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Cholinergic aspects of schizophrenia

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While increased dopamine activity is central to our current understanding of the pathophysiology of schizophrenia, dysregulation of a single neurotransmitter is unlikely to explain the disorder adequately. It is argued here that the muscarinic aspects of schizophrenia should be reassessed for a number of reasons. These include current evidence that cholinergic modulation affects both positive and negative symptoms, and neuroendocrine and polysomnographic data that suggest an increased muscarinic cholinergic activity in schizophrenia. In addition, the interactions between the dopaminergic and cholinergic systems are becoming better understood and appear to occur especially in regions that are thought to be relevant in schizophrenia. The fact that the highest affinity of clozapine, with its unique therapeutic profile, is to the muscarinic receptor encourages further evaluation. Finally, the use of anticholinergic agents to treat extrapyramidal side-effects and the fact that many antipsychotic agents have intrinsic anticholinergic activity suggest that the role of the cholinergic system in schizophrenia needs to be more clearly delineated.

The dopamine hypothesis has dominated biochemical and pharmacological thinking about schizophrenia for the past three decades (Carlsson, 1974; Meltzer & Stahl, 1976). Despite a large body of pharmacological evidence supporting this hypothesis, there is little direct evidence of altered dopamine functioning in schizophrenia, and increased dopamine activity (the dopamine hypothesis) cannot account for the negative symptoms of schizophrenia (Angrist *et al*, 1980; Crow, 1980; Tandon *et al*, 1995). The unique therapeutic activity of clozapine, viewed in the context of its rich and distinctive pharmacological profile, has also prompted a reconsideration of neurotransmitters other than dopamine. This has led to a reappraisal of the role of the dopamine system in schizophrenia. While the dopamine system is still central to our understanding of schizophrenia pathophysiology, it appears that interactions between dopamine and other neurotransmitter systems are relevant to the production and expression of the symptoms of schizophrenia. This presentation will focus on the role of cholinergic mechanisms and dopamine–cholinergic interactions in schizophrenic pathophysiology.

The cholinergic aspects of schizophrenia are often viewed as the 'side-effect system' in schizophrenia and are not considered essential to issues of therapeutic efficacy (Richelson, 1984). To some extent, at least, I will try to dispel that impression by proposing that the cholinergic system is, in fact, quite relevant to the pathophysiology of schizophrenia; does indeed have a role in the therapeutics of schizophrenia with regard to both positive and negative symptoms; may possibly have a role in the treatment of tardive dyskinesia; and is perhaps relevant to the causation of the disorder as well.

It should be emphasised, however, that the cholinergic system is only one of the elements in the many interactions between neurotransmitter systems that appear to be involved in schizophrenia. Schizophrenia is not likely to be explained by the excess or deficiency of a single neurotransmitter, but rather by abnormalities in several transmitter systems. Perhaps what is needed in the pharmacological treatment of schizophrenia is the partial blockade of several systems; a modulation of transmission, if you will, rather than the simple antagonism of a single system. The focus here will be on the muscarinic aspects of schizophrenia.

HISTORICAL ASPECTS

Interest in the muscarinic system in schizophrenia predates interest in the dopamine system. In the 1940s and 1950s, before the advent of current antipsychotic medications, cholinergic stimulation was among the treatments advocated for schizophrenia (Cohen *et al*, 1944). In atropine coma rebound therapy, patients were given high doses of atropine in the belief that rebound from the induced coma might have beneficial effects on the positive symptoms of schizophrenia. With the introduction of antipsychotics in the 1950s, interest in that treatment waned, since neuroleptics clearly conferred superior therapeutic benefits.

In the 1970s, a number of researchers suggested that an imbalance between the cholinergic and dopaminergic systems might be important in schizophrenia (Friedhoff & Alpert, 1973; Janowsky *et al*, 1973). They suggested, in fact, that there might be a cholinergic deficiency that could be corrected by the administration of cholinergic agents. The few therapeutic trials with cholinergic agents, however, yielded mixed results. Furthermore, the cholinergic system is difficult to manage therapeutically, and cholinergic agents, in particular, have pronounced systemic side-effects which make their use difficult in the treatment of any disorder.

In the 1980s there was again a renewal of interest in the cholinergic system as some investigators suggested that anticholinergics might decrease the efficacy of neuroleptics in the treatment of the positive symptoms of schizophrenia (Johnstone *et al*, 1983; Singh *et al*, 1987). Although it has long been known that there are multiple syndromes in schizophrenia, it has only been in the past couple of decades, principally through the work of Timothy J. Crow (Crow, 1980), Nancy C. Andreasen (Andreasen & Olsen, 1982), and William T. Carpenter, Jr (Carpenter *et al*, 1988),

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that the distinction between positive and negative symptoms has received attention. Along with the suggestion that anticholinergics have an adverse effect on positive symptoms, it was also noted that anticholinergics might *decrease* negative symptoms at certain stages of schizophrenic illness (Tandon *et al*, 1988). But findings were sometimes contradictory, which may have contributed to the current impression that cholinergic systems are not especially important in schizophrenic pathophysiology but are only important with regard to the extrapyramidal side-effects (EPS) associated with neuroleptics.

REASONS TO RE-EVALUATE THE ROLE OF THE CHOLINERGIC SYSTEM IN SCHIZOPHRENIA

There are a number of reasons why the role of the cholinergic system in schizophrenia should be reassessed. First, there is evidence to suggest that cholinergic modulation does, in fact, significantly (but differentially) affect positive and negative symptoms (Tandon *et al*, 1991*a*, 1992*a*). These effects vary at different stages of the illness: they are most pronounced during acute psychotic exacerbations but are less prominent during the more chronic stages of illness.

There is also evidence from substantial neuroendocrine and polysomnographic data which suggests that muscarinic cholinergic activity is increased in schizophrenia (Tandon *et al*, 1991*b*, 1992*b*). Again, this alteration is most pronounced during acute stages and less pronounced during more stable phases.

Third, we are gaining a better understanding of the nature of the interactions between the dopaminergic and cholinergic systems in various regions of the brain, and we know that interactions are particularly significant in regions considered to be relevant in schizophrenia (Buchsbaum, 1990; Tandon *et al*, 1999).

Fourth, clozapine is an extremely interesting agent in that it does not cause EPS or tardive dyskinesia, appears to be more effective in treating negative symptoms, and is effective in otherwise treatment-refractory people with schizophrenia (Kane *et al*, 1988; Jibson & Tandon, 1996). Considerable efforts have been made to relate clozapine's efficacy and other clinical attributes to its effects on the serotonin or dopamine receptor subtypes, when, in fact, its highest affinity is to the muscarinic receptor. In the context of its unique therapeutic profile – its efficacy in otherwise refractory patients, minimal EPS, the virtual absence of tardive dyskinesia – the cholinergic system might warrant a closer look.

Finally, the frequent use of anticholinergic agents to treat EPS and the fact that many antipsychotic agents have intrinsic anticholinergic activity suggest a clear need to delineate the precise role of the cholinergic system in schizophrenia. Modulating the cholinergic system may give rise to new treatment strategies for managing positive and negative symptoms.

EFFECT OF ANTICHOLINERGICS ON POSITIVE AND NEGATIVE SYMPTOMS

Anticholinergics are commonly used in the treatment of EPS, which frequently accompany neuroleptic treatment in schizophrenia. It is assumed that anticholinergic drugs do not adversely affect positive schizophrenic symptoms; clinical impressions generally support this belief, as do numerous studies documenting the absence of any beneficial effects of anticholinergic withdrawal on schizophrenic symptoms. On the other hand, anticholinergics have been shown to antagonise the therapeutic effects of neuroleptics on positive symptoms (Johnstone *et al*, 1983; Tandon *et al*, 1990*b*). Furthermore, in drug-free patients with schizophrenia during a psychotic exacerbation, anticholinergics increase positive symptoms fairly consistently (Chouinard *et al*, 1987; Tandon *et al*, 1992*a*).

A closer review of the literature reveals that most studies showing no adverse effects of anticholinergics on positive symptoms were conducted in the chronic neuroleptic-stabilised phase of the illness, whereas investigations documenting adverse effects of anticholinergic drugs on positive symptoms were conducted in the acute phase of the illness. This observation suggests that anticholinergics may have adverse effects on positive symptoms only in the presence of increased dopamine activity. In stabilised patients, dopamine hyperactivity is presumably corrected, and, as observed in a study of anticholinergic effects on positive and negative symptoms in medication-free, stable schizophrenia sufferers (Goff *et al*, 1994), anticholinergic agents may have no adverse effects on positive symptoms. Furthermore, since anticholinergic agents are only used in conjunction with neuroleptics in schizophrenia, their direct adverse effects on positive symptoms may be obscured by the more potent direct beneficial effects of dopamine blockade resulting from concomitant neuroleptic treatment. This might explain why the adverse effects of anticholinergics on positive symptoms are not readily apparent in the general clinical setting. In drug-free patients, this 'confounding' effect of neuroleptic medication is removed.

In contrast to the adverse effects of anticholinergic agents on positive symptoms, cholinomimetic agents have transient beneficial effects on positive symptoms. While the effects of cholinergic modulation on positive symptoms are weaker than those of dopaminergic modulation, they may be particularly meaningful in certain situations. For example, cholinergic stimulation may be efficacious in augmenting neuroleptic effects in patients with treatment-refractory positive symptoms of schizophrenia. Clozapine is an atypical neuroleptic proven to be more effective in treatment-refractory patients, although its precise mechanism of action is not known. In view of clozapine's potent M_1 cholinergic affinity (Bolden *et al*, 1991) and its behaviour as a partial agonist at the M_1/M_4 receptor *in vivo* (Rivest & Marsden, 1991; Meltzer *et al*, 1994; Zorn *et al*, 1994), the cholinergic activity of clozapine has been proposed as one mechanism to explain its superior efficacy in treatment-refractory patients with schizophrenia (Tandon & Kane, 1993).

There have been some suggestions over the past decade that increased cholinergic activity might be one mechanism that contributes to the development of negative symptoms in schizophrenia. It should be noted that there is a relatively high incidence of anticholinergic drug misuse in people with schizophrenia, although this is not the case among drug-misusers in general.

Patients with schizophrenia describe anticholinergic drugs as having an "energizing, stimulating, and socializing" effect (Fisch, 1987). In chronic patients, anticholinergics reduce negative symptoms (Fayen *et al*, 1988; Tandon *et al*, 1988), but it is not clear whether they are, indeed, primary negative symptoms rather than secondary negative symptoms due to EPS. In drug-free patients, biperiden (an oral

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anticholinergic agent with relative M_1 specificity) significantly decreases negative symptoms (Tandon *et al*, 1992*a*). In view of the potential adverse effects of anticholinergic agents on positive symptoms, anticholinergics should be considered mainly as a treatment strategy for enduring negative symptoms that persist after positive symptoms subside.

Our findings do not indicate the need for any radical change in the current usage of anticholinergics in the treatment of patients with schizophrenia. Greater attention needs to be paid to the impact of anticholinergics on symptoms, however, and there may be certain clinical settings in which adjunctive cholinergic or anticholinergic strategies may be useful in the treatment of schizophrenia. In particular, cholinergic augmentation (with M_1 agonists or partial agonists) could prove to be an effective treatment for otherwise neuroleptic-refractory positive symptoms. The recent availability of cholinergic compounds such as tacrine and donepezil should make such treatment possible, and this should certainly be borne in mind when considering the withdrawal of anticholinergic agents that the patient may be receiving. Conversely, anticholinergic agents may effectively treat some enduring negative symptoms. Trials to evaluate the efficacy and safety of these treatment strategies in schizophrenia are currently under way.

ALTERATION OF CHOLINERGIC FUNCTION IN SCHIZOPHRENIA

Contrary to the assertions of researchers in the 1970s and 1980s, who suggested that there might be a reduction in cholinergic function in schizophrenia, it appears, rather, that muscarinic cholinergic activity is increased in schizophrenia, particularly during psychotic exacerbations. Rapid eye movement (REM) sleep and neuroendocrine abnormalities observed in patients during the acute phase of schizophrenia support the hypothesis that muscarinic cholinergic activity is increased (Tandon & Greden, 1989; Tandon *et al*, 1991*a*,*b*, 1996; Riemann *et al*, 1994). While some investigations have suggested that this increase in muscarinic cholinergic activity may be the primary abnormality in schizophrenia, and that abnormalities in the dopamine system develop secondarily (Yeoman, 1995), we believe that this increase in muscarinic activity is a compensatory mechanism, which represents a 'homeostatic' response to the perturbations in dopaminergic activity.

We suggest that as dopamine increases at the onset of an acute psychotic exacerbation, cholinergic activity increases as well, in an attempt to maintain the dopamine/acetylcholine balance. This increased cholinergic activity exerts a dampening effect on the emergence of positive symptoms associated with increased dopamine activity but results in the intensification of negative symptoms that are known to occur in this phase of illness. With antipsychotic treatment, dopaminergic activity declines, which is associated with improvement in positive symptoms; the compensatory increase in cholinergic activity is also reduced, since it is no longer necessary, and a reduction in negative symptoms occurs as well. This model is consistent with the observation that anticholinergics have an adverse impact on positive symptoms only in the presence of increased dopaminergic activity and not when there is an absence of dopaminergic hyperactivity. The model is diagrammatically depicted in Fig. 1 (Tandon & Greden, 1989).

Our model encompasses the following elements: (a) assumption of a link between increased dopamine activity and positive symptoms; (b) the direct association of muscarinic activity with negative symptoms; (c) an increase in positive symptoms resulting from decreasing muscarinic activity; (d) indirect evidence of increased muscarinic activity in the psychotic phase; (e) the covariance of positive and negative symptoms in the psychotic phase (Tandon *et al*, 1990*a*, 1993*a*,*b*); and (f) the presence of several sites of dopamine/cholinergic interactions in the brain.

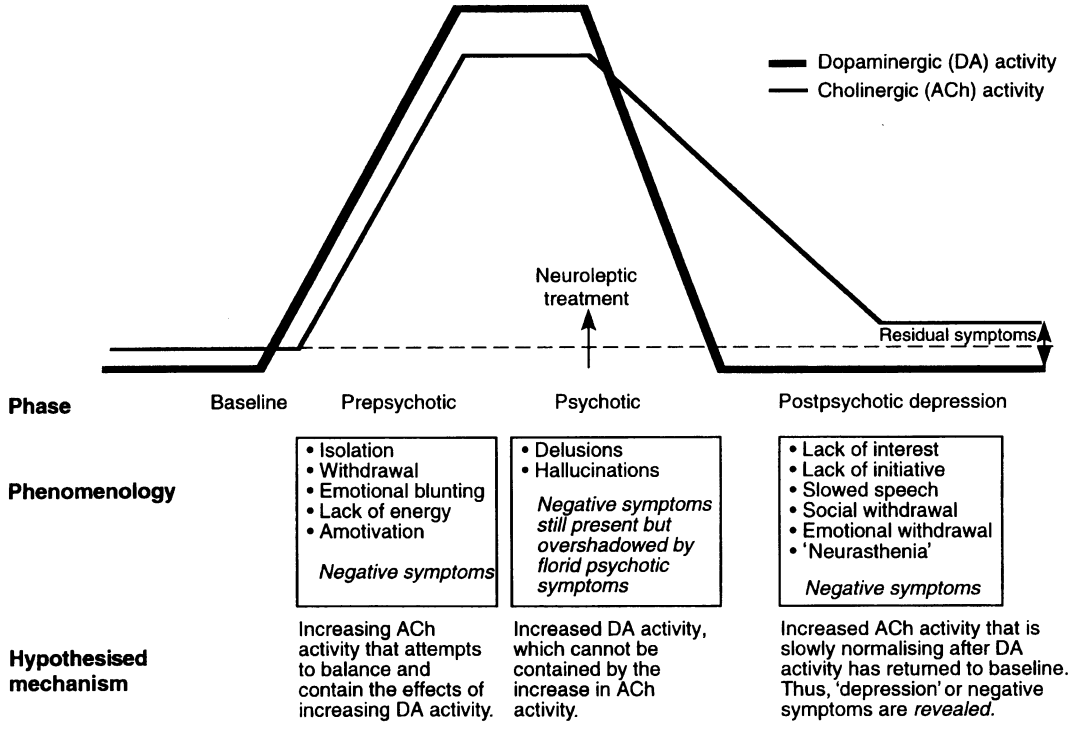

Fig. 1 Dopaminergic–cholinergic interactions and the phenomenology of an acute psychotic episode (adapted from Tandon & Greden, 1989).

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EFFECTS OF DIFFERENT ANTIPSYCHOTIC AGENTS ON THE MUSCARINIC SYSTEM

Clozapine has significant activity at the muscarinic site. It has a unique clinical profile: it is effective in the treatment of refractory patients, causes minimal EPS, and confers virtually no risk of tardive dyskinesia. Clozapine and olanzapine have very high affinity for the M_1 receptor and are relatively selective. Thioridazine, which also has very potent anticholinergic activity, is much less selective. If the affinities for the M_1 and M_2 receptors are compared, the ratio $M_1:M_2$ is about 15 for clozapine and olanzapine, but only about 5 for thioridazine, which is why significant peripheral anticholinergic side-effects occur more commonly with thioridazine (Table 1). It is M_2 blockade that is associated with peripheral anticholinergic side-effects.

The central nervous system side-effects associated with agents that have antimuscarinic activity include memory impairment, cognitive impairment, drowsiness, confusion, delirium, increased manifestations of tardive dyskinesia, seizures, and coma; and they may even lead to death. Peripheral side-effects may be blurring of vision, decreased sweating and salivation, constipation, erectile dysfunction and tachycardia. However, the frequency with which some of these anticholinergic side-effects are actually noted does not correlate well with expectations based on *in vitro* receptor affinities of these agents. Thus, we find that 18% of patients taking thioridazine, 14% of patients taking clozapine, 9% of patients taking olanzapine, and 7% of patients taking haloperidol and risperidone (compared with 3–5% on placebo) complain of constipation. Despite the fact that there are significant differences in *in vitro* antimuscarinic affinity between these agents, there is no equivalent correlative increase in constipation across these agents.

Similarly, 6% of patients on thioridazine, 4–5% of patients on clozapine and olanzapine, and 2% of patients on haloperidol and risperidone complain of blurred vision. Some 16% of patients on thioridazine complain of dry mouth, whereas the rates for those treated with haloperidol, clozapine, risperidone and olanzapine are similar (5–7%) and not much different from those found with placebo. Indeed, about a third of patients on clozapine complain of hypersalivation. Twenty-five per cent of patients on thioridazine exhibit tachycardia, while only 3–5% of those on haloperidol, risperidone, and olanzapine. The disparity between the clinical anticholinergic side-effects of these agents and their *in vitro* affinity for muscarinic receptors is striking.

Clozapine, in fact, has some interesting cholinergic-like effects: hypersalivation in a third of patients who respond to anticholinergic treatment, and increased dreaming, increased REM density and activity (Hinze-Selch *et al*, 1997; Tandon, 1997). The fact that clozapine has significant affinity for muscarinic receptors (like olanzapine and thioridazine) yet differs with regard to anticholinergic side-effects may be explained by its partial agonist activity at the muscarinic receptor (Tandon & Kane, 1993; Meltzer *et al*, 1994; Zorn *et al*, 1994; Zeng *et al*, 1997). In the case of olanzapine, the occurrence of anticholinergic side-effects is also lower than would be expected from its high M_1 affinity. Whether it also has partial agonist activity at the muscarinic site remains to be demonstrated, although a modest M_4 agonist potency has been reported (Zeng *et al*, 1997).

These observations raise the issue of whether cholinergic potentiation with an M_1 agonist, or perhaps with a partial agonist, can be an effective strategy for treating positive symptoms that are refractory to conventional antipsychotic medication. It is possible that this approach may present some benefits with regard to tardive dyskinesia and cognitive function as well. New agents may now allow more effective study of the muscarinic system, which has been relatively neglected in the past, in part because it is a difficult system to investigate and in part because of its complexity.

Table 1 Binding of antipsychotic agents to human muscarinic receptor subtypes[1]

Antipsychotic agent	Muscarinic receptor				
	M_1	M_2	M_3	M_4	M_5
Conventional					
Chlorpromazine	25	150	70	40	40
Chlorprothixene	10	30	20	20	25
Haloperidol	1500	2000	1500	500	1000
Thioridazine	2.5	15	15	10	15
Atypical					
Clozapine	3	50	20	10	10
Olanzapine	6	80	40	20	15
Quetiapine	300	3000	2000	400	6500
Risperidone	11 000	3700	13 000	2900	15 000
Zotepine	20	150	70	80	250

1. Affinity is expressed in terms of Kd (the equilibrium dissociation constant) in nanomoles. The smaller the number the greater the affinity. (Data taken from several sources, particularly Bolden *et al*, 1992.)

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