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Muscarinic cholinergic hyperactivity in schizophrenia
Relationship to positive and negative symptoms*

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Based on the implication of increased muscarinic ACh activity in the production of negative symptoms, the association of decreasing cholinergic activity with positive symptoms, and the covariance of positive and negative symptoms in the psychotic phase of schizophrenia, a model of (DA) dopaminergic/(ACh) cholinergic interactions in schizophrenia was recently formulated. It suggests that DA/ACh balance is of central importance in schizophrenic pathophysiology and that muscarinic ACh activity increases in an attempt to maintain this balance in the face of increasing DA activity that occurs in the psychotic phase of the illness. The model further suggests that the muscarinic system exerts a damping influence on the emergence of positive symptoms associated with DA hyperactivity, but that this compensatory increase in muscarinic activity is accompanied by an intensification of negative symptoms. In the present study, we tested two important postulates of this model. We tested the prediction that muscarinic activity is increased in schizophrenia by comparing the effect of biperiden, an antimuscarinic M-1 agent, on REM latency in 12 drug-free schizophrenic inpatients and matched normal controls. We found that biperiden caused a smaller increase in REM latency in schizophrenic patients, suggesting that muscarinic activity is increased in schizophrenia. We tested the prediction that an anticholinergic agent would increase positive symptoms and decrease negative symptoms by studying the effect of 8 mg of biperiden/day for 2 days on positive and negative symptoms (assessed by the BPRS) in 30 medication-free schizophrenic inpatients. Biperiden produced a significant increase in positive symptoms ($t = 6.36$, df $= 29$, $P < 0.001$) and reduction in negative symptoms ($t = -2.05$, df $= 29$, $P < 0.05$). These findings suggest that central muscarinic activity is increased in the psychotic phase of schizophrenia and is relevant to the expression of positive and negative symptoms.

Key words: Cholinergic; Symptoms; Psychotic; Pharmacology; Sleep; (Schizophrenia)

INTRODUCTION

The cholinergic system has intermittently been suspected of being involved in the pathophysiology of schizophrenia, but its precise role has been inadequately investigated and is still poorly understood. Some of the earliest pharmacological interventions in schizophrenia actually involved manipulation of the cholinergic system with anticholinergic agents such as hyoscine (Kraepelin, 1919) and atropine (Forrer and Miller, 1958), or cholinergic stimulation with acetylcholine (Cohen et al., 1944) and arecoline (Pfeiffer and Jenney, 1957). Despite these historical precedents, cholinergic mechanisms currently are considered relatively unimportant in schizophrenia and primarily discussed with regard to undesirable extrapyramidal side effects of neuroleptics. Evidence from

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several lines of research, however, suggests that this viewpoint warrants reconsideration and that the cholinergic system may play a prominent role in schizophrenic pathophysiology (Tandon and Greden, 1989).

Centrally active cholinomimetic agents and cholinesterase inhibitors lead to behavioural syndromes strikingly similar to the negative schizophrenic syndrome (Davis et al., 1976; Greden et al., 1987), anticholinergic agents may alleviate negative symptoms (Fayen et al., 1988; Tandon et al., 1988, 1990a), schizophrenic patients with negative symptoms tend to 'abuse' anticholinergics and report activating and energizing effects (Fisch, 1987; Wells et al., 1989), shortened REM latency in schizophrenia (Zarcone et al., 1987; Douglass et al., 1989) appears to be related to the severity of negative symptoms (Tandon et al., 1989a), and post-dexamethasone cortisol levels are directly correlated to the severity of negative symptoms (Safer et al., 1985; Faustman et al., 1989; Tandon et al., 1989b). Both short REM latency and increased post-dexamethasone cortisol levels are consistent with increased cholinergic activity (Sitaram et al., 1979; Carroll et al., 1980; Berger et al., 1989). Collectively, these data implicate increased cholinergic muscarinic activity in the production of negative symptoms (Tandon and Greden, 1989, 1990). On the other hand, anticholinergics may antagonize the therapeutic effects of neuroleptics specifically with regard to positive symptoms (Johnstone et al., 1983, 1988; Singh et al., 1987), anticholinergics exacerbate positive symptoms in drug-free schizophrenic patients (Tandon et al., 1990a), and physostigmine reverses the increase in positive schizophrenic symptoms induced by methylphenidate (Janowsky et al., 1973). These data indicate an association between decreasing cholinergic activity and positive symptoms.

In an effort to explain these findings and explain the covariance of positive and negative symptoms with neuroleptic treatment (Van Kammen et al., 1987; Tandon et al., 1990b), Tandon and Greden (1989) proposed a model of dopaminergic/cholinergic interactions in schizophrenia that suggests: (a) cholinergic/dopaminergic *balance* is of central importance in schizophrenic pathophysiology; (b) muscarinic activity increases in an attempt to maintain this balance in the face of increasing dopaminergic activity that occurs in the psychotic phase of the illness; (c) the muscarinic cholinergic system exerts a damping effect on the emergence of positive symptoms associated with dopaminergic hyperactivity; and that (d) this compensatory increase in muscarinic activity is in turn accompanied by an intensification of negative symptoms during and following the psychotic phase of the illness.

In the present study, we tested two major postulates of this model. We tested the prediction that muscarinic cholinergic activity is increased in schizophrenia by comparing the effect of biperiden, a specific M-1 antimuscarinic agent, on rapid-eye-movement (REM) sleep in 12 drug-free schizophrenic patients and 12 matched normal controls. We evaluated the effect of cholinergic modulation on positive and negative symptoms by studying the effect of biperiden on positive and negative symptoms in 30 otherwise drug-free schizophrenic patients.

SUBJECTS AND METHODS

The goals of this study were to: (1) compare the effects of an antimuscarinic anticholinergic agent on EEG sleep in 12 medication-free schizophrenic patients and age- and sex-matched normal controls; and (2) evaluate the effects of an anticholinergic agent on positive and negative symptoms in 30 otherwise medication-free schizophrenic patients.

Subject inclusion/exclusion criteria

General inclusion/exclusion criteria for all research candidates were: (i) age = 18–45 years; (ii) informed consent; (iii) medication-free for at least 2 weeks; (iv) absence of any serious medical illnesses or major physiological disturbances during the 3 months prior to the study; (v) no primary sleep disorder as assessed by a sleep disorders questionnaire and night 1 full montage sleep recording; (vi) absence of any medical condition that significantly affects sleep; (vii) no alcohol abuse or withdrawal in the past 3 months; and (viii) no use of cannabis, opiates, cocaine, or other 'street drugs' in the past 3 months.

Specific inclusion/exclusion criteria for schizophrenic patients were: (i) meets general inclusion/

exclusion criteria for all subjects, as listed above; (ii) meets DSM-III-R (American Psychiatric Association, 1987) and RDC criteria (Spitzer et al., 1978) for schizophrenia; (iii) currently meets criterion A of DSM-III-R (presence of characteristic psychotic symptoms); (iv) currently does not meet criteria for any other axis 1 or axis 2 disorder; and (v) has received no depot neuroleptics in the 6 months prior to the study.

Specific inclusion/exclusion criteria for normal controls were: (i) meets general inclusion/exclusion criteria for all subjects, as listed above; (ii) meets criteria for 'never mentally ill' (RDC) (Spitzer et al., 1978) with no prior or current treatment by a psychiatrist, psychologist, or other mental health professional; (iii) no family history of first-degree relatives with schizophrenia, other psychotic illnesses, or major mood (depressive/manic) disorders; and (iv) normal physical exam and screening battery, including urine drug screen and EKG.

Diagnostic evaluation procedures

The following steps were taken to establish the diagnosis and inclusion/exclusion criteria: (a) unstructured independent clinical interviews conducted by a faculty psychiatrist or research fellow; (b) a structured psychiatric interview using the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978) for schizophrenic patients and SADS-L (Spitzer and Endicott, 1979) for normal controls, both administered by formally trained research nurses with considerable experience in the administration of the SADS; (c) a comprehensive family diagnostic evaluation conducted by a psychiatric social worker that focused on the patient's course of illness and that provided supplemental information from family members about the patient's history, clinical features, and family history of psychiatric disorder; (d) a review of all previous available records; (e) comprehensive clinical and laboratory assessments to screen for physical disorders, that included a detailed review of systems, physical examination, chest X ray, hemoglobin, CBC with differential, electrolytes, liver functions, thyroid functions, VDRL, urinalysis and urine drug screen, electrocardiogram (EKG), and head CT scan; (f) a sleep disorders questionnaire administered to assess for a primary sleep disorder. Additionally, the sleep-EEG on night 1 was a full-montage study to serve for adaptation and exclusion of a primary sleep disorder.

Methods

Following the diagnostic evaluation, schizophrenic patients and normal controls were included for further participation in the study only if they met all the inclusion and exclusion criteria and after informed consent had been obtained. The two studies were conducted in the following manner:

(1) Sleep studies. 12 schizophrenic patients and age (± 3 years)- and sex matched controls participated in the sleep studies. Each subject underwent three nights of polysomnography. Schizophrenic patients were studied in their own hospital beds by remote cable telemetry, while normal controls were studied in our sleep laboratory. Subjects received no drugs on nights 1 and 2, but received 6/10 mg of biperiden on night 3. Sleep recordings started at approximately 11:00 p.m. ('lights out') and ended at 6:30 a.m. The first night was a standard full-montage polysomnographic study that included one EEG lead (C3/A2), one referential electro-oculogram (EOG) to record both horizontal and vertical eye movements, submental electromyogram (EMG), respiratory monitoring (nasal-oral thermistors, abdominal and thoracic strain gauges, and finger oximetry), electrocardiogram, and EMG of the anterior tibialis muscle. For the next two nights, only sleep staging the EKG monitoring was performed (EEG, EOG, EKG, and chin EMG). All polygraph records were scored visually on the basis of 1 min epochs according to Rechtschaffen-Kales criteria (Rechtschaffen et al., 1968) by experienced technicians blind to patient diagnosis and medication status. Sleep variables analyzed included sleep continuity, sleep architecture, and REM sleep indices. REM sleep latency (RL), defined as the time from sleep onset to the first REM period of at least 3 min duration minus intermittent awake minutes, was the principal dependent variable. Change in REM latency following biperiden (difference in REM latency between nights 2 and 3) was compared between the two groups by a Students' t test. Change in REM latency following biperiden was employed as a measure of central cholinergic activity since muscarinic cholinergic mechanisms play a significant role in regulating REM sleep (Sitaram et al., 1979; Berger et al., 1989), and assessing this

measure following a specific M-1 antimuscarinic challenge may be a useful way of teasing out this cholinergic component. Two controls had significantly disrupted sleep following biperiden (with less than 20 min of sleep) and were therefore excluded from the analyses. The final sample for this study thus consisted of 12 schizophrenic patients and ten normal controls.

(2) Effect of biperiden on positive and negative symptoms. For this study, the sample consisted of 30 medication-free schizophrenic inpatients (19 men and 11 women with a mean age = 30 ± 6 years). After having been maintained in a medication-free state for at least 2 weeks, patients received 6 or 10 mg of biperiden on night 1, and 4 mg biperiden p.o. bid for the next 2 days. Two nurse-clinician raters, blind to medication-status and rationale of the study, independently rated the patients on the 18-item Brief Psychiatric Rating Scale (Overall and Gorham, 1962) before starting biperiden on biperiden day 1 (baseline) and after 2 days of treatment with biperiden on day 4 (post-biperiden). Scores on BPRS items assessing motor retardation, blunted affect, and emotional withdrawal (rated 1 for not present to 7 for severe) were summed and used as the BPRS negative symptom cluster. These items collectively constitute the 'ANER' factor (Guy, 1976; Hedlund and Viewig, 1980). The BPRS items assessing conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content were summed as the BPRS positive symptom cluster. These items collectively constitute the 'THOT' factor. The BPRS was employed to rate positive and negative symptomatology because it is a reliable, sensitive, and effective measure of psychopathology and of treatment-related symptom changes (Hedlund and Viewig, 1980).

Biperiden was employed as the antimuscarinic anticholinergic agent because, as a relatively specific M-1 antimuscarinic antagonist (Svyalahti et al., 1987; Eltze and Figala, 1988), it causes significantly fewer peripheral anticholinergic side-effects than other commonly used oral anticholinergic agents and is better tolerated (Avissar and Schreiber, 1989). Furthermore, M-1 receptors are located in the brain areas considered relevant in schizophrenia (Bonner et al., 1987; Watson et al., 1987) and are thus the receptor system most likely to be implicated in schizophrenic symptomatology. Since the usual daily dosage of biperiden in the treatment of parkinsonian symptoms is 4–12 mg/day, we elected to use 8 mg in two divided doses. The 4 day duration of the study was selected because (i) the effect of a single dose on symptomatology may be limited by the inability of the system to respond this quickly to anticholinergic modulation; and (ii) compensatory changes to the initial primary effect of biperiden might occur over a long period, thereby interfering with the evaluation of the primary effect. Paired two-tailed t tests were performed to compare the symptom ratings.

RESULTS

Effect of biperiden on REM latency in schizophrenic patients/normal controls

Biperiden was fairly well tolerated by most schizophrenic patients and normal controls. As stated previously, two normal controls had less than 20 min sleep on the biperiden night, necessitating their omission from the data analysis. Following biperiden, mean REM latency increased from 75 ± 11 min to 134 ± 20 min in normal controls and from 67 ± 16 to 102 ± 19 in schizophrenic patients (Fig. 1). While there was no significant difference in baseline REM latency between the two groups, there was a statistical trend towards difference with regard to change in REM latency following biperiden ($t = 1.6$, df = 10, $P = 0.08$, one-tailed), with schizophrenic patients showing less prolongation of REM latency.

Effect of biperiden on positive/negative symptoms in schizophrenic patients

The effect of 2 days treatment with 8 mg/day of biperiden on positive and negative symptoms was

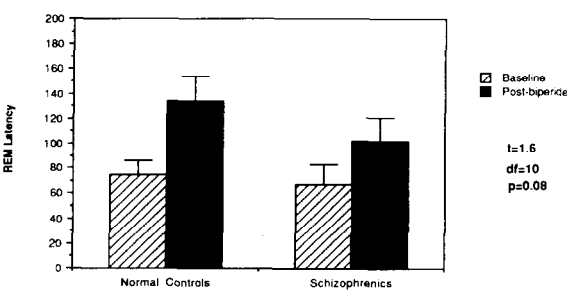

Fig. 1. Change in REM latency following biperiden.

assessed in 30 otherwise drug-free schizophrenic inpatients. Positive and negative symptoms were monitored by the BPRS 'THOT' and 'ANER' factors, respectively. The 18-item BPRS total scores at baseline ranged from 28 to 72 (mean $\pm$ SD = 48.3 $\pm$ 8.5). In this study, inter-rater reliability coefficients (measured by the Pearson product moment correlations) between the two independent raters for the 18 individual BPRS items ranged from 0.65–0.95, with a median of 0.83. The inter-rater reliability coefficients for the positive and negative symptom clusters were 0.90 and 0.85 respectively.

Baseline positive symptom cluster scores ranged from 5 to 20 (mean $\pm$ SD = 11.9 $\pm$ 4.1). There was a significant increase in positive symptom severity following biperiden ($t = 6.5$, df = 29, $P < 0.001$), with post-biperiden positive symptom cluster scores ranging from 6 to 22 (mean $\pm$ SD = 14.4 $\pm$ 4.5) (see Fig. 2).

Baseline negative symptom cluster scores ranged from 3.5 to 17 (mean $\pm$ SD = 8.7 $\pm$ 3.8). There was a significant decrease in negative symptom severity following biperiden ($t = -2.1$, df = 29, $P < 0.05$), with post-biperiden negative symptom cluster scores ranging from 4 to 18 (mean $\pm$ SD = 8.0 $\pm$ 3.6) (see Fig. 2).

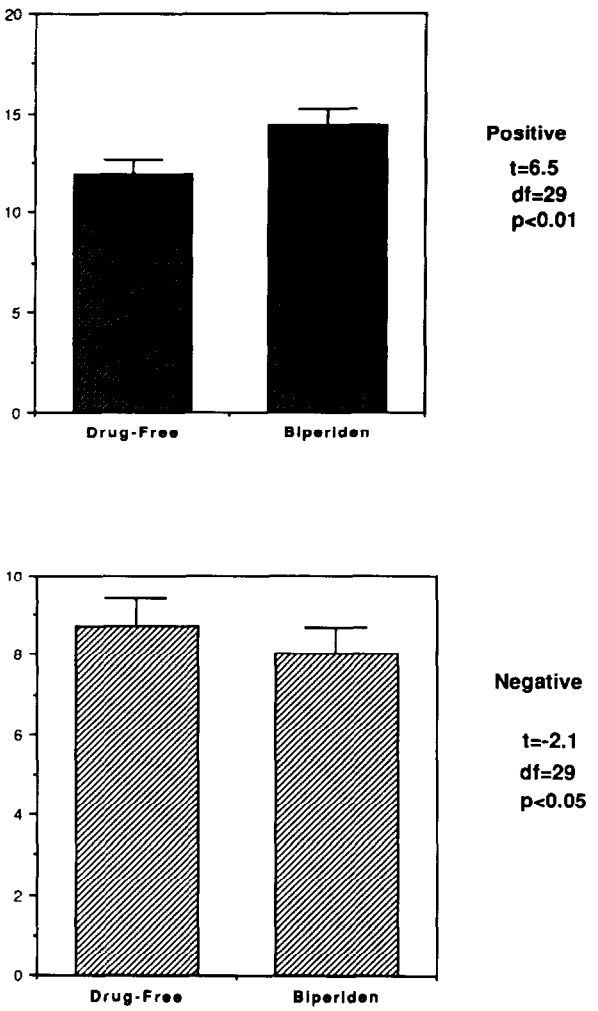

Fig. 2. Change in positive and negative symptoms following biperiden in medication-free schizophrenics.

DISCUSSION

These findings suggest that muscarinic cholinergic activity is increased in schizophrenia, and that this may be relevant to the expression of positive and negative symptoms, as suggested by the increase in positive symptoms and decrease in negative symptoms following biperiden. Our findings are thus consistent with the hypothesized dopaminergic/cholinergic model (Tandon and Greden, 1989) that postulates that:

(a) central muscarinic cholinergic activity is increased in schizophrenia;
(b) this increased cholinergic activity is associated with negative symptoms; and
(c) decreasing cholinergic activity is associated with an increase in positive symptoms.

Evidence for increased cholinergic activity in psychotic phase of schizophrenia

The lesser increase in REM latency following biperiden in schizophrenic patients in comparison to normal controls indicates that central cholinergic activity may be increased in schizophrenia. Additional support for the presence of increased cholinergic activity in schizophrenia is provided by the significantly reduced REM latency in drug-free schizophrenic patients (Zarcone et al., 1987; Tandon et al., 1989a), greater decrease in REM latency following RS-86 (a specific M-1 muscarinic agent) in schizophrenic patients in comparison to normal controls (Berger et al., 1988; Hohagen et al., 1990), and the increased platelet phosphoinositide turnover and diacylglycerol accumulation (both are secondary messengers of the M-1 muscarinic system) (Baraban et al., 1989) in the psychotic phase of the illness. Post-mortem studies of cholinergic

parameters in brains of schizophrenic patients have so far yielded conflicting findings with regard to muscarinic receptor number, choline acetyltransferase (ChAT) activity, and other measures (Domino et al., 1973; McGeer and McGeer, 1977; Watanabe et al., 1983; Toru et al., 1988), with increase/decrease/and no change noted.

Evidence for association between increased muscarinic activity and negative symptoms

The reduction in the severity of negative symptoms following biperiden implicates increased muscarinic activity in the production of negative symptoms. The phenomenological similarity between the 'physostigmine syndrome' and the negative syndrome (Davis et al., 1976; Greden et al., 1987), reduction of negative symptoms in chronic schizophrenic patients following anticholinergics (Fayen et al., 1988; Tandon et al., 1988), anticholinergic 'abuse' by chronic schizophrenic patients with predominantly negative symptoms with energizing and socializing effects (Fisch et al., 1987; Wells et al., 1989), association between decreased REM latency and negative symptom severity (Tandon et al., 1989a), and association between negative symptom severity and post-dexamethasone cortisol levels (Saffer et al., 1985; Faustman et al., 1989; Tandon et al., 1989b) provide strong support for the implication of muscarinic hyperactivity in the production of negative symptoms.

Evidence for association between reducing cholinergic activity and positive symptoms

The significant increase in positive symptoms following biperiden in otherwise medication-free schizophrenic patients indicates an association between decreasing cholinergic activity and increasing positive symptoms in this phase of the illness. This association derives additional support from the finding that anticholinergics antagonize therapeutic effects of neuroleptics only with reference to positive symptoms (Johnstone et al., 1983; Singh et al., 1987; Johnstone et al., 1988) and that the exacerbation of positive symptoms in schizophrenic patients following methylphenidate (a dopamine agonist) is reversed by physostigmine (Janowsky et al., 1973).

These data suggest that muscarinic cholinergic activity may be increased in the psychotic phase of schizophrenia and that this mechanism may be involved in the production of negative schizophrenic symptoms. These data also indicate that positive symptoms intensify when cholinergic activity is decreased in the acute psychotic phase of schizophrenia. On the basis of this evidence, it appears that cholinergic/dopaminergic balance may play an important role in schizophrenic pathophysiology, and that the cholinergic system may exert a damping effect on the emergence of positive symptoms associated with dopaminergic hyperactivity. Failure of the cholinergic system to return to baseline may be an important mechanism in the production of residual negative or 'deficit' symptoms. Fluctuations in cholinergic activity at different stages of schizophrenia may partially explain the longitudinal course and prognosis of schizophrenic illness and may, in part, help to explain the variability and heterogeneity of schizophrenia (Tandon and Greden, 1990).

We emphasize that we are not proposing an exclusive monotransmitter (cholinergic) hypothesis of negative symptoms or schizophrenia. Indeed, dopaminergic mechanisms are obviously important, serotonergic and noradrenergic mechanisms have been linked with negative symptoms, and other neurotransmitters may be involved as well. Exactly how these systems may interact remains unclear. Cholinergic hyperactivity may be involved in the production of negative symptoms in a subgroup of schizophrenic patients; alternatively, cholinergic interactions with other neurotransmitter systems may be important in the pathogenesis of negative schizophrenic symptoms in certain phases of the illness.

The hypothesis suggested is supported indirectly by data from several lines of research, is internally consistent, is congruent with current knowledge about schizophrenia and may explain some apparently discrepant findings. Despite the preliminary nature of current evidence, it probably is reasonable to pursue further the hypothesis that the cholinergic system plays a role in schizophrenic pathophysiology, and that muscarinic hyperactivity may be an important mechanism in the production of negative schizophrenic symptoms.

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