have thus far been equivocal; the beneficial cognitive effects of donepezil or rivastigmine as add-on treatments to SGAs observed in preliminary open-label studies and case reports were not confirmed in randomized, double-blind, and placebo-controlled studies (see Friedman et al., 2002; Sharma et al., 2006). Most recently, a small, randomized, double-blind clinical trial \( n = 8 \) indicated that adjunctive treatment with the AChEI galantamine, improved short-term memory and attention in schizophrenic or schizoaffective patients who were stabilized on risperidone (Schubert et al., 2006). Although such data are certainly encouraging, much larger studies will be required to verify the validity of this approach as a reliable therapeutic intervention.

There may be several factors that underlie the equivocal nature of the studies noted above, such as cigarette smoking (and thus the confounding cholinergic receptor effects of nicotine) by the research subjects, exposure to other drugs of abuse, differences in the neuropsychological measures employed, etc. An important factor (not commonly discussed) that could certainly influence responses to the adjunctive agent is the unique medication history of the study subject. Specifically, factors such as the history of antipsychotic drug exposure, the particular antipsychotic agent currently being administered, and how long the patient has been exposed to this compound could be especially important to the adjunctive treatment response. In our chronic animal studies, we have found that several antipsychotics (e.g., both FGAs and SGAs) can lead to decreases in cholinergic markers, as well as more specific effects on cholinergic receptors (e.g., decreases in \( \alpha_7 \) nAChRs in association with risperidone and increases in \( M_2 \) mAChRs in association with olanzapine). Interestingly, alterations in \( \alpha_7 \) nAChRs are believed to contribute to the deficits in sensory gating, sustained attention, and cognitive performance in schizophrenia (reviewed in Freedman, 2004). Therefore, it is interesting to hypothesize that a cognitively impaired psychiatric patient who has been chronically treated with risperidone (where baseline \( \alpha_7 \) nAChR activity may be decreased) would be particularly responsive to an \( \alpha_7 \) nAChR agonist or an AChEI as an adjunctive agent. In contrast, a patient who has been treated with olanzapine might be less responsive to an AChEI where olanzapine-related elevations in the \( M_2 \) autoreceptor might limit the effectiveness of the increases in synaptic acetylcholine. Obviously, such assertions are speculative at this point,
but they represent the types of patient-specific (i.e., tailored) therapeutic strategies that should be investigated further.

Antipsychotics Crossover: Therapeutic Implications

When antipsychotic therapy is ineffective, the patient’s lack of adherence to the treatment regimen is commonly cited as the basis for the failure. Accordingly, many contemporary clinical studies focus on drug compliance and on methods of ensuring compliance (e.g., depot drug injections). However, the results of our animal studies (where compliance is not a concern) clearly indicate that chronic (uninterrupted) antipsychotic treatment with representative FGAs and SGAs can lead to undesirable effects on neurotrophins, cholinergic proteins, and cognitive function. In addition, we have recently published evidence to indicate that changing from one antipsychotic drug to another during chronic treatment can significantly reduce the extent of NGF and BDNF deficits that occur when a single antipsychotic is given continuously (Pilail et al., 2006). Such results could have important implications for the chronic effects of antipsychotics on CNS cholinergic function as well as cognition. In clinical practice, switching antipsychotic drugs to achieve the best balance between efficacy and side effects is a common occurrence. Other reasons for switching antipsychotics include (interestingly) poor patient compliance, cost (especially with SGAs), and unresponsiveness of cognitive symptoms. It should be noted that, although the practices described above are common, few randomized and controlled clinical trials have been published to guide the clinician to the best protocols to follow (reviewed in Remington et al., 2005). Future animal experiments are planned in our laboratories to specifically address this issue by assessing the cellular and biochemical consequences (and effects on cognitive function) of switching between SGAs. The results of such studies would be expected to provide initial (preclinical) indicators to which compounds would be better choices should a drug switch be indicated.

Conclusions

Schizophrenia is a devastating mental illness that is associated with a lifetime of disability, and for sufferers of this illness to function in society, the amelioration of psychotic symptoms is imperative. Fortunately, a variety of antipsychotic drugs have been shown to be effective in this regard; however, multi-year, prospective clinical studies designed specifically to identify the antipsychotics that have optimal effects on cognition have not been conducted (and generally would be cost-prohibitive). Therefore, relevant animal studies, such as those described in this review, are essential because they allow for meticulous time-course experiments in antipsychotic naive subjects (a rarity in schizophrenia patients), the rigorous control of environmental conditions (eliminating confounding clinical factors, such as substance abuse, poor nutrition, etc.), and the evaluation of antipsychotic effects on neurobiological substrates of cognition (i.e., at the cellular and molecular level). A growing body of evidence from such animal studies indicates that several antipsychotics, including both SGAs and FGAs (if administered for sufficient periods of time), can be associated with impairments in memory-related task performance, as well as alterations in central cholinergic function. Given the well-documented importance of central cholinergic neurons to information processing and cognitive function, it is important that the mechanisms of such chronic antipsychotic effects be identified. A better understanding of these mechanisms would be expected to facilitate optimal treatment strategies to maintain or improve cognitive function in schizophrenia and provide a more educated approach to psychiatric drug discovery and development.

Cholinergic Dysfunction, Cognition, and Antipsychotics

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