

Cortical Acetylcholine, Reality Distortion, Schizophrenia, and Lewy Body Dementia: Too Much or Too Little Cortical Acetylcholine?

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Aberrations in cortical cholinergic transmission have been hypothesized to mediate the development and manifestation of psychotic cognition. Based primarily on hypotheses about mesolimbic dopaminergic hyperactivity in schizophrenia, the actions of antipsychotic drugs, the trans-synaptic regulation of the excitability of basal forebrain corticopetal cholinergic neurons, and the role of cortical cholinergic inputs in attentional functions, we hypothesized that persistent disinhibition of cortical cholinergic inputs mediates the fundamental cognitive dysfunctions which form the basis for the development of positive symptoms in schizophrenia. In contrast to this hypothesis, Perry and Perry (1995), based on evidence from hallucinating patients with Lewy Body Dementia (LBD), concluded that the extensive *loss* of cortical acetylcholine allows irrelevant information to enter “conscious awareness” and thus hallucinations to emerge. The discussion of these contrasting hypotheses highlights the need for more dynamic and precise theories describing the cognitive variables and neuronal processes which contribute to the development and manifestation of psychotic cognition. While the hypothesis that a disinhibited cholinergic system mediates the evolution of psychotic symptoms corresponds more convincingly with current theories about the cognitive functions of cortical cholinergic inputs, both hypotheses stress the critical role of cortical acetylcholine in the highest levels of cognitive functioning. © 1998 Academic Press

INTRODUCTION

As coined by Kraepelin’s term “dementia praecox,” cognitive dysfunctions represent the unifying, cardinal symptom of schizophrenia. However, current clinical nosology focuses on reality distortion, i.e., delusions and

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hallucinations, as the predominant symptoms of psychosis (e.g., Andreasen, Arndt, Alliger, Miller, & Flaum, 1995). Moreover, impairments in cognitive functions are often classified as negative symptoms (e.g., Kibel, Lafont, & Liddle, 1993) and considered independent from psychosis, or even to represent a separate consequence of the chronicity and severity of the illness (e.g., Mortimer, Lund, & McKenna, 1990). The detachment of impairments in cognitive functions from the disease-defining symptoms has been frequently cited as a major obstacle toward a theory-driven research into the cognitive processes that contribute to the development of schizophrenic symptoms (Brockington, 1992; David & Cutting, 1994).

While nosology-driven research *per se* does not attempt to unpack the theoretical constructs "delusion" or "hallucination" (e.g., Sarter & Smith, 1995) yet expects to dissociate the neuronal mechanisms of positive and negative symptoms¹ (Tandon, Shipley, Greden, Mann, Eisner, & Goodson, 1991), more analytical approaches, using psychological or cognitive frameworks and terminology, are likely to yield hypotheses about the cognitive dysfunctions which contribute to the evolution of schizophrenic symptoms. In general terms, attentional dysfunctions, such as impairments in the ability to detect, select, and discriminate stimuli and associations for extended processing, have been suggested to contribute decisively to the development and escalation of the positive symptoms of schizophrenia (Cohen & Servan-Schreiber, 1992; Freedman, Waldo, Bickford-Wimer, & Nagamoto, 1991; Gray, Feldon, Rawlins, Hemsley, & Smith 1991; Marder, Asarnow, & Van Putten, 1984; Margo, Hemsley, & Slade, 1981; McGhie & Chapman, 1961; Nuechterlein, Buchsbaum, & Dawson, 1994; Serper, Davidson, & Harvey, 1994; Spring, 1992; Strauss, 1993; Venables, 1964).

While *hyperattentive* dysfunctions (i.e., the breakdown of filtering functions, the overprocessing of irrelevant stimuli and the resulting exhaustion of processing capacity; e.g., Grillon, Courchesne, Ameli, Geyer, & Braff, 1990) have been considered a main force in the evolution of schizophrenia, traditional neuropsychological tests such as the continuous performance test (CPT) are not designed to reveal the specific nature of the attentional impairments in these patients (e.g., Cullum, Harris, Waldo, Smerhoff, Madison, Nagamoto, Griffith, Adler, & Freedman, 1993; Elliott & Sahakian, 1995; Lieb, Merklin, Rieth, Schüttler, & Rieth, 1994; McKenna, Tamlyn, Lund, Mortimer, Hammond, & Baddeley, 1990; Pigache, 1996; Weiss, 1996). However, schizophrenic patients were shown to *outperform* normals with

¹ Nosology-driven reasoning has also resulted in rather pessimistic judgements about the potential of animal research in schizophrenia. While it is likely that symptomatic entities such as "delusions" and "hallucinations" cannot be convincingly demonstrated in animals (see Frith, 1992, p. 29; but see also Nielsen, Eison, Lyon, & Iversen, 1983; Nielsen, Lyon, & Ellison, 1983), it is certainly possible to develop animal models of the fundamental cognitive dysfunctions which may incite the development of psychotic cognition (e.g., Gray et al., 1991; Killcross, Dickinson, & Robbins, 1994; Sarter, 1994).

respect to their ability to detect and process stimuli in experiments that employed a human version of operant procedures designed for the assessment of sustained attention in laboratory animals (Mar, Smith, & Sarter, 1996; see also Bentall & Slade, 1985; Mussgay & Hertwig, 1990). As such hyperattentive dysfunctions are hypothesized to give rise to psychotic symptoms (see Hemsley, 1994), the search for the neuronal mechanisms mediating schizophrenia needs to focus on alterations in neuronal circuits that underlie attentional processing (see Freedman, Waldo, Bickford-Wimer, & Nagamoto, 1991). Obviously, such alterations in neuronal activity would be predicted to normalize as a result of antipsychotic drug treatment (e.g., Bilder, Turkel, Lipschutz-Broch, & Lieberman, 1992).

As will be discussed below, candidates for such neuronal circuits include the cortical cholinergic afferent projection system. The hypothesis that hyperactivity of cholinergic inputs to the cortex mediates the hyperattentive dysfunctions which give rise to psychotic symptoms will be evaluated in light of Perry and Perry's (1995) diametrically opposed suggestion that *loss* of cholinergic cells underlies hallucinations in patients with Lewy Body Dementia (LBD). The two contrasting views provide valuable insights into the complex relationships between the cognitive dynamics of hallucinations and delusions and changes in cortical cholinergic transmission.

Neuronal Systems Mediating Hyperattentive Functions

Several lines of research, using different technical approaches and species, have consistently supported the hypothesis that the basal forebrain cholinergic neurons that project to all cortical areas and layers mediate attentional functions. A full evaluation of this issue is beyond the scope of this discussion (for review see Everitt & Robbins, 1997; Robbins & Everitt, 1995; Sarter & Bruno, 1997). In addition to the substantial evidence demonstrating the role of cortical cholinergic inputs in sustained and selective attention (e.g. McGaughy, Kaiser, & Sarter, 1996; Muir, Everitt, & Robbins, 1994), we have recently also demonstrated that this system regulates aspects of processing capacity and/or the allocation of processing resources in rats (Turchi & Sarter, 1997). It is also important to note that the "arousal"-setting functions of other major cortical afferent systems, primarily the noradrenergic projections from the locus coeruleus (e.g., Aston-Jones, Chiang, & Alexinsky, 1991; Foote, Aston-Jones, & Bloom, 1980) may be dissociable from the defined attentional functions of cortical cholinergic inputs (McGaughy, Sandstrom, Ruland, Bruno, & Sarter, 1997).

Experimental evidence concerning the effects of increases in cortical cholinergic transmission on attentional processes is rare. Our initial experiments on cortical acetylcholine (ACh) release in rats while their attentional performance was challenged by manipulations designed to increase the demands on attentional processing suggested demand-associated increases in ACh efflux

(Sarter, Bruno, Givens, Moore, McGaughy, & McMahon, 1996; see also Himmelheber, Sarter, & Bruno, 1997). In the present context, however, experimental information is needed about the fundamental attentional consequences of abnormal increases in cortical ACh release that, as will be discussed further below, are hypothesized to mediate the essential cognitive pathology of schizophrenia.

Some relevant, yet circumstantial evidence is available from studies on the attentional effects of infusions of benzodiazepine receptor (BZR) inverse agonists into the basal forebrain in animals. BZR inverse agonists generally reduce the inhibitory effects of GABA and have been demonstrated to increase cortical ACh release. Moreover, the effects of BZR inverse agonists on cortical ACh release interact with the state of activity of this system (Moore, Sarter, & Bruno, 1993, 1995; Sarter & Bruno, 1994). Thus, these compounds serve as tools to disinhibit the activity of cortical cholinergic inputs and to test the behavioral and cognitive consequences of cortical cholinergic hyperactivity. A task designed and validated for the measurement of sustained attention, or vigilance (McGaughy & Sarter, 1995), was employed to test the effects of infusions of BZR agonists and inverse agonists into the substantia innominata region of the basal forebrain (Holley, Turchi, Apple, & Sarter, 1995). In brief, this task requires animals to discriminate between signals and non-signals and reveals signal-length-dependent hit rates which decrease over time on task (for details see McGaughy & Sarter, 1995). While the infusion of a BZR agonist, which reduces stimulated cortical ACh release, produced a selective decrease in the relative number of hits—similar to the consequences of lesions of the cholinergic system (McGaughy et al. 1996), infusions of a BZR inverse agonist (the β -carboline β -CCM), shown to increase cortical ACh release, selectively increased the number of false alarms ("claims" for signals when no signals were presented). This finding has been discussed in terms of reflecting the over-processing of stimuli or even "noise" due to an overactive cholinergic system (see also Sarter, 1994). This effect of a BZR inverse agonist shows impressive face validity in the context of studies demonstrating an increased probability of hallucinating patients to "detect" signals while none were presented (Bentall & Slade, 1985).

Similar suggestions about the effects of BZR inverse agonists on the processing of stimuli were derived from a very different line of research which focused on measures of autonomic reactivity as an index for the processing of non-signal stimuli (Quigley, Sarter, Hart, & Berntson, 1994). These studies used the BZR partial inverse agonist FG 7142 that has also been demonstrated to elevate cortical ACh release (Moore, Stuckman, Sarter, & Bruno, 1995). Quigley et al. (1994) demonstrated that following the administration of FG 7142, the cardiovascular effects of a non-signal stimulus corresponded with the effects of a stimulus pretrained to serve as a conditioned stimulus (CS) for an aversive event in untreated animals. In other words, the pro-

cessing of a neutral stimulus following the administration of FG 7142, as reflected by a combination of sympathetic activation and vagal withdrawal, increased to the extent typical for a CS. Importantly, this effect of FG 7142 has been demonstrated to depend on the integrity of the basal forebrain cholinergic system and, importantly, is mimicked by the intraventricular administration of cholinomimetic drugs (Berntson, Hart, Ruland, & Sarter, 1996). Recent studies demonstrated that cholinergic inputs into the medial prefrontal cortex, but not into the lateral parts of the prefrontal cortex of rats, mediate the autonomic correlates of the overprocessing of this stimulus in this animal model (Hart, Sarter, & Berntson, unpublished results). Collectively, the results from these studies provide support for the hypothesis that disinhibited cortical cholinergic transmission mediates an abnormal overprocessing of stimuli. As discussed above, such "hyperattentional" dysfunctions are hypothesized to form the basis for the development of psychotic symptoms.

Cortical Cholinergic Hyperactivity in Schizophrenia: Evidence and Concepts

The hypothesis that increases in cortical cholinergic transmission mediate psychotic cognition predicts that such increases are found in schizophrenic patients and are normalized by antipsychotic treatments. It is important to note that while postmortem measures of the activity or distribution of the enzymes choline acetyltransferase (ChAT) or acetylcholinesterase (AChE) provide general indications of the integrity of cholinergic neuronal systems (e.g., Karson, Casanova, Kleinman, & Griffin, 1993), these markers do not readily reveal changes in the activity of cholinergic terminals, specifically because neither enzyme is the rate limiting factor in the synthesis or the release of ACh. Thus, ChAT or AChE data from schizophrenic patients do not inform about dynamic changes in the regulation of cortical ACh release but may, at best, point to morphological aberrations in cholinergic systems. Conversely, the absence of changes in the activity of these enzymes does not exclude that dynamic changes in cholinergic transmission are part of the circuits mediating schizophrenic symptomatology (e.g. Haroutunian, Davidson, Kanof, Perl, Powchik, Losonczy, McCrystal, Purohit, Bierer, & Davis, 1994). Valid measures of the activity of cholinergic inputs require *in vivo* assessments of the dynamics of ACh release; unfortunately, such measures are not available from patients. However, a surprisingly strong body of circumstantial evidence, as well as basic neuropharmacological considerations which relate to current hypotheses about the role of mesolimbic dopamine in schizophrenia (see below),² support the hypothesis that cortical cholinergic

² Earlier speculations about striatal catecholamine-acetylcholine imbalances are not within the scope of this discussion (e.g., Frederickson & Richelson, 1979).

hyperactivity is an indispensable component of the neuronal activity changes underlying schizophrenia (Sarter, 1991).

If hypercholinergic activity contributes to the development of schizophrenic symptoms, administration of cholinesterase inhibitors, while not selectively affecting cortical ACh when given systemically, would be expected to advance such symptoms. However, the acute administration of physostigmine in schizophrenic patients (Davis & Berger, 1978) or normal humans (Tandon, Greden, & Haskett, 1993) clearly does not produce positive symptoms. Considering the attentional dysfunctions resulting from cholinergic hyperactivity (see above), such symptoms following a single, acute administration of a cholinesterase inhibitor would not be expected, as the process from attentional dysfunctions to the manifestation of such symptoms is assumed to require chronic and the escalating impairments in the discrimination, selection, and processing of relevant stimuli. If this assumption is correct, then *chronic* administration of cholinesterase inhibitors would be expected to produce positive symptoms. Indeed, in the 1960s, a substantial number of reports described the psychosis that resulted from chronic exposure to insecticides in field scientists and farmworkers. For example, a healthy 26-year-old scientific officer (described in Gerson & Shaw, 1961) was diagnosed with a 50% reduction in cholinesterase levels and "had schizophrenic ideas of religious influence, of being close to God, of being called to Rome to replace the Pope, and other related bizarre ideas; he was actively hallucinating" (p. 1371; see also Bowers, Goodman, & Sim, 1964). In the 1950s, potent cholinesterase inhibitors such as diisofluoropropylphosphate ("dyflos") were also tested in schizophrenics and reported to trigger psychotic episodes (Rowntree, Nevis, & Wilson, 1950). To the extent that the effects of systemically administered drugs assist in the discussion of the hypothesis that cortical cholinergic hyperactivity mediates the development of schizophrenic symptoms, the psychotic effects of chronic administration of cholinesterase inhibitors in humans provide support for this hypothesis (for further references see Karczmar, 1981).

It has also been frequently proposed that, if a hypercholinergic component plays a role in the mediation of positive symptoms, administration of anticholinergic drugs such as the muscarinic receptor blockers scopolamine and atropine should improve schizophrenic symptomatology (e.g. Tandon & Greden, 1989). In addition to the requirement for chronic treatment of dynamic cognitive dysfunctions stressed above, the interpretation of negative results from the studies on the effects of anticholinergic drugs on positive symptoms ignores another important aspect of reasoning about therapeutic mechanisms. If a hypercholinergic system plays a role, then *blockade* of cholinergic transmission by an anticholinergic drug is not to be equated with the desirable *normalization* of cholinergic transmission. The effects of cholinergic receptor blockers are to suppress cholinergic transmission and, thus, do not inform about the potential beneficial effects of a normalization of cholinergic trans-

mission. Indeed, a general worsening of the patient's status following muscarinic receptor blockade might be expected (see Berger, 1981; Tandon, Shipley, Greden, Mann, Eisner, & Goodson, 1991). In contrast to the effects of cholinergic antagonists, accumulating evidence suggests that antipsychotic dopamine receptor antagonists normalize enhanced cortical cholinergic transmission (see below).

Current Theories of Schizophrenia: Extension to Cortical ACh

The neuronal mechanisms and circuits which are in the focus of current theories of schizophrenia require an efferent, or down-stream, extension to include systems hypothetically responsible for attentional dysfunctions and, consequently, schizophrenic symptomatology. Most theories assume a developmental dysmorphogenesis in telencephalic regions which, in the course of neuronal and cognitive maturation, and possibly in interaction with stressors, yield an aberrant activity in mesolimbic dopaminergic inputs (e.g., Breier, Su, Saunders, Carson, Kolachana, De Bartolomeis, Weinberger, Weisenfeld, Malhotra, Eckelman, & Pickar, 1997; Weinberger, 1987; Raedler, Knable, & Weinberger, 1998). Thus, overactive mesolimbic dopamine, rather than representing the primary pathological mechanism, gains its prominent role as a mediator of the functional effects of the telencephalic dysmorphogenesis, and as a major site hypothesized to mediate the therapeutic effects of antipsychotic dopamine receptor antagonists.

The exact nature of the abnormal regulation of mesolimbic dopamine in schizophrenia, and accordingly, the therapeutic mechanisms of antipsychotic drugs, have remained controversial. Traditionally, mesolimbic dopaminergic afferents have been hypothesized to be overactive, and antipsychotic dopamine receptor antagonists have been thought to act by blocking this dopaminergic hyperactivity. However, dopaminergic *hypo*activity, specifically in cortical areas, has also been discussed, though neither assumption clearly explains the increase in D2 dopamine receptors in the brains of schizophrenic patients (e.g. Davis, Kahn, Ko, & Davidson, 1991; see also Lidow, Williams, & Goldman-Rakic, 1998). In an attempt to integrate various concepts and data, Grace (1993) proposed the existence of an upregulation of subcortical dopaminergic systems due to tonically reduced levels of cortical dopamine release. While a comprehensive discussion of this theory is beyond the scope of this discussion, an increased dopaminergic transmission in mesolimbic areas, specifically the nucleus accumbens, continues to be considered a cardinal component in the aberrant neuronal mechanisms which are normalized by antipsychotic drugs (Breier et al., 1997; Grace, Bunney, Moore, & Todd, 1997).

The abnormal regulation of nucleus accumbens dopamine has been related to associational impairments (e.g. Cohen & Servan-Schreiber, 1992; Grace, 1993) or even to the "aberrations of consciousness in schizophrenia" (Gray,

1995). However, the available information about the basic behavioral functions of this system suggests that accumbens hyperdopaminergic transmission is unlikely to serve as a primary mediator of the cognitive dysfunctions of schizophrenia (e.g., Mermelstein & Becker, 1995; Robbins, Cador, Taylor, & Everitt, 1989; Salamone, 1996; Wise & Hoffman, 1992). Accumbens dopamine, however, controls the excitability of basal forebrain neurons, particularly of the cholinergic, corticopetal neurons, whose attentional functions were discussed above. This interaction involves, minimally, a GABAergic efferent projection to the basal forebrain area. The anatomical, physiological, neurochemical, and behavioral evidence in support of basal forebrain GABA-cholinergic interactions has been discussed extensively elsewhere (e.g. Mogenson, Swanson, & Wu, 1983; Sarter, 1994; Sarter & Bruno, 1997; Zaborszky, 1992)).

While the precise synaptic mechanisms and the role of different dopamine receptor subtypes in the nucleus accumbens remain unclear, this circuit (see Fig. 1) predicts that dopamine receptor stimulation in the nucleus accumbens, specifically in the shell of this nucleus, via decreases in the activity of GABAergic projections to the cholinergic cell bodies in the basal forebrain, increases the excitability of cholinergic efferents to the cortex. Furthermore, it predicts that increased cortical ACh efflux is normalized by infusions of dopamine receptor antagonists into the nucleus accumbens. Evidence in support of these predictions is accumulating.

Systemic administration of dopaminergic agonists such as apomorphine and amphetamine, decrease the release of GABA in the basal forebrain (Bourdelaïs & Kalivas, 1990, 1992) and increase cortical ACh release (e.g., Bianchi, Tanganelli, & Biani, 1979; Casamenti, Bianchi, Beani, & Pepeu, 1980; Day & Fibiger, 1993; Nistri, Bartolini, Deffenu, & Pepeu, 1972). Moreover, local cortical administration of amphetamine does not reproduce the effect of systemic administration on cortical ACh release (Day & Fibiger 1992). As would be expected, lesions of the mesolimbic dopaminergic system attenuate the ability of amphetamine to increase cortical ACh release (Day, Tham, & Fibiger, 1994).

Few data are available about the effects of dopamine receptor antagonists on basal forebrain GABA or cortical ACh. Consistent with the above model, Ferre and co-workers (Ferre, O'Connor, Snoprud, Ungerstedt, & Fuxe, 1994) showed that infusions of the D2 antagonist raclopride into the accumbens increase GABA release in the ventral pallidum. A series of studies from our laboratories (Moore, Fadel, Sarter, & Bruno, 1998) demonstrated that increases in cortical ACh release produced by systemic administration of the benzodiazepine receptor partial inverse agonist FG 7142 (see Moore et al., 1995) were effectively normalized by infusions of haloperidol into the nucleus accumbens (see Fig. 2). Moreover, intra-accumbens infusions of the D1 antagonist SCH 23390 or the D2 antagonist sulpiride also attenuated the increased cortical ACh release (Moore et al., 1998). Although the mecha-

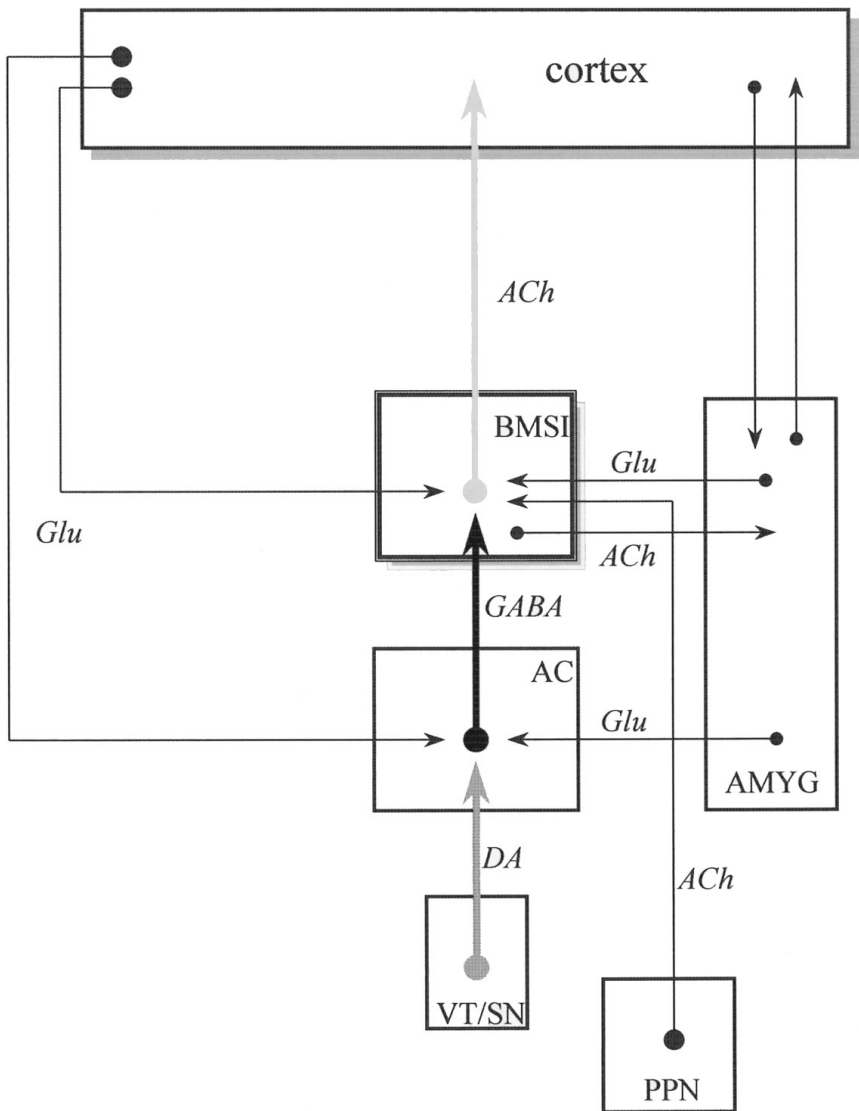


FIG. 1. Nucleus accumbens—basal forebrain, dopamine–GABA–cholinergic connections and major associated circuits. As discussed in the text, overactivity in the dopaminergic inputs to the nucleus accumbens in schizophrenia is associated with a disinhibition of basal forebrain cholinergic inputs. Increased activity in cortical cholinergic inputs is hypothesized to represent a major mediator of the (hyper)-attentional dysfunctions of schizophrenia and, consequently, of the positive symptoms of the disease (see text). Furthermore, this model predicts that antipsychotic dopamine receptor antagonists normalize overactive cortical cholinergic inputs (for evidence see text). Additional major afferents of the nucleus accumbens and the basal forebrain are indicated. Abbreviations: AC, nucleus accumbens; ACh, acetylcholine; AMYG, amygdala; BMSI, basal nucleus of Meynert/substantia innomina of the basal forebrain; DA, dopamine; GABA, γ -aminobutyric acid; Glu, glutamate; PPN, pedunculo-pontine nucleus; VT/SN, ventral tegmentum/substantia nigra.

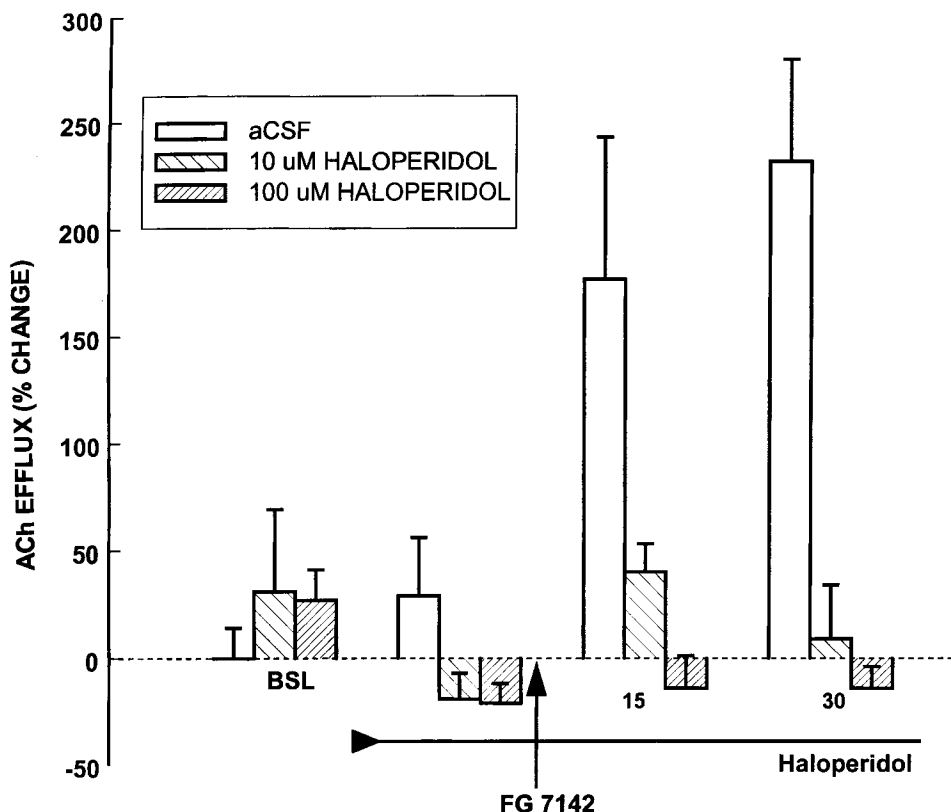


FIG. 2. Effects of haloperidol infusions into the nucleus accumbens on the increased cortical acetylcholine (ACh) release produced by systemic administration of the benzodiazepine receptor partial inverse agonist FG 7142 (8 mg/kg, i.p.; see Moore et al. [1998, 1995] for methodological aspects concerning the microdialysis technique and for more information concerning the effects of FG 7142 on cortical ACh; see also Sarter and Bruno, [1994]). Haloperidol was administered through a microdialysis probe placed into the shell region of the nucleus accumbens (10,100 μ M in the perfusate; 2 μ l/min). Cortical ACh release was assessed in the medial prefrontal cortex. The ordinate depicts percent change ACh efflux relative to baseline. Haloperidol was added to the perfusate after the first collection of cortical dialysate (see the horizontal line below the abscissa which depicts the presence of haloperidol; groups of bars from the left to the right represent results from consecutive collection intervals separated by 15 min). FG 7142 was administered after the second collection of cortical dialysate. FG 7142 given alone (i.e., while CSF was administered to the accumbens; open bars) increased cortical ACh release by up to about 200%. Co-administration of haloperidol effectively blocked this increase in cortical ACh release. These data demonstrate that increased cortical ACh release is normalized by infusions of an antipsychotic compound into the nucleus accumbens (Moore et al., 1998).

nisms involved in the FG 7142-induced activation of cortical ACh release complicate the interpretation of these findings, they support the hypothesis that dopamine receptor antagonists, particularly antipsychotic compounds, restore normal activity in cortical cholinergic inputs.³

Behavioral data demonstrating the functional significance of these accumbens dopamine–basal forebrain GABA–cortical ACh-interactions are rare. Swerdlow, Braff, and Geyer (1990) demonstrated that the disruption of pre-pulse inhibition (PPI) following infusions of dopamine into the nucleus accumbens could be reversed by infusions of the GABA_A agonist muscimol into the area of the substantia innominata of the basal forebrain. These data suggest that the effects of mesolimbic dopaminergic manipulations are mediated via the GABAergic output to the basal forebrain and, given evidence for the GABAergic modulation of corticopetal cholinergic neurons (e.g., Sarter & Bruno, 1994), further suggest a role of the latter projection in the PPI-disrupting effects of accumbens dopamine receptor stimulation (see also Kodsi & Swerdlow, 1995).

As accumbens dopamine reduces GABAergic outflow to the basal forebrain, in schizophrenia, overactive accumbens dopaminergic inputs would be expected to reduce basal forebrain GABA, thereby disinhibiting the cholinergic neurons of this area. Therefore, BZR agonists which reverse the reduction in GABAergic inhibition are predicted to produce therapeutic effects. Infusions of BZR agonists into the basal forebrain, or administered systemically, attenuate increases in cortical ACh release (Sarter & Bruno, 1994). According to the hypothesis described above, these normalizing effects of BZR agonists on activated cortical ACh release predict that these compounds should benefit schizophrenic symptomatology, at least to the extent that an overactive cholinergic system mediates such symptoms. Indeed, BZR agonists are known to reduce hallucinations and psychosis in schizophrenic patients, although the antipsychotic efficacy of these drugs appears more variable than is the case for dopamine receptor antagonists (Jaspert & Ebert, 1994; Llorca, Wolf, & Estorges, 1991; Wolkowitz & Pickar, 1991). Furthermore, co-treatment with BZR agonists allow reduction of the dose of traditional antipsychotic compounds (e.g., Pecknold, 1993), and some limited evidence suggests the possibility that BZR agonists prevent relapse in schizophrenia (Kirpatrick, Buchanan, Waltrip, Jauch, & Carpenter, 1989).

In summary, accumulating, albeit largely circumstantial, evidence suggests that the efferent circuits of accumbens dopamine involve the regulation

³ There is accumulating evidence suggesting direct effects of dopamine on basal forebrain neurons by reducing GABAergic inhibition locally (e.g., Chrobak & Napier, 1993; Heidenreich, Mailman, Nichols, & Napier, 1995; Maslowski-Cobuzzi & Napier, 1994; Momiyama & Sim, 1996; Napier, 1992). While anatomical evidence suggests that cholinergic neurons are among those affected by dopamine (Gaykema & Zaborszky, 1996), evidence for a direct dopaminergic regulation of the excitability of corticopetal cholinergic neurons appears not yet available.

of cortical cholinergic inputs via a GABAergic projection to the basal forebrain, and that disinhibition of corticopetal cholinergic neurons mediates the hyperattentional dysfunctions which, in the long term, contribute essentially to the emergence of positive symptoms.

A Diametrically Opposed View: Hallucinations Based on Cortical Cholinergic Deafferentation

Lewy Body Dementia appears to be a variation of Alzheimer's disease characterized, neurologically, by the presence of Lewy bodies and, clinically, by fluctuations in cognitive performance. Important for the present discussion, up to 50% of the patients with LBD exhibit hallucinations and delusions (for review see Perry, McKeith, & Perry, 1996). While few data on the effects of antipsychotic medication in these patients or in patients with Alzheimer's disease are available (e.g., Gottlieb & Kumar, 1993), they appear to indicate that these drugs do not robustly reduce the hallucinations and delusions; to the contrary, a significant, detrimental neuroleptic sensitivity in LBD patients has been discussed (e.g., McKeith, Fairbairn, & Harrison, 1996).

Perry and co-workers (Perry, Irving, Kerwin, McKeith, Thompson, Collerton, Fairbairn, Ince, Morris, Cheng, & Perry, 1993; Perry & Perry, 1995) found that neocortical ChAT levels in hallucinating patients with LBD were significantly lower than in LBD patients without hallucinations. Based on this finding and reports about psychotic symptoms following the administration of muscarinic antagonists (e.g. Sauder, Shalansky, & Hewko, 1994) and several other drugs with anticholinergic properties (see Table 2 in Perry & Perry, 1995), Perry and Perry (1995) suggested that in the absence of acetylcholine, irrelevant sensory and associational information is processed, yielding psychotic symptoms (see also Warburton & Wesnes, 1979). Obviously, this hypothesis is entirely diametrical to the one developed above that proposes that cortical cholinergic hyperactivity augments the processing of irrelevant information and thus fosters psychotic symptoms.

While hypotheses about the involvement of specific neuronal systems in the effects of systemically administered compounds are notoriously difficult to substantiate, particularly in light of the complex pre- and postsynaptic effects of muscarinic antagonists in central and peripheral systems (Sarter, Bruno, & Dudchenko, 1990), the greater loss of cortical cholinergic afferents in hallucinating vs. non-hallucinating LBD patients is intriguing. As psychotic symptoms in demented patients predict a steeper decline in residual cognitive abilities, hallucinating LBD patients, in general terms, may represent a more severely affected subgroup of patients (Ballard, Lowery, Harrison, & McKeith, 1996; Del-Ser, Munoz, & Hachinski, 1996; McShane, Keene, Gedling, & Hope, 1996). However, the rare data on the effects of cholinomimetics in LBD patients do not support the possibility that administration of a cholinesterase inhibitor benefit the psychotic symptoms in these

patients (Lebert, Souliez, & Pasquier, 1996). Thus, the correlative evidence presented by Perry et al. (1993) presently remains the most convincing evidence in support of the hypothesis that cholinergic cell loss mediates the manifestation of psychotic symptoms in LBD.

Psychotic symptoms, particularly hallucinations, indicate a break-down in the neuronal mechanisms of information processing and thus may arise from many types of pathological processes (e.g., Andersen & Rizzo, 1994), possibly including massive loss of basal forebrain cholinergic cell bodies. However, the current fundamental hypotheses about the role of cortical ACh in the augmentation of the processing of sensory and associational inputs (Everitt & Robbins, 1997; Robbins & Everitt, 1995; Sarter & Bruno, 1997) do not relate well to the possibility that the absence of this system mediates the loss of filtering functions and the pathological overprocessing of irrelevant stimuli which spur the development of psychotic symptoms (see above). The loss of cortical cholinergic inputs represents a critical component in the development of dementia (for an extensive discussion of this complex hypothesis see Sarter et al. 1997), and it is less obvious how the loss of this cortical input system may mediate the productive character of psychotic symptomatology that is associated with cortical activation (e.g., Silbersweig, Stern, Frith, Cahill, Holmes, Grootoink, Seaward, McKenna, Chua, Schnorr, Jones, & Frackowiak, 1995; Waddington, 1990). At the very least, a hypothesis focusing on the role of the loss of cholinergic inputs in psychosis needs to be completed by assumptions about the driving mechanisms underlying the overprocessing of irrelevant information which may represent the elementary dysfunction of psychosis. While the trans-synaptic consequences of cholinergic cell loss may well contribute to the psychotic symptoms in LBD, cholinergic cell loss *per se* remains an unlikely candidate for a primary neuronal mechanism mediating hallucinations and delusions.

CONCLUSIONS

The search for the neuronal mechanisms mediating psychotic symptoms begins with the definition of the elementary dysfunctions that trigger the development of such symptoms. The available evidence provides a case for a role of cortical cholinergic inputs in the early steps of information processing. The hypothesis that cortical cholinergic hyperactivity mediates the hyperattentive dysfunctions which contribute to the evolution of hallucinations and delusions in schizophrenia is supported by several lines of evidence, ranging from the effects of neuroleptics on cortical ACh release to the effects of chronic exposure to cholinesterase inhibitors on cognitive processes. While this hypothesis may not necessarily be in conflict with the possibility that hallucinations in LBD patients are related to the secondary consequences of the extensive loss of cortical cholinergic afferents, support for the latter hypothesis remains limited and, moreover, this hypothesis is

difficult to integrate with current concepts about the information processing capabilities of cortical cholinergic inputs. Either hypothesis, however, sheds light on the significance of cortical cholinergic inputs in mediating fundamental aspects of cognition including, in the terms of Perry and Perry (1995), conscious awareness.

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