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Cortical Cholinergic Transmission and Cortical Information Processing in Schizophrenia

Martin Sarter, Christopher L. Nelson, and John P. Bruno

Send reprint requests to Dr. M. Sarter, Department of Psychology, University of Michigan, 525 E. University Avenue, Ann Arbor, MI 48109-1109; e-mail: msarter@umich.edu.

Models of the neuronal mediation of psychotic symptoms traditionally have focused on aberrations in the regulation of mesolimbic dopaminergic neurons, via their telencephalic afferent connections, and on the impact of abnormal mesolimbic activity for functions of the ventral striatum and its pallidal-thalamic-cortical efferent circuitry. Repeated psychostimulant exposure models major aspects of the sensitized activity of ventral striatal dopaminergic transmission that is observed in patients exhibiting psychotic symptoms. Based on neuroanatomical, neurochemical, and behavioral data, the hypothesis that an abnormally reactive cortical cholinergic input system represents a necessary correlate of a sensitized mesolimbic dopaminergic system is discussed. Moreover, the abnormal cognitive mechanisms that contribute to the development of psychotic symptoms are attributed specifically to the aberrations in cortical cholinergic transmission and to its consequences on the top-down regulation of sensory and sensory-associational input functions. Experimental evidence from studies demonstrating repeated amphetamine-induced sensitization of cortical cholinergic transmission and the ability of antipsychotic drugs to normalize the activity of cortical cholinergic inputs, and from experiments indicating the attentional consequences of manipulations that increase the excitability of cortical cholinergic inputs, supports this hypothesis. Relevant human neuropathological and psychopharmacological data are discussed, and the implications of an abnormally regulated cortical cholinergic input system for pharmacological treatment strategies are addressed. Given the role of cortical cholinergic inputs in gating cortical information processing, even subtle changes in the regulation of this cortexwide input system that represent a necessary transsynaptic consequence of sensitized mesolimbic dopaminergic transmission profoundly contribute to the neuronal mediation of psychotic symptoms.

Keywords: Schizophrenia/cortex/acetylcholine/nucleus accumbens/dopamine/attention

This article discusses the role of the cortical cholinergic input system in the mediation of schizophrenia symptoms. Neuropathological data suggesting an abnormal regulation of the cortical cholinergic input system in schizophrenia remain rare and inconclusive, mostly because dynamic alterations in the activity of cholinergic neurons cannot be readily revealed by neuropathological assessments of the activity of non-rate-limiting enzymes of cholinergic transmission (e.g., choline acetyltransferase, acetylcholine esterase; Haroutunian et al. 1994; Powchik et al. 1998; Mancama et al. 2003). However, neuropathological studies documented a decrease in the density and expression of muscarinic receptors in the cortex of schizophrenia patients (Crook et al. 2001; Hyde and Crook 2001). Recently, Raedler et al. (2003), using [123I]iodoquinuclidinyl benzilate single photon emission computed tomography, confirmed the decrease in muscarinic receptors in unmedicated patients. Several mechanisms could account for the downregulation of muscarinic receptors; it could, for instance, be a consequence of abnormally high levels of extracellular acetylcholine (ACh).

Suggestions about the cholinergic system's involvement in schizophrenia have also been derived from psychopharmacological studies (e.g., Davis et al. 1978). Tandon and colleagues (Tandon and Greden 1989; Tandon et al. 1999) proposed that cholinergic hyperactivity mediates negative symptomatology, including attentional impairments. Their hypothesis corresponds with many lines of evidence discussed below, including the suggestion that cortical cholinergic (re)activity is particularly high during psychotic exacerbations and that the activity of the cholinergic system covaries with perturbations in dopaminergic activity. Tandon and colleagues' focus on the mediation of negative symptoms by the cholinergic system has been corroborated by their findings on the effects of *acutely* administered cholinergic drugs (e.g., Tandon et al. 1993). However, *long-term* exposure to cholinomimetic drugs may result in the manifestation of psychotic symptoms. Evidence in support of this statement remains necessarily anecdotal, but several cases of accidental chronic exposure to cholinesterase inhibitors (Gershon and Shaw 1961; Bowers et al. 1964; Karczmar 1981) indicated that persistent, abnormal increases in extracellular ACh levels are sufficient to produce or exacerbate psychosis. Furthermore, the symptoms of these patients were—as predicted by the model described below—treated successfully by antipsychotic drugs.

The widespread abuse of anticholinergic drugs (e.g., trihexyphenidyl, benztropine) by schizophrenia patients, who report a wide spectrum of subjective and functional benefits from taking these drugs (Fisch 1987; Wells et al. 1989), also provides indirect support for the idea that attenuation of an overly active or reactive cholinergic system mediates beneficial effects. However, the degree to which such positive effects can be objectified remains unsettled (Johnstone et al. 1983; Strauss et al. 1990), as do the functions of smoking and the status of nicotine receptors in schizophrenia (Salokangas et al. 1997; Adler et al. 1998; Dalack et al. 1998).

Collectively, the clinical and neuropathological evidence concerning the role of the cholinergic system in schizophrenia is limited for several reasons, including, as already mentioned, the absence of methods available to document dynamic changes in the regulation of cholinergic neurons in the human brain (see also Heimer 2000). Emerging tracers for the imaging of cholinergic receptors and aspects of cholinergic transmission in the human brain (Mach et al. 1997; Mulholland et al. 1998; Nishiyama et al. 2000; Tsukada et al. 2001) are likely to pave the way for more direct and informative assessments of the status of cortical cholinergic transmission in schizophrenia patients.

Sensitization of Mesolimbic Dopaminergic Neurons and Regulation of Cortical Cholinergic Inputs

Sensitized Mesolimbic DA in Schizophrenia. The hypothesis that abnormal regulation of ventral striatal, specifically nucleus accumbens (NAC), dopaminergic transmission represents a neuronal hallmark of schizophrenia has been substantiated in recent years. Most etiologic scenarios agree that the mesolimbic hyperdopaminergic state in schizophrenia is a result of developmental abnormalities in telencephalic circuits that cause a dysregulation of midbrain dopaminergic neurons (Weinberger and Lipska 1995; O'Donnell and Grace 1998; Grace 2000; Laruelle 2000; Lewis and Levitt 2002).

Imaging studies demonstrated increased amphetamine-induced (AMPH-induced) displacement of dopamine (DA) D2 receptor ligands in schizophrenia patients, suggesting a sensitized striatal dopaminergic input system (Breier et al. 1997; Laruelle and Abi-Dargham 1999; Laruelle et al. 1999). Although the interpretation of the mechanisms mediating the AMPH-induced displacement of D2 ligands is not without controversy (Tsukada et al. 1999), the use of AMPH in these studies corresponds with the psychotogenic effects of repeated exposure to AMPH and other psychostimulants in humans and in animal models of schizophrenia. Alternatively, the risk for psychostimulant addiction represents a corollary of schizophrenic neuropathology (e.g., Segal et al. 1981; Robinson and Becker 1986; LeDuc and Mittleman 1995; Lieberman et al. 1997; Yui et al. 1999*a*; Castner et al. 2000; Laruelle 2000).

A hyperactive dopaminergic system in schizophrenia patients can be demonstrated even in never-medicated patients; such demonstration requires the presence of psychotic symptoms (Laruelle et al. 1996, 1999; Strakowski et al. 1997; Abi-Dargham et al. 1998; Laruelle and Abi-Dargham 1999; Laruelle 2000; Seeman and Kapur 2000). Patients with first episode manic or schizophrenic psychosis did not exhibit increased responses to a second dose of amphetamine, suggesting that they already exhibited a maximally sensitized dopaminergic system (Strakowski et al. 1997). A sensitized mesolimbic DA system has been hypothesized to be a necessary component of the neuronal circuits mediating the expression of positive symptoms (Robinson and Becker 1986; Lieberman et al. 1997; Yui et al. 1999*a*; Laruelle 2000).

The relationship between the positive symptoms of schizophrenia and dopaminergic inputs to *cortical* areas is less clear (e.g., Davis et al. 1991). Aberrations in the functions of dopaminergic inputs to the prefrontal cortex (PFC), including reductions in the density of DA D1 receptors (Okubo et al. 1997) and increases in DA synthesis (Lindstrom et al. 1999), have been extensively discussed as representing the primary mediator of the cognitive impairments of schizophrenia (Murphy et al. 1996*a*, 1996*b*; Goldman-Rakic and Selemon 1997; Zahrt et al. 1997). Moreover, and more central to the present hypothesis, abnormalities in prefrontal neurotransmission, possibly in interaction with structural abnormalities of the PFC in schizophrenia patients (e.g., Lewis et al. 1999; Gluck et al. 2002), contribute via corticofugal projections to the abnormal regulation of striatal, including NAC, DA transmission (e.g., Deutch 1993; Bertolino et al. 1999; Carr et al. 1999; Moore et al. 1999*b*; Soares and Innis 1999; Finlay 2001). Grace (1993) proposed that the primary consequence of the defective regulation of NAC DA afferents in schizophrenia is a decrease in tonic DA release associated with an increase in phasic, activity-related DA release, possibly due in part to reduced local autoinhibitory mechanisms (Grace 1993; Flaum and Schultz 1996; O'Donnell and Grace 1998; Moore et al. 1999*b*). Chronic treatment with antipsychotic drugs is hypothesized to normalize DA transmission by producing a depolarization blockade (Grace et al. 1997; Grace 2000) that, in the case of atypical antipsychotic drugs, has been proposed to be selective for the limbic A10 DA neurons (Chiodo and Bunney 1983).

Thus, the available evidence points to the NAC, particularly its shell region, as the critical component of abnormally regulated neuronal circuits mediating the expression of positive symptoms (O'Donnell and Grace 1998), or even the aberrations of consciousness, in schizophrenia (Gray 1995). Grace and coworkers, as well as Gray and others, have focused on NAC-ventral pallidal—mediodorsal thalamic—prefrontal connections to

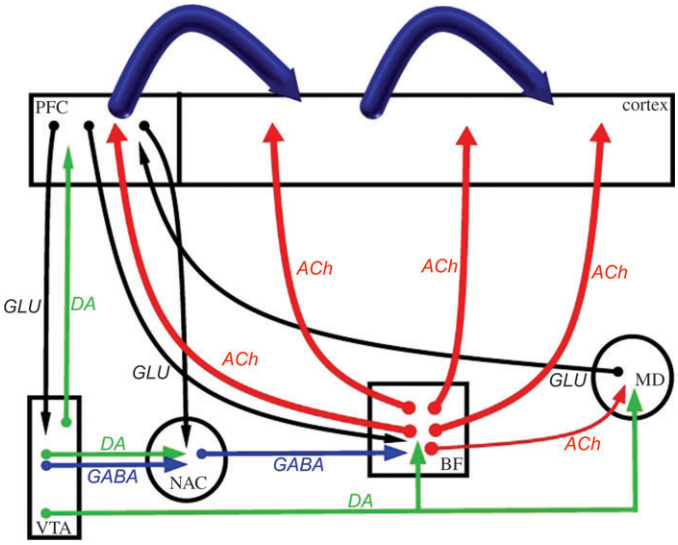

Fig. 1. Schematic and selective representation of the circuitry involved in the dysregulation of cortical cholinergic (ACh, in red) inputs, arising from the BF, in schizophrenia. *Note.*—ACh = acetylcholine; BF = basal forebrain; DA = dopamine; GABA = γ-aminobutyric acid; GLU = glutamate; MD = mediodorsal thalamic nucleus; NAC = nucleus accumbens; PFC = prefrontal cortex; VTA = ventral tegmental area. Most etiological scenarios suggest that, as a result of developmental telencephalic dysmorphogenesis, an abnormal telencephalic regulation of the activity of mesolimbic neurons (via cortical GLU projections, in black) mediates the expression of the mostly positive symptoms of schizophrenia. The mesolimbic dopaminergic system refers primarily to the dopaminergic neurons that arise from the VTA and project to the NAC and the PFC. Evidence indicates that, in acute schizophrenia patients, mesolimbic dopaminergic neurons exhibit the characteristics of a sensitized system, and this aspect of the disease is modeled by the effects of psychostimulant sensitization. There is also a mesoaccumbens GABAergic pathway that is likely to be affected by abnormal telencephalic inputs (Carr and Sesack 2000), but the regulation of NAC signal transmission by GABAergic inputs is not well known. The GABAergic projection from the NAC to the BF (in blue) represents the major although not the exclusive pathway by which the effects of an abnormally regulated mesolimbic dopaminergic system are imported to the BF (e.g., not shown are multisynaptic circuits through amygdaloid regions that are likely to contribute to BF dysregulation). As a result of abnormal BF afferent activity, cortical cholinergic inputs are excessively reactive. Pathological increases in cortical cholinergic transmission directly impair sensory and associational input processing and disrupt filtering capacity. Indirectly, and primarily as a result of an abnormally reactive cholinergic input to the PFC, the orchestration of top-down mechanisms, normally designed to optimize, in a modality-specific fashion, posterior cortical input processing, is disrupted. Such disruption of top-down mechanisms is thought to impair source monitoring capabilities (this function is symbolized by the thick curved arrows at the figure's top). The BF cholinergic projection to the MD is also shown because, via this projection (and also possibly via noncholinergic BF projections to the MD; e.g., Young et al. 1984; Mogenson et al. 1987; Hreib et al. 1988), the MD's projections to the PFC (e.g., Sarter and Markowitsch 1984) may also be abnormally regulated and thus further impair information processing in the PFC. Additionally, the PFC directly innervates BF neurons, and thus, pathological PFC activity augments the abnormal regulation of the BF (Sarter and Bruno 2002). Finally, conceptualize the consequences of dysregulation of NAC information flow for cortical information processing (see also O'Donnell et al. 1997). As will be discussed below, the NAC has even more direct and widespread consequences on cortical information processing by regulating the excitability of the corticopetal cholinergic system that arises from medial and ventral pallidal regions, specifically from the nucleus basalis of Meynert, the substantia innominata, and the horizontal nucleus of the diagonal band (henceforth termed collectively "basal forebrain" [BF]; figure 1). Furthermore, the abnormal regulation of cortical cholinergic inputs is hypothesized to mediate the attentional abnormalities that contribute to the expression of the positive symptoms of schizophrenia.

Transsynaptic Regulation of Cortical Cholinergic Activity. The NAC has been traditionally discussed as a structure linking motivational processes with the initiation of behavior, specifically with the selection of stimuli with incentive or aversive properties. Dopaminergic inputs to the NAC, originating in the ventral tegmental area, converge with telencephalic (glutamatergic) projections on medium spiny NAC efferents (Sesack and Pickel 1990; Wu et al. 1993; Taber and Fibiger 1995; Finch 1996; Whitelaw et al. 1996; Blaha et al. 1997; Floresco et al. 1998; Mulder et al. 1998; You et al. 1998). This interaction is generally considered to be critical for the selection of stimuli to act as conditioned reinforcers and to guide instrumental behavior (Cador et al. 1989, 1991; Everitt et al. 1989; Salamone 1994; Brown and Bowman 1995). Furthermore, the degree to which such stimuli control behavioral activity has been hypothesized to be a function of NAC dopaminergic activity (Schultz et al. 1997; Young et al. 1998).

The regulation of NAC output neurons by NAC dopaminergic inputs is complex and depends strictly on interactions with NAC glutamatergic inputs from telencephalic regions (Burns et al. 1994; Taber and Fibiger 1997). O'Donnell (1999) stressed that the effects of DA on NAC output neurons cannot be simplified as excitatory or inhibitory but depend on whether these neurons

direct dopaminergic projections from the VTA to the BF (e.g., Gaykema and Zaborszky 1996; Zaborszky and Cullinan 1996) and the MD (Beckstead et al. 1979; Cornwall and Phillipson 1988) are also likely to contribute directly and indirectly to the abnormal regulation of the cortical cholinergic inputs, but data specifying these dopamine-cholinergic interactions in the BF, or the dopaminergic regulation of MD efferents, are rare (Momiyama and Sim 1996; Lavin and Grace 1998). In general, this scenario extends traditional models of schizophrenia that have focused on the mesolimbic DA system and represents the hypothesis that dysregulation of the cortical cholinergic input system is the primary mediator of the impairments in cortical information processing in schizophrenia, specifically of the attentional abnormalities that contribute to the manifestation of psychotic symptoms.

exhibit a highly polarized resting membrane potential (down state) or depolarized plateaus (up state) and on the DA receptor subtypes activated (O'Donnell 1999). In fact, D1 and D2 receptors mediate different effects of DA on NAC output neurons, and these effects interact with the state of these neurons (for review, see Nicola et al. 2000). Moreover, prefrontal, hippocampal, and amygdaloid projections to the NAC are differently modulated by DA D1 and D2 receptors (O'Donnell and Grace 1996; Charara and Grace 2003). Finally, increases in activity of DA NAC inputs are observed in association with converging glutamatergic activity (Youngren et al. 1993; Darracq et al. 2001; Floresco et al. 2001*a*, 2001*b*, 2001*c*; Howland et al. 2002), suggesting that the modulatory function of DA is partly regulated by glutamatergic inputs to the NAC.

O'Donnell (1999) further suggested that DA activates cell ensembles (possibly via gap junction modulation) that then maintain an up state, thereby robustly enhancing the processing of telencephalic inputs by the NAC (O'Donnell and Grace 1993; O'Donnell 1999). It is intriguing to extrapolate such a scenario to the consequences of psychostimulant sensitization, as the resulting abnormally reactive DA activity in the NAC would be expected to produce a more extensive and persistent formation of such functional cell ensembles, thereby pathologically expanding the range and degree to which telencephalic inputs are selected, and thus act as incentive stimuli and control behavior. Abnormally reactive NAC DA inputs may also suppress the relative contributions of hippocampal and amygdaloid afferents to NAC functioning, while allowing prefrontal throughput to dominate the state of NAC outputs (Charara and Grace 2003). As will be discussed below, such a breakdown in NAC functions is complemented and augmented by abnormal increases in the reactivity of cortical cholinergic inputs.

The main efferent pathway of the NAC shell reaches the ventral pallidum (Mogenson et al. 1983; Zahm and Brog 1992; Zahm and Heimer 1993; Usuda et al. 1998; Zahm et al. 1999) and appears to be largely GABAergic (GABA is γ-aminobutyric acid; Walaas and Fonnum 1980; Zaborszky and Cullinan 1992; Zahm and Heimer 1993). There is evidence for other types of NAC projections to the BF (e.g., Napier et al. 1995), but this anatomical organization remains unsettled. NAC GABAergic projections make direct contact with BF cholinergic neurons (Ingham et al. 1988; Zaborszky 1992; Zaborszky and Cullinan 1992). BF cholinergic neurons innervate practically all cortical areas and layers and thus gate all cortical information processing (Mesulam 1990).

Neuropharmacological evidence supports the transsynaptic regulation of the excitability of BF corticopetal (cholinergic) neurons by NAC GABAergic efferents. For example, infusions of DA agonists into the NAC increase firing rates of neurons in the BF (Yang and Mogenson 1989), suggesting that DA, within the NAC, inhibits the GABAergic projection to the BF. Kalivas and colleagues demonstrated that systemic administration of AMPH decreases GABA efflux in the ventral pallidum (Bourdelais and Kalivas 1990) and that the effects of systemic apomorphine (a DA agonist) on BF GABA efflux are potentiated by a prior depletion of forebrain DA (Bourdelais and Kalivas 1992; see also Mele et al. 1998). Conversely, infusions of DA D1 and D2 receptor antagonists into the NAC increase GABA efflux in ventral pallidal areas, which include the substantia innominata and the nucleus basalis of Meynert (Ferre et al. 1994; see also Yamamoto et al. 1994).

As would be predicted from the anatomical evidence in support of a NAC efferent regulation of GABAergic activity in the BF, manipulations of NAC neurotransmission alter the regulation of cortical cholinergic transmission. For example, increases in cortical ACh efflux, produced by the systemic administration of a negative GABA modulator, the benzodiazepine receptor (BZR) partial inverse agonist FG 7142, are blocked by systemic administration of haloperidol, or intra-NAC infusions of haloperidol or the D2 receptor antagonist sulpiride (Moore et al. 1999*a*). Although the use of a BZR partial inverse agonist to stimulate cortical ACh complicates the interpretation of the results, these and more recent findings (below) correspond with the hypothesis that NAC DA receptor stimulation inhibits GABAergic outputs to BF cholinergic neurons and that infusions of D2 antagonists into the NAC reinstate the GABAergic inhibition of corticopetal cholinergic neurons. The finding that FG 7142–induced increases in medial prefrontal cortical ACh efflux were not attenuated by local cortical perfusion of DA receptor antagonists (Moore et al. 1999*a*) corresponds with the assumption that the effects of systemically administered DA antagonists on cortical ACh efflux primarily involve NAC mechanisms (see also Bianchi et al. 1979; Day et al. 1994).

Mesolimbic projection systems regulate the excitability of BF neurons via additional multisynaptic circuits, including the bidirectional connections between the mesolimbic DA neurons and the amygdala (Fallon et al. 1978; Kelley et al. 1982; Wright et al. 1996), and the amygdala and the BF (e.g., Jolkkonen et al. 2002), and the direct projections of the ventral tegmentum to the BF (Gaykema and Zaborszky 1996; Momiyama and Sim 1996; Zaborszky and Cullinan 1996; Smiley et al. 1999). Thus, in addition to the route via the NAC, telencephalic pathology contributes to the dysregulation of the BF corticopetal system via multiple neuronal routes (figure 1).

Within the BF, GABAergic activity has been demonstrated to affect profoundly the excitability of corticopetal cholinergic projections. Our previous studies substantiated the regulation of cortical ACh efflux by BF GABAergic inputs by demonstrating that the

systemic or intra-BF administration of positive and negative GABA modulators (BZR agonists and inverse agonists) bidirectionally regulates cortical ACh efflux (Sarter and Bruno 1994; Bruno and Miller 1995).

As the GABAergic efferents of the NAC are contacted by glutamatergic afferents (Meredith 1999), NAC manipulations of glutamatergic transmission are expected to affect cortical ACh efflux. A series of experiments demonstrated that blocking NMDA or AMPA/kainate ionotropic glutamate receptors in the shell region of the NAC resulted in marked and lasting increases in medial prefrontal basal ACh release (Neigh-McCandless et al. 2002). It appears unlikely that decreases in BF GABAergic activity were solely responsible for these robust increases in basal ACh efflux; rather, direct stimulation of BF cholinergic neurons, via multiple afferent routes, including ventral tegmental (e.g., Momiyama and Sim 1996) and amygdaloid connections (see above; see also Givens and Sarter 1997), converge with decreases in BF afferent GABAergic activity to yield the observed increases in cortical ACh release (figure 1). Although the determination of the exact neuronal mechanisms mediating these effects requires more experimentation and may differ from the mediation of the effects of systemic or intra-NAC psychostimulants (Mele et al. 1998), these data support the notion that alteration of NAC output profoundly changes the regulation of cortical ACh efflux.

Behavioral studies concerning DA-GABAergic, NAC-BF interactions are rare. Patel and Slater found that the ability of NAC infusions of DA agonists to stimulate locomotion is attenuated by infusions of muscimol into the ventral pallidal area (Patel and Slater 1988; see also Mogenson et al. 1983; Sarter et al. 1990; Mele et al. 1998). Likewise, Swerdlow and colleagues (1984, 1990*a,* 1990*b*) demonstrated that infusions of GABA into the ventral pallidum reverse the disruption of prepulse inhibition in the acoustic startle test that results from infusions of DA into the NAC. Pierce and Kalivas (1997) indicated that psychostimulant-sensitized motor activity is attenuated by infusions of muscimol into the ventral pallidum. These findings support the hypothesis that the functional consequences of NAC DA receptor stimulation are mediated in part by a decrease in GABAergic output to the BF (see also Kitamura et al. 2001; figure 1).

Collectively, the available data correspond well with the hypothesis that NAC DA contributes potently to the regulation of BF corticopetal cholinergic neurons. Therefore, because abnormal regulation of NAC neurotransmission is part of the circuitry mediating the expression of psychotic symptoms (see above), the associated dysregulation of BF corticopetal cholinergic neurons is expected to represent an essential component of this circuitry (see also Heimer 2000). As will be discussed next, the effects of psychotogenic treatments on the regulation of cortical cholinergic transmission further support this hypothesis.

Increases in Cortical ACh Efflux by Psychotogenic Manipulations

Repeated, intermittent exposure to AMPH represents a robust psychotogenic manipulation and, in fact, is sufficient to initiate and maintain schizophrenic symptomatology (Bell 1965; Ellinwood 1967; Segal et al. 1981; Robinson and Becker 1986; Lieberman et al. 1990, 1997; Flaum and Schultz 1996). In humans, AMPH-induced psychosis involves obsessive and compulsive behavioral and cognitive activities, hallucinations, and paranoid delusions (Rylander 1972; Ellinwood et al. 1973; Segal and Janowski 1978). As discussed above, sensitization of the mesolimbic dopaminergic system represents a major consequence of repeated AMPH administration (see also Pierce and Kalivas 1997). Based on the transsynaptic regulation of BF corticopetal cholinergic projections by the NAC (discussed above), repeated psychostimulant administration has been predicted to also affect the regulation of cortical cholinergic transmission.

We investigated the effects of repeated AMPH administration on cortical ACh release using in vivo microdialysis in rats (Nelson et al. 2000). AMPH was administered once every other day for five total administrations initially. AMPH-induced increases in cortical ACh efflux were not immediately affected by this pretreatment regimen. However, administration of AMPH 19 days after the initial regimen resulted in significant augmentation of, or sensitization of, the increase in cortical ACh efflux (for details and control experiments, see Nelson et al. 2000). Further studies demonstrated that the augmented increase in cortical ACh efflux remained a reliable effect of repeated AMPH exposure, even when AMPH "challenges" were given following longer time intervals after the completion of the initial treatment regimen (Nelson, Sarter, Bruno, unpublished results).

The available, although limited, evidence on the effects of other psychotogenic manipulations supports the general idea that increases in cortical ACh efflux represent an essential component of the neuronal effects of such manipulations. Administration of the psychotogenic noncompetitive NMDA receptor antagonist ketamine (Krystal et al. 1994; Lahti et al. 1999; Newcomer et al. 1999) produces large (>250%) increases in cortical ACh efflux (Nelson et al. 2002*a*). However, in contrast to AMPH, repeated exposure to ketamine does not seem to alter the increase in ACh efflux observed following the initial ketamine exposure (Nelson et al. 2002*a*). Administration of phencyclidine (PCP) likewise increases cortical ACh efflux, but this effect does not change as a result of pretreatment with PCP (Jentsch et al. 1998*a*). These data indicate interesting and unsettled dissociations between the effects

of repeated exposure of different psychotogenic treatments, particularly when considering that repeated PCP also sensitizes the ventral striatal dopaminergic system and increases AMPH-induced behaviors (Jentsch et al. 1998*b*; see also the ketamine-induced augmentation of AMPH-induced increase in DA release in humans; Kegeles et al. 2000).

These data support the general hypothesis that psychotogenic treatments result in persistent increases in the excitability of cortical cholinergic inputs. However, these data do not address the degree to which NAC mechanisms are necessary for the mediation of the effect of repeated AMPH on the regulation of cortical ACh efflux. Additional neuronal mechanisms, including changes in the presynaptic regulation of ACh efflux, may contribute to the increases and sensitization of ACh efflux following psychotogenic manipulations. Furthermore, the present data collectively do not suggest that sensitization of NAC DA systems is sufficient to predict sensitization of cortical ACh efflux, and marked differences between the neuronal mediation of the effects of repeated psychostimulant versus NMDA receptor antagonist administration must explain their differential effects on ACh efflux following repeated exposure. The reduced prefrontal dopaminergic transmission produced by repeated NMDA antagonist administration (Jentsch et al. 1999), but not repeated psychostimulant exposure (Hamamura and Fibiger 1993; Stephans and Yamamoto 1995; Pierce and Kalivas 1997), and additional cortical pathology that is possibly produced by NMDA antagonists (e.g., Sharp et al. 2001), are key to understanding the different potencies of NMDA antagonists and psychostimulants in sensitizing cortical ACh efflux. The NMDA antagonist–induced decrease in prefrontal dopaminergic transmission may be sufficient to attenuate interactions between ventral tegmental dopaminergic neurons and telencephalic glutamatergic inputs to the mesolimbic dopaminergic system (O'Donnell and Grace 1998), thereby limiting the induction of persistent alteration in the regulation of BF corticopetal cholinergic neurons following repeated exposure. Moreover, repeated NMDA receptor antagonist exposure also disrupts the regulation of the BF via prefrontal and amygdaloid afferents (Zaborszky et al. 1997; see the discussion in Jolkkonen et al. 2002; Rosenkranz and Grace 2002; Sarter and Bruno 2002) and thereby contributes to the inability of repeated exposure to NMDA antagonists to permanently change the regulation of BF neurons. In contrast, following repeated AMPH exposure, interactions between prefrontal and mesolimbic neurons form the basis for the neuroplastic changes (e.g., Cador et al. 1999) that underlie the demonstration of sensitized cortical ACh efflux. Obviously, if sensitization of cortical ACh efflux represents an effect of repeated exposure specifically to psychostimulants, the significance of this conclusion for the understanding of schizophrenia must reflect the specific validity, including the limitations, of psychostimulant sensitization as a mechanism and model of psychosis (see below for more discussion).

To complete the review of psychotogenic manipulations known to affect the regulation of cortical ACh efflux, the effects of certain BZR inverse agonists, particularly the partial inverse agonist β-carboline FG 7142, traditionally classified as an anxiogenic compound, have been reconceptualized as indicating psychotogenic properties (Sarter et al. 2001*a*). The behavioral and cognitive effects of these drugs can be explained by using a cognitive framework, focusing on abnormal stimulus-processing mechanisms and stimulus-filtering deficits, similar to the cognitive frameworks used to explain the emergence of psychotic symptoms (see below). Furthermore, FG 7142 increases mesolimbic DA efflux (Tam and Roth 1985; Brose et al. 1987; Bradberry et al. 1991; McCullough and Salamone 1992; Bassareo et al. 1996) and, with remarkable efficacy, *basal* cortical ACh efflux (up to 400% over baseline reported in Moore et al. 1995*b*). Furthermore, as already mentioned, administration of haloperidol or sulpiride, given systemically or into the NAC, attenuates the effects of FG 7142 on cortical ACh efflux (Moore et al. 1999*a*), further supporting the relevance of this drug as a psychotogenic treatment. Likewise, the effects of FG 7142 in several tests of cognitive performance in monkeys and rats were attenuated by administration of typical and atypical antipsychotic drugs (Murphy et al. 1996*a*, 1996*b*; Ninan and Kulkarni 1999). In summary, increases in cortical ACh efflux were demonstrated to be part of the effects of a wide range of psychotogenic manipulations, and they were attenuated by antipsychotic drug administration.

Behavioral and Cognitive Consequences of a Sensitized Cortical Cholinergic Input System, and Relevance for Psychotic Cognition

Behavioral and Cognitive Consequences. The integrity of the cortical cholinergic input system is necessary for a wide range of attentional functions. Furthermore, increases in cortical ACh efflux have been selectively observed in rats performing in tasks taxing attentional capacities (Voytko 1996; Everitt and Robbins 1997; Perry et al. 1999; Sarter and Bruno 1999; Arnold et al. 2002). The present discussion will focus on the functional consequences of an abnormally reactive, or even sensitized, cortical cholinergic input system, particularly as a result of NAC dysregulation (see above).

Berridge and Robinson (1998) proposed that activation of NAC DA mediates the motivational salience attribution to the neural representation of stimuli associated with rewarding or aversive experiences. In essence, this hypothesis describes the functions of NAC DA to convert an event or stimulus from a neutral

"cold" representation into an attractive and significant stimulus that "grabs attention" (Berridge and Robinson 1998, p. 313; see also Cardinal et al. 2002). As a result of the sensitization of the NAC DA input system, normally insignificant stimuli or mental representations gain pathological levels of significance, and their processing then consumes substantial attentional resources, thereby limiting the evaluation of behavioral alternatives and thus triggering compulsive responses (Robinson and Berridge 1993; Drevets et al. 2001). Findings that repeated psychostimulant administration–induced structural changes in mesolimbic and cortical regions may limit the capacity for subsequent neuroadaptive processes (Kolb et al. 2003) have raised concerns about the reversibility of sensitization-induced alterations in neuronal information processing.

It has been suggested that the cognitive consequences of an abnormally reactive mesolimbic dopaminergic system give rise to the positive symptoms of schizophrenia (Kapur 2003). However, crucial components of such cognitive consequences, particularly the overprocessing of stimuli and associations, irrespective of their behavioral or cognitive significance, and the associated depletion of processing resources available for other activities, can be attributed more conclusively to a sensitization of the BF corticopetal cholinergic system. Several experiments have begun to characterize the profound attentional impairments that result from an overly reactive or abnormally disinhibited BF corticopetal cholinergic input system. For example, intrabasalis infusions of a BZR inverse agonist augment the increases in cortical ACh efflux that result from the presentation of an activating appetitive stimulus (Moore et al. 1995*a*) and, in rats tested in an operant task designed to assess sustained attention performance, impair performance by increasing the number of claims for signals in nonsignal trials (i.e., the number of false alarms; Holley et al. 1995). Likewise, infusions of NMDA into the BF augment stimulated cortical ACh efflux (Fadel et al. 2001) and produce the same pattern of attentional impairment (Turchi and Sarter 2001*b*). Importantly, this type of impairment is completely different from the selective decrease in the animals' ability to detect signals (i.e., hits) that results from lesions of the cortical cholinergic input system (McGaughy et al. 1996; McGaughy and Sarter 1998), from infusions of a BZR agonist or an NMDA receptor antagonist into the BF (Holley et al. 1995; Turchi and Sarter 2001*b*), or from infusions of antisense blocking the expression of NMDA receptors in the BF (Turchi and Sarter 2001*a*). In other words, the attentional consequences of manipulations that render the cortical cholinergic input system abnormally reactive are distinctive, and they do not match those resulting from a loss, or attenuation of activity, of BF cholinergic neurons.

The effects of repeated administration of AMPH on attentional performance substantiate this hypothesis. When a "sensitizing" administration regimen similar to that used by Nelson et al. (2000) to demonstrate AMPH-induced augmentation of increases in cortical ACh efflux (see above) was used, repeated AMPH produced a "sensitized" impairment in the performance of this task that again was characterized by an increased false alarm rate (Deller and Sarter 1998). Recent data from our lab indicate that, following a pretreatment regimen with amphetamine characterized by escalating doses and intermittent withdrawal periods and demonstrated to produce persistent behavioral sensitization (Paulson et al. 1991), increases in false alarms manifested after discontinuation of the pretreatment period at baseline, not necessitating amphetamine challenges (Martinez et al. 2003). Correspondingly, Crider and colleagues assessed the effects of repeated AMPH on the performance of rats in a conditioning paradigm requiring the animals to suppress processing of an irrelevant stimulus and observed evidence for an AMPH-induced impairment in the animals' ability to filter such stimuli. Furthermore, this effect was attenuated by the administration of haloperidol (Crider et al. 1982).

The exact cognitive mechanisms underlying the behavioral consequences of increases in the reactivity of cortical cholinergic inputs remain unsettled. Although the performance effects in these experiments could not be explained by overt behavioral mechanisms, including stereotypic responding and switching behavior, speculations in terms of abnormal increases in ACh mediating a lowering of the threshold for the detection of signals, or an "overprocessing" of "noise" and irrelevant stimuli, do not fully explain these impairments in performance. Analyses of response times indicated that increases in the false alarm rate are due in part to a disruption of the animals' ability to switch from the processing of the dominant response rule for signal trials to the rule that governs rewarded lever selection for nonsignal trials (Burk and Sarter 2001). Thus, increases in false alarms, observed following manipulations that augment the activity of cortical cholinergic inputs, likely were a result of multiple, interacting mechanisms, including abnormal levels of signal detectability ("sensitivity"), unusually "risky" criteria for reporting a signal, and a disruption of cognitive flexibility.

The consequences of abnormal increases in cortical cholinergic transmission for cortical information processing can also be extrapolated from the effects of iontophoretically applied ACh on cortical neuronal activity in interaction with sensory input. Cholinergic activity in the cortex produces a complex combination of inhibitory and excitatory effects (e.g., Hasselmo and Bower 1992; McCormick et al. 1993; Kimura and Baughman 1997; Tang et al. 1997), which, in more functional terms, enhances the effects of glutamatergic inputs via NMDA receptors (Aramakis et al. 1997) and desynchronizes cortical efferent neurons (Givens et al. 2003).

Abnormally high levels of cholinergic activity in the cortex reduce intralaminar inhibition (Xiang et al. 1998) and thus disrupt normal oscillatory cortical activity (Liljenstrom and Hasselmo 1995), generating abnormally synchronized and laterally spreading activity (Dickson and Alonso 1997; Xiang et al. 1998).

In the visual cortex, application of ACh generally enhances stimulus-driven neuronal activity; importantly, this enhancement is accompanied by a decrease of directional selectivity of visual cortical units (Sato et al. 1987; Muller and Singer 1989). Likewise, application of muscarinic agonists facilitates the responses of neurons to frequencies outside the band that optimally drives these neurons (''best frequency'') in the auditory cortex (McKenna et al. 1989). Moreover, in one study, pairing auditory stimuli with BF stimulation changed auditory cortical receptive fields, such that they then became receptive for the frequency of the stimuli as the new ''best frequency'' (Bakin and Weinberger 1996). In the somatosensory cortex, stimulation of the cholinergic BF enhances the responses of neurons to stimulation of the skin (Rasmusson and Dykes 1988; Webster et al. 1991). Although some of these data were interpreted as reflecting adaptive consequences of cortical ACh on information processing, particularly the receptive field changes following paired BF and sensory stimulation, ACh stimulation–mediated decreases in directional selectivity of visual cortical units, or the response of auditory neurons to stimuli that were not previously ''best frequencies,'' indicate that sufficiently high levels of cortical ACh release mediate the processing of normally filtered information or, more generally, an abnormally augmented processing of sensory information. This hypothesis corresponds with the demonstration that BF electrical stimulation, when paired with a neutral stimulus, empowers this stimulus to exert behavioral control akin to a conditioned stimulus (McLin et al. 2002).

A recent study in human volunteers (Thiel et al. 2002) demonstrated that administration of the acetylcholinesterase inhibitor physostigmine, which results in high levels of ACh and thus abnormal levels of cholinergic receptor stimulation, yielded increases in the auditory cortical metabolic activity (measured by functional magnetic resonance imaging [fMRI]) in response to an auditory unconditioned stimulus, thereby attenuating the difference between the response to this stimulus and a shock-conditioned stimulus. These data elegantly illustrate the overprocessing of irrelevant stimuli as a result of abnormally high levels of cholinergic transmission.

In the PFC, cholinergic inputs appear to have a special role in the filtering of distractors. We demonstrated that prefrontal neurons increase their activity when animals are presented with a visual distractor while performing a visual sustained attention task (Gill et al. 2000). The increase in neuronal activity was demonstrated to depend on the integrity of cholinergic inputs to the recording area. The role of prefrontal cholinergic inputs in the mediation of the effects of distractors is also indicated by the attentional impairments resulting from bilateral loss of cholinergic inputs specifically to the PFC. Animals with such lesions showed augmented distractor effects, suggesting that the loss of this input impaired their capacity to filter distractors (Gill et al. 1999) and to limit their top-down influence on cortical information processing (Sarter et al. 2001*b*). The consequences of an abnormally high reactivity of prefrontal cholinergic inputs for filtering functions are more difficult to predict in the absence of data but may involve complex consequences for the attentional processing of signal-noise relationships, including impairments in the ability to switch between the processing of signals and noise (see above). This issue deserves more research. Irrespective of the exact nature of this effect, the impaired processing of signals, and their resulting limitation in guiding behavior, would be an expected consequence of an abnormal reactivity of cholinergic inputs to prefrontal regions.

The cognitive and behavioral consequences of abnormally reactive cortical cholinergic inputs need to be understood in the context of the more general prefrontal ''executive'' functions in controlling the brain's information processing capacities. The ''executive'' top-down control of attentional processes and capacities is organized primarily by prefrontal regions and, via efferent circuits, optimizes in a modality-specific fashion the detection of the location and the processing of sensory stimuli, including the temporal binding of related inputs and the switching between sets of inputs (Desimone and Duncan 1995; Shulman et al. 1997; Kastner et al. 1998; Garavan et al. 2000; Hopfinger et al. 2000; Bunge et al. 2001; Engel et al. 2001; Miller and Cohen 2001; Treue 2001; Corbetta and Shulman 2002; Macaluso et al. 2002). The ability of prefrontal regions to initiate such top-down processes is hypothesized to depend on proper cholinergic innervation (Sarter et al. 2001*b*). Moreover, the activity of cholinergic inputs into posterior cortical areas is influenced by prefrontal transmission (Nelson et al. 2002*b*), possibly via prefrontal projections directly to the BF, indirectly via prefrontal efferents to the mesolimbic dopaminergic system, and via multisynaptic prefrontal connections to posterior cortical regions (figure 1). Additionally, abnormal activity in thalamic inputs to the cortex interacts with converging dysregulated cholinergic inputs to disrupt further input processing in schizophrenia (Andreasen et al. 1996). Thus, the consequences of a dysregulated cortical cholinergic input system escalate, as an impaired prefrontal ''anterior attention system'' (Posner and Dehaene 1994) yields impaired top-down mechanisms (Frith and Dolan 1996). Our data indicate that cholinergic transmission in posterior cortical areas is regulated by prefrontal cholinergic and glutamatergic activity (Nelson et al. 2002*b*). As a result of abnormal increases in prefrontal cholinergic

transmission, such top-down regulation of posterior cortical input functions presumably is disrupted, and such a functional disconnection between prefrontal and posterior cortical regions has been hypothesized to underlie schizophrenia patients' inability to determine whether the source of an input derives from mental imagery or the outside world (Frith and Dolan 1996; Lawrie et al. 2002; Kim et al. 2003).

In summary, the available evidence suggests that abnormal increases in the reactivity of cortical cholinergic inputs mediate a complex disruption of normal stimulus processing mechanisms, ranging from—at the cellular level—abnormal expansions of receptive fields combined with decreases in stimulus selectivity, to—at the level of neuronal systems—synchronization and abnormal spread of activity, and—in terms of cognitive functions—impairments characterized by cognitive inflexibility, signal detection abnormalities, and impaired top-down optimization of posterior cortical regions for input processing. As will be discussed next, such impairments correspond with the core dysfunctions described in cognitive theories of the development of psychotic symptoms.

Relevance for Psychotic Cognition. It seems straightforward to suggest that relatively limited yet persistent impairments in the detection and selection of information for further processing worsen rapidly, as the increasing preoccupation with irrelevant information consumes more and more attentional resources and increasingly limits the updating of the memory with information about significant versus insignificant inputs. These impairments eventually restrict the degree to which the subject's cognitive activity reflects reality (Gray et al. 1991). However, a comprehensive cognitive theory describing the development of psychotic symptoms as a result of the dynamic, escalating cognitive consequences of years of initially more subtle impairments in the ability to select stimuli and associations for further processing, to filter irrelevant inputs, and to organize processing resources to competing tasks, does not appear to be available (for evidence for early precursors of attentional dysfunctions in children at risk for schizophrenia, see Dworkin et al. 1993; Erlenmeyer-Kimling et al. 1993; Marcus et al. 1993; Mirsky et al. 1995; Egan et al. 2000). Likewise, treatment-induced recovery represents a slow cognitive process (see the informative first person account by Anonymous 1992), but a cognitive theory that would address the primary cognitive effects of antipsychotic drugs and the mechanisms by which these effects mount to attenuate schizophrenic symptoms is also lacking (see the discussion in Andreasen 2000).

Since the original descriptions by Kraepelin (1912) and Bleuler (1950), impairments in cognitive functions, specifically in the ability to select and process relevant stimuli and associations, and to filter those that are irrelevant for the task or cognitive process at hand, have been hypothesized to represent the unifying component of schizophrenia, and to contribute to, or at least to be associated with, the (positive) core symptoms of schizophrenia. In the 1960s, the (mostly) descriptive analyses (McGhie and Chapman 1961; Shakow 1962; Venables 1964) stressed the patients' inability to filter irrelevant sensory stimuli and associations from processing, and the resulting exhaustion of attentional resources for the processing of relevant inputs (e.g., patient 15 in McGhie and Chapman 1961, p. 51: "If something else is going on somewhere, even just a noise, it interrupts my thoughts and they get lost"). More contemporary, cognitive psychology–inspired theories focus on patients' inability to employ top-down processes to select significant cognitive cues and stimuli as well as to reject distracting inputs (Braff 1993; Andreasen et al. 1998; Javitt et al. 2000). Furthermore, ample evidence supports the notion that stimulus detection and discrimination functions are impaired and that attentional capacities, including the capacity for switching attention (Smith et al. 1998) and processing errors (Alain et al. 2002), are reduced in schizophrenia patients. These impairments likely are associated with, or even due to, the exhaustion of attentional resources by the processing of task-irrelevant information (e.g., Nuechterlein and Dawson 1984; Grillon et al. 1990; Granholm et al. 1991; Spring 1992; Goldberg et al. 1998; Seidman et al. 1998; Alain et al. 2002; Potts et al. 2002). Gray's theory of schizophrenia hypothesizes that the long-term, escalating consequences of such impairments impede subjects' ability to use and update past experiences to interpret and properly respond to current information processing, and thus contribute to the development of psychotic symptoms (Gray 1998).

The relationship between the attentional impairments and the main symptom clusters of schizophrenia is complex and poorly understood. Clinical research that focuses on the descriptive classification of symptoms using standard scales (e.g., Scale for the Assessment of Negative Symptoms, Scale for the Assessment of Positive Symptoms) and the assessment of patients' attentional impairments using regular psychometric tests (e.g., Continuous Performance Task [CPT]) have limited capability in determining the specific characteristics of the attentional disorder of patients (Elvevag et al. 2000) and in revealing the role of attentional impairments in the development of schizophrenic symptoms (Elliott and Sahakian 1995; Green et al. 2000; Phillips and David 2000). In fact, the clinical literature occasionally classified attentional impairments as a negative symptom, or suggested inconsistent relationships between attentional impairments and positive symptoms (but see Addington et al. 1991; Brockington 1992).

Numerous studies focused on the performance of schizophrenia patients in sustained attention (or vigilance) tasks, determining subjects' ability to detect,

discriminate, and process relevant stimuli against irrelevant and distracting "background noise." Although schizophrenia patients are said to suffer from "hypervigilance," studies using standardized CPTs for the assessment of attentional abilities rarely demonstrated the characteristics of the specific attentional impairments of schizophrenia patients (e.g., Nuechterlein and Dawson 1984; Mussgay and Hertwig 1990; Spring 1992). However, other, more experimental studies revealed the "hyperattentional" nature of their deficits, in both medicated and medication-withdrawn subjects (Mar et al. 1996; Salo et al. 1996; Light and Braff 2000). The hypothesis that such attentional impairments are intrinsically related to the neurobiological bases and the development of positive symptoms of this disorder, while entailing complexities and not being universally accepted (Green and Nuechterlein 1999), has been extensively substantiated (e.g., Freedman et al. 1991; Serper et al. 1994; Servan-Schreiber et al. 1996; Berman et al. 1997; Jones et al. 1997; Velligan et al. 1997; Cohen et al. 1998; Nelson et al. 1998; Brebion et al. 1999; Cadenhead and Braff 2000; Dawson et al. 2000; Phillips and David 2000).

The description of the attentional impairments of schizophrenia patients corresponds with the cognitive consequences of an abnormally reactive cortical cholinergic input system discussed above. It seems worthwhile to stress again that in contrast to the consequences of an abnormally reactive cortical cholinergic input system, the attentional impairments resulting from loss of cortical cholinergic inputs or reduction in the excitability of this neuronal system differ fundamentally (references above). Thus, the fundamental cognitive dysfunction in schizophrenia is hypothesized to be mediated by a dysregulation of the cortical cholinergic input system that is characterized specifically by augmented levels of cortical cholinergic transmission.

Treatment Implications

The hypothesis that psychosis is mediated by an abnormally reactive cortical cholinergic input system does not predict that blockade of cholinergic transmission by, for example, administering muscarinic or nicotinic receptor antagonists, will produce antipsychotic effects. In fact, such drugs have been extensively documented to produce tremendous cognitive impairments and in fact cause extensive disruption of information processing, including symptoms of thought disorders akin to those in schizophrenia (Perry and Perry 1995). Rather, the crucial role of cortical cholinergic inputs in elementary aspects of information processing (see above) implies that persistent *normalization* of cortical cholinergic transmission is required to improve the patient's status. The available data indicate that such normalization of cortical cholinergic activity is achieved by the administration of DA D2 antagonists—that is, by typical antipsychotic drugs (Moore et al. 1999*a*; see above). Kapur interprets the antipsychotic efficacy of such drugs as the long-term result of the "dampening of salience of abnormal experiences" (2003, p. 13). The present discussion is in keeping with this perspective, except that the normalization of the reactivity of cortical cholinergic inputs is considered to be the critical underlying neuronal mechanism of such effects.

Our previous research on the regulation of BF cholinergic neurons also suggests that positive GABA modulators, particularly BZR agonists, are capable of normalizing an overreactive cortical cholinergic input system (Sarter and Bruno 1994). While chronic treatment with such drugs appears limited by rapid BZR downregulation, several studies demonstrated the usefulness and potency of BZR agonists in exhibiting antipsychotic effects (Llorca et al. 1991; Delini-Stula et al. 1992; Jaspert and Ebert 1994; Delini-Stula and Berdah-Tordjman 1995; Delini-Stula and Berdah-Tordjman 1996) in preventing symptom progression (Carpenter et al. 1999) and relapse (Kirkpatrick et al. 1989), and, when coadministered with typical antipsychotic drugs, in enhancing the therapeutic efficacy and reducing the daily doses of the antipsychotic drug required (Bodkin 1990; Wolkowitz and Pickar 1991; Wassef et al. 1999).

Although, as mentioned above, experimental evidence suggests that administration of typical antipsychotic drugs normalizes an overly reactive cortical cholinergic input system, the effects of atypical antipsychotic compounds in models addressing the role of the cholinergic system in psychosis are not known. Several experiments documented that the acute administration of atypical antipsychotic drugs (clozapine, olanzapine) potently increases basal hippocampal and cortical ACh efflux (Parada et al. 1997; Ichikawa et al. 2002; Shirazi-Southall et al. 2002). However, the effects of these drugs in interaction with psychotogenic manipulations, or in animal models of schizophrenia, and following chronic administration, cannot be predicted from acute effects in naïve animals. For example, the high antimuscarinic potency of clozapine (Sethy et al. 1996), reflected by the finding that the discriminative stimulus properties of this drug potently generalize to those of atropine and scopolamine (Nielsen 1988), suggests that the increase in ACh release produced by acute administration of atypical antipsychotic drugs is due, at least in part, to presynaptic muscarinic receptor blockade (see also Parada et al. 1997; Raedler et al. 2000). After chronic administration of atypical antipsychotic drugs, alterations in muscarinic receptor regulation are likely to develop (e.g., Marks et al. 1984), and thus, the regulation of cortical ACh efflux may be fundamentally different when compared to the effects of the acute administration of such drugs. Moreover, chronically administered clozapine fundamentally changes NAC throughput (e.g., Compton and Johnson 1989), thus altering the telencephalic influence on the

regulation of cortical cholinergic inputs. Collectively, the effects of chronically administered clozapine, and in interaction with abnormal mesolimbic dopaminergic activity, remain unclear, but the data on the effects of acutely administered atypical antipsychotic drugs on cortical ACh efflux may not generalize to these important conditions.

Systematic psychopharmacological approaches to investigating the cholinergic system's role in schizophrenia remain to be developed. Present efforts are hampered by the availability of drugs that modulate cortical cholinergic transmission, as opposed to direct receptor agonists or antagonists. As such compounds are developed (e.g., Felder et al. 2001), it will be important to assess the effects of chronic administration on cortical cholinergic transmission in animal models of positive symptoms (see also the discussion in Crook et al. 2000).

Finally, it is important to note that the present discussion on the role of an abnormally reactive cortical cholinergic input system focuses on the manifestation of the positive symptoms of schizophrenia. However, evidence cited above suggests that muscarinic receptor downregulation represents a persistent marker of schizophrenia and has been speculated to contribute to the cognitive impairments of such patients. Moreover, downregulated muscarinic receptors may further elevate the reactivity of mesolimbic dopaminergic transmission (Gerber et al. 2001) and thus amplify the transsynaptic dysregulation of the cortical cholinergic input system. Based on these findings and considerations, novel muscarinic agonists or positive modulators of muscarinic transmission are being developed for the treatment of schizophrenia (Shannon et al. 1999, 2000; Felder et al. 2001; Stanhope et al. 2001). Although the present model can be interpreted as predicting that such treatments involve a risk for triggering psychotic episodes, the available evidence about the chronic effects of reduced muscarinic cholinergic transmission for the regulation of mesolimbic DA systems, and about the effects of chronic administration of positive modulators of muscarinic receptors, remains inadequate to predict such risks.

Summary and Conclusions

The present hypothesis extends previous descriptions of the neuronal circuitry that, if abnormally regulated, underlies the expression of mostly the positive symptoms of schizophrenia. Moreover, the attentional functions attributed to normal cortical cholinergic transmission suggest that abnormal increases in the reactivity of cortical cholinergic inputs mediate attentional impairments that contribute to the development and expression of such symptoms. Such a dysregulation of cortical cholinergic inputs is a necessary correlate of a sensitized mesolimbic DA system and, in turn, worsens the regulation of mesolimbic systems (Gerber et al. 2001). Thus, the cortical consequences of abnormally regulated ventral striatal circuitry are profound, as they are based on a cortexwide abnormal modulation of cortical information processing by cholinergic inputs. Moreover, a deregulated cortical cholinergic input system causes a disruption of the top-down regulation of sensory and associational input processing; such a disruption is the key to understanding the neuronal basis of the source monitoring failures in schizophrenia.

The primary limitation of this hypothesis concerns the fact that most of its support derives from animal anatomical and neuropharmacological experimentation, and the attentional and cholinergic consequences of psychostimulant sensitization. For reasons discussed above, relevant human neuropathological and psychopharmacological data remain scarce. Clearly, the ability to monitor the activity of cortical cholinergic transmission in humans, and the demonstration of altered reactivity in acute psychotic patients, would be a most critical test of this hypothesis. Furthermore, experiments designed to assess cortical functioning in patients while their attentional capacities are taxed will assist in defining the consequences of abnormally regulated attentional systems (Ojeda et al. 2002).

Another possible limitation of a hypothesis that builds on the sensitization model concerns the necessity of a "challenging" manipulation, typically reexposure to a psychostimulant, for the demonstration of the abnormal regulation of corticopetal cholinergic projections and associated attentional impairments. Indeed, some authors (e.g., Murphy et al. 2001) have considered this variable to be one of the major limitations of the hypothesis. However, as discussed above (see also Laruelle 2000), a sensitized cortical cholinergic input system, similar to the mesolimbic DA system, is specifically associated with an active disease period. In patients, a variety of stressors and stressor-triggered flashbacks can initiate an active disease period (e.g., Ventura et al. 1989; Lieberman et al. 1997; Yui et al. 1999*a*, 1999*b*). As stressors are also capable of revealing a sensitized mesolimbic DA system (e.g., Robinson and Becker 1986; Moghaddam 2002), and therefore possibly a sensitized cortical cholinergic input system (see also Imperato et al. 1992), the drug challenge models the effects of such stressors and is therefore an essential aspect of the model. It remains to be demonstrated, however, that relevant stressors are indeed capable of producing the attentional impairments in previously sensitized animals that are mediated by an abnormally reactive cortical cholinergic input system.

The present model predictably is overly simplistic, as, for example, other BF afferent networks, particularly those originating in other telencephalic regions (e.g., the amygdala), are likely to further contribute to the multisynaptic dysregulation of BF-cortical networks (references above; figure 1). Furthermore, the status of cortical muscarinic and nicotinic receptors as well as of other cortical receptor systems modulated by cholinergic

inputs (e.g., Ball et al. 1998) remains unclear but is critical for the understanding of the long-term consequences of increased reactivity of cortical cholinergic transmission. Finally, we need to better understand the fundamental consequences of an abnormally increased cortical cholinergic input system for cortical information processing.

It is difficult to conceive of a model describing the neuronal circuitry mediating schizophrenic symptoms that does not include the corticopetal cholinergic input system. Given the afferent circuitry of the BF (figure 1), the validity of hypotheses about the central role of the mesolimbic DA system in schizophrenia (Kapur 2003), the validity of the sensitization model in terms of modeling core aspects of the mesolimbic DA dysregulation in schizophrenia, and the transsynaptic influences of the mesolimbic system on the regulation of the excitability of BF neurons (see above), it is extremely likely that the capacity of the cortical cholinergic input system to modulate cortical information processing is affected in schizophrenia. The present model describes specific neuropharmacological mechanisms that explain dysregulation of the cortical cholinergic input system as a correlate of an abnormally reactive mesolimbic DA system, and it explains a wide range of attentional abnormalities that are hypothesized to contribute to the manifestation of psychosis. Furthermore, experimental data indicate that antipsychotic DA receptor antagonists act, at least in part, by normalization of cortical cholinergic transmission. Animal models characterized by an abnormally reactive cortical cholinergic input system, and future efforts designed to monitor the state of the cortical cholinergic input system in schizophrenia patients, will be critical in testing the present model and determining the exact role of this potent neuronal regulator of cortical information processing in schizophrenia.

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The Authors

Martin Sarter, Ph.D., is at the Department of Psychology, University of Michigan, Ann Arbor, MI. Christopher L. Nelson, Ph.D., is at the Department of Neuroscience, The Chicago Medical School, Chicago, IL. John P. Bruno, Ph.D., is at the Department of Psychology, Ohio State University, Columbus, OH.

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