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The Adenosine Antagonist Theophylline Impairs P50 Auditory Sensory Gating in Normal Subjects

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In the P50 suppression paradigm, when two auditory stimuli are presented 500 ms apart, the amplitude of the second response (S2), compared with the first (S1), is markedly attenuated in healthy subjects. This is an index of sensory gating. Most schizophrenic patients fail to inhibit the P50 response to the second stimulus, which is assumed to reflect an inhibitory deficit. Adenosine is a neuromodulator with mostly inhibitory activity which is released by physiological stimuli. Since this inhibitory pattern resembles the phenomenon of sensory gating, the contribution of adenosine to P50 suppression was investigated in normal volunteers after treatment with the adenosine antagonist theophylline or placebo. P50 recordings were conducted in thirteen healthy subjects at baseline and 5, 30, 60, and 90 min after oral administration of theophylline (0.66 mg/kg, maximum dose of 500 mg) or placebo in a cross-over design. Baseline results from 17 drug-treated schizophrenic patients were included for comparison. Compared with placebo, theophylline treatment significantly increased P50 ratio (S2/S1) from 0.28 ± 0.03 to 0.82 ± 0.11 at 30 min and 0.61 ± 0.07 at 60 min (mean ± SEM), which were not significantly different from the schizophrenia group (0.74 ± 0.05). The increased P50 ratio by theophylline was due to a combined decrease in S1 and increase in S2 amplitude. The impairment of P50 suppression by theophylline in normal subjects suggests a modulatory role of adenosine in sensory gating, which may be related to P50 suppression deficit in schizophrenia and is in agreement with a hypoadenosinergic model of schizophrenia.
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KEY WORDS: *Schizophrenia; Sensory gating; Event related potentials; P50; Theophylline; Adenosine; Purinergic system*

The suppression of the P50 component of the auditory event-related potential has been used as an index of sensory gating in neuropsychiatric research (Freedman et al. 1983; Adler et al. 1998 for review). The P50 wave is

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a small amplitude positive wave occurring about 50 ms after an auditory stimulus. In the P50 suppression paradigm, when two stimuli are presented 500 ms apart, the amplitude of the second peak (S2), compared with the first (S1), is usually attenuated in healthy subjects, whereas in patients with schizophrenia or acute mania this suppression is impaired (Adler et al. 1998). The hippocampus has been suggested to mediate P50 suppression and it is generally assumed that impaired suppression in schizophrenia is due to an inhibitory deficit, which leads to an overflow of information and diminished capacity to filter out irrelevant stimuli (Adler et al. 1998). The neurochemical basis of the P50 suppression is not yet completely understood, but cholinergic, GABAergic and monoaminergic systems have been proposed to modulate this phenomenon (Adler et al. 1998; Hershman et al. 1995; Light et al. 1999).

The neuromodulator adenosine exerts potent inhibitory influence on synaptic activity in the CNS (Brundege and Dunwiddie 1997). Four distinct subtypes of adenosine receptors (A1, A2A, A2B and A3) have been cloned and characterized (for review, see Ralevic and Burnstock 1997). A1 receptors are widespread, with high levels in the hippocampus, cerebral cortex, thalamus and cerebellum. By acting on presynaptic A1 receptors, adenosine inhibits the release of several neurotransmitters (including glutamate) and activation of postsynaptic A1 receptors produces neuronal hyperpolarization (Brundege and Dunwiddie 1997). Extracellular adenosine levels markedly increase under excitotoxic conditions and its inhibitory actions provide an important endogenous mechanism of neuroprotection (Brundege and Dunwiddie 1997; Ralevic and Burnstock 1998). Unlike the widespread distribution of A1 receptors, A2A receptors are mostly expressed in dopamine-rich regions, co-localized with D2 receptors (Svenningsson et al. 1999). Activation of A2A receptors reduces the affinity of D2 receptors for agonists, including endogenous dopamine (Ferre et al. 1991; Ferre 1997). Adenosine provides an inhibitory tone in several brain regions, including the hippocampus, and the stimulating effects of the non-selective adenosine A1/A2A antagonists caffeine and theophylline are attributed to the antagonism of this inhibitory tone (Fredholm et al. 1999).

We have recently proposed that a deficit of adenosinergic activity could contribute to the pathophysiology of schizophrenia (Lara and Souza 2000). The interactions of adenosine with the dopaminergic and glutamatergic systems (mainly through A2A and A1 receptors, respectively) would account for the putative alterations of these neurotransmitter systems in schizophrenia and can be supported by the ability of adenosine agonists to reverse the behavioral effects of amphetamine (Ferre 1997; Rimondini et al. 1998) and NMDA antagonists (Browne and Welch 1982; Kafka and Corbett 1996; Popoli et al. 1999; Sills et al. 1999). A deficient neuroprotective role of adenosine in schizophrenia would also render the brain more susceptible to insults and could contribute to the clinical and cerebral deterioration observed in these patients (Mathalon et al. 2001). Evidence of altered adenosinergic activity in schizophrenia includes the upregulation of striatal A2A receptors (Kurumaji and Toru 1998), which could be compensatory to low adenosinergic activity (Lara and Souza 2000) and the clinical improvement of schizophrenic patients with add-on dipyridamole, an inhibitor of adenosine uptake (Akhondzadeh et al. 2000), probably through a non-dopaminergic mechanism (Brunstein et al. 2001). Moreover, clozapine may increase adenosinergic acitivity (Pinna et al. 1999; Lara et al. 2001a), high doses of caffeine exacerbated psychotic symptoms in schizophrenic patients (Lucas et al. 1990) and the A2A receptor is a candidate for a schizophrenia susceptibility gene on 22q12-13 (Deckert et al. 1997).

Of particular interest regarding the P50 suppression paradigm is the work by Mitchell et al. (1993), who showed that when two independent excitatory pathways to CA1 pyramidal neurons are used to evoke field excitatory post-synaptic potential (EPSP), prior activation of one pathway at a physiological level inhibits the EPSP in the other pathway when evoked immediately after. This activity-dependent inhibition lasted ~750 ms, peaking at 250 ms, which is a quite similar time-course compared with the P50 suppression paradigm regarding the interstimuli (S1-S2) intervals (Adler et al. 1998). Importantly, this inhibition was mediated by adenosine, since it was blocked by theophylline and the A1 antagonist CPT, and potentiated by drugs that increase adenosine extracellular availability by inhibiting adenosine uptake and degradation (Mitchell et al. 1993).

Given that P50 suppression consists of an activity-dependent inhibition, which resembles the inhibitory role of adenosine in the CNS, the contribution of adenosine to sensory gating was evaluated in healthy subjects submitted to the P50 suppression paradigm before and after oral administration of the adenosine antagonist theophylline or placebo. A group of medicated schizophrenic patients was also included for comparison and for validation of our neurophysiological technique.

MATERIAL AND METHODS

Subjects

This study was approved by the Ethical Committee on Human Experimentation of the Hospital de Clínicas de Porto Alegre (HCPA), carried out in accordance with the Declaration of Helsinki and all the participants signed an informed consent form after complete explanation about the potential risks involved in this protocol as well as the purpose of this study in lay terms.

Seventeen healthy volunteers were recruited for this

study among university students and employees. They were submitted to a semi-structured interview by medical doctors with psychiatric training. Exclusion criteria were DSM-IV in axis I diagnosis (evaluated with MINI), clinical illness and any current use of medicines or drugs of abuse, except for oral contraceptives. All volunteers included in the analysis were non-smokers at the time of the study. Subjects with familiar history of schizophrenia or other psychotic disorders in first or second degree were also excluded, as well as those having a familiar history of any axis I mental disorder in first degree. Seventeen DSM-IV schizophrenic outpatients (nine smokers), previously diagnosed and treated in the hospital outpatient unit were also included for comparison. They were clinically stable for at least six months and were not in use of new generation antipsychotic medications, which can improve P50 suppression (Nagamoto et al. 1996; Light et al. 2000).

Pharmacological Challenge

Since the present study intended to evidence the effect of adenosine receptor antagonism on sensory gating, we chose a relatively high but within the therapeutic dose of theophylline as used for acute asthma treatment (6.66 mg/kg up to a maximum dose of 500 mg). This dosage is assumed to produce considerable antagonism of both A1 and A2A receptors in the CNS, without a significant inhibition of phosphodiesterase activity (Fredholm et al. 1999). Also, volunteers were instructed to abstain from xanthine-containing drinks (coffee, teas, and colas) for at least one week before the first recording, totaling two weeks of wash-out period. Because nicotine can transiently improve P50 suppression in schizophrenic patients (Adler et al. 1998), all patients abstained from nicotine for a minimum of 2 h. Schizophrenic patients also abstained from xanthines for at least 4 h.

The seventeen healthy volunteers were subjected to P50 event-related potential recordings at baseline and four times after oral treatment. Four subjects were excluded from the analysis due to unstable baseline P50 ratio over time (two subjects) or due to overlapping P30 wave (two subjects). Therefore, analysis included 13 healthy non-smoking volunteers (M/F= 8/5, mean age = 27 ± 4 years). Moreover, baseline P50 ratios of 17 drug-treated schizophrenic patients (M/F = 16/1, mean age = 36 ± 9 years, chlorpromazine equivalents = 468 ± 274 mg, smoking/non-smoking = 9/8) were included for methodology validation and for comparison. Healthy subjects were submitted to two electrophysiologic recording sessions. Under single blinding conditions, they were randomly assigned to theophylline syrup (100 mg per 15 ml, mean dose = 446 ± 64 mg) mixed with artificial fruit juice or placebo (artificial fruit juice of similar taste, volume and color) in the first session, and one week later, at approximately the same time of the day, to the complementary treatment. P50 evoked potentials were recorded 25 min before and 5, 30, 60 and 90 min after treatment administration. These time points were chosen based on pharmacokinetics of theophylline, which reaches maximum serum concentration around 30–40 min after oral administration and has a mean half-life of 9 h in healthy volunteers (Trepanier et al. 1998).

Electrophysiologic Recordings

The method for electrophysiologic recordings was based on previously described protocols, with slight modifications (Nagamoto et al. 1996). In brief, subjects were recorded seated, relaxed, and awake with eyes open and fixed on a distant target to decrease drowsiness during the recording. Electroencephalographic activity was recorded from a disk electrode affixed to the vertex (Cz) and referenced to both mastoids. An electroencephalogram (EEG) was made using the 4-channel system Nihon-Kohden MEM-4104K for recording of evoked responses integrated with auditory stimulator. The mean signal was registered in two channels, one for each side of the cranium, and amplified 20,000 times with a bandpass filter between 10 Hz and 10 kHz. EEG was collected during 1 s for each paired stimulus presented. Trials were rejected if they contained artifacts as indicated by an EEG tension of ± 50 μV within the second which includes both P50 waves, starting 0.1 s before the first stimulus. The rejection rate was typically less than 20% and the recording session lasted 5 to 7 min. Auditory stimuli were presented in a conditioning-testing paradigm with an interpair interval of 500 ms and interstimuli interval of 10 s. A 0.04 ms square wave pulse was amplified in the auditory frequencies (20–12,000 Hz) and delivered through earphones that produce a 2.5 ms sound with an intensity of 60 dB sound pressure level above the auditory acuity threshold, which was measured 15 min before the recordings. Thirty non-rejected waves were added together to give a grand average signal, which was used for analysis. The most positive peak between 40 and 90 ms after the conditioning stimulus (S1) was selected as the P50 final latency and the wave amplitude was measured relative to the previous negativity, determining the initial latency and the first P50 wave. The test wave (S2) was determined using the corresponding peak between 500 ± 10 ms away from S1 latency and its amplitude also measured relative to the previous negative peak. Test/conditioning (S2/S1) ratios were calculated by dividing the test P50 amplitude (S2) by the conditioning P50 amplitude (S1). The data were collected by an unblind researcher (E.S.G.) and analyzed by two independent trained raters blinded to treatment and diagnosis (J.B. and A.S.P.). After comparison, the values generated by one of the raters was used and when respective measurements differed more than 5 ms in latency (8% of the waves), they performed a new collaborative rating.

Statistical Analysis

Comparisons of P50 parameters (P50 ratios, S1 and S2 amplitudes and latencies) were performed between the recordings from placebo and theophylline treatments as well as between recordings before and after each treatment in healthy subjects. The P50 ratios by gender were also compared at baseline and after theophylline treatment. The results of healthy subjects were also compared with both baseline recordings of schizophrenic patients and baseline recordings of the non-smokers subgroup of schizophrenia patients. In addition, schizophrenic patients were compared regarding their smoking status.

Comparison parameters were considered apart as dependent variables and the characteristic of the group (theophylline or placebo) as the independent variable. The Wilcoxon test was used for asymmetric paired data from healthy volunteers. Comparisons between schizophrenic patients and healthy subjects were analyzed using a Kruskal-Wallis distribution-free analysis of variance, followed by Mann-Whitney U test if indicated. Statistical significance was considered at $p < .05$ level. All analyses were implemented with the software SPSS 8.0 for Windows.

RESULTS

In agreement with several previous reports, healthy subjects presented a strong suppression of the P50 response to the second click at baseline (S2/S1 = 0.28 ± 0.03 – mean ± S.E.M for all results), with all but one volunteer presenting more than 50% suppression, whereas 15 of the 17 schizophrenic patients showed less than 40% suppression (S2/S1 = 0.74 ± 0.05) (Figure 1; Figure 3 for scattergram). Schizophrenic patients, as a group or as subgroups regarding smoking status, showed statistically significant impaired suppression when compared with baseline measurements of healthy controls ($p < .001$). Also comparing only non-smoking males, healthy controls (n = 8) showed better suppression than schizophrenic patients (n = 8) ($p = .002$).

There was no statistically significant difference between males (S2/S1 = 0.25 ± 0.04) and females (S2/S1 = 0.32 ± 0.08) in the baseline recordings of healthy subjects and between smokers (S2/S1 = 0.76 ± 0.08) and non-smokers (S2/S1 = 0.72 ± 0.08) in the schizophrenic patients group.

Compared with placebo, theophylline significantly increased P50 ratio at 30 min (S2/S1 = 0.82 ± 0.11) and 60 min (S2/S1 = 0.61 ± 0.07) post-treatment, which was not significantly different from the schizophrenia group as a whole and the subgroup of non-smoking schizophrenic patients (Figure 1). Compared with pretreatment, theophylline significantly increased P50 ratio in all post treatment times. There was a small but statistically significant placebo effect over time compared with the pretreatment recording at all time points, except for 60 min. Representative tracings of a normal subject 30 min after placebo or theophylline as well as a schizophrenic patient are shown in Figure 2. S1 latencies were not statistically different among groups at any time (Table 1).

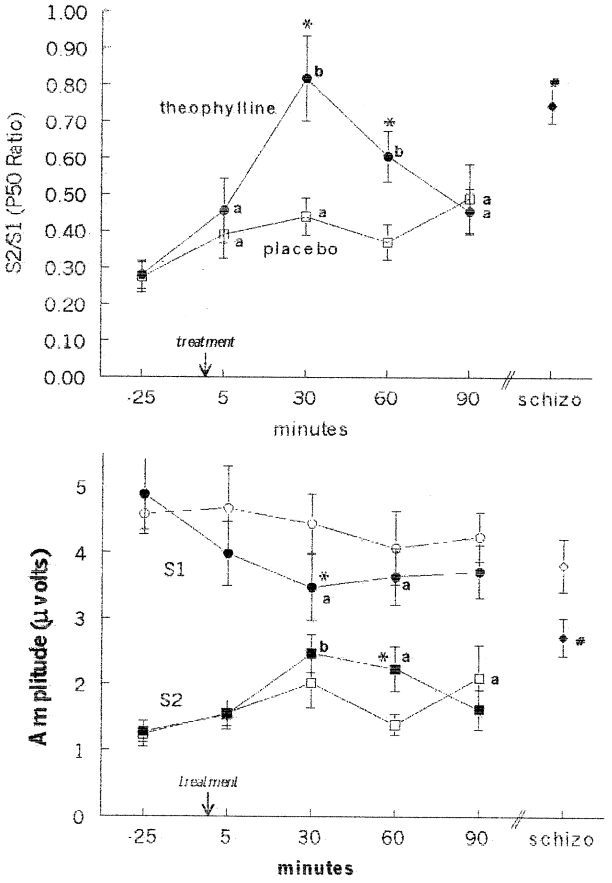

Figure 1. P50 measures of healthy subjects treated with placebo or theophylline and baseline P50 measures of schizophrenic patients. Upper panel: P50 ratios (S2/S1); lower panel: conditioning (S1) and test (S2) amplitudes. Healthy subjects received theophylline (●) or placebo (□) 25 min after a baseline recording. Data from schizophrenic patients (◆) are also shown for comparison. Data are mean ± SEM. ★ = $p < .05$ for comparisons within the same time point and a = $p < .05$ and b = $p < .01$ compared with pretreatment values (Wilcoxon test). # = $p < .05$ denotes differences from all points, except for 30 and 60 min of theophylline group (upper panel) and for 30 and 60 min from theophylline group and for 90 min from placebo group for S2 waves (lower panel) (Mann-Whitney U test).

The effect of theophylline treatment on P50 ratio was similar at all post-treatment times regarding gender subgroups, except at 5 min, when females showed a trend ($p = .06$) for higher P50 ratios (poorer suppression) than males (Table 2).

The effect of theophylline was due to a decrease in S1 amplitude combined with an increase in S2 amplitude, which peaked at 30 min (Figure 1; Figure 3 for scatter-

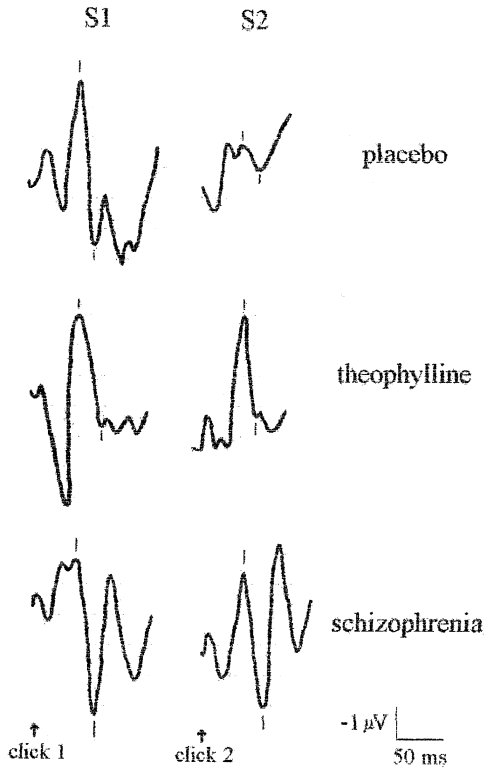

Figure 2. Auditory event-evoked responses to paired stimuli in a healthy subject 30 min after placebo or theophylline treatment as well as in a schizophrenic patient at baseline. The arrow indicates the click stimulus and the tracings illustrate P50 waves.

gram). Compared with controls at baseline, schizophrenic patients showed a non-significantly lower S1 amplitude and a significantly higher S2 amplitude, which was quite similar to the profile induced by theophylline in healthy subjects at 30 min. In order to allow for more detailed assessment of data, in Figure 3 we show scattergrams of S2/S1 ratio (top panel), S1 wave (middle panel) and S2 wave (bottom panel) of each normal subject and schizophrenic patient. Since the peak effect of theophylline varied between 30 and 60 min in control subjects and both time points were significantly different from placebo and comparable to schizophrenia (Figure 1), average values of these two time points are presented (designated "mean 30-60′") in all scattergrams. As can be seen, the effect of theophylline on P50 ratio, S1, and S2 responses occurs in the majority of subjects, resembling the group profile of schizophrenic patients.

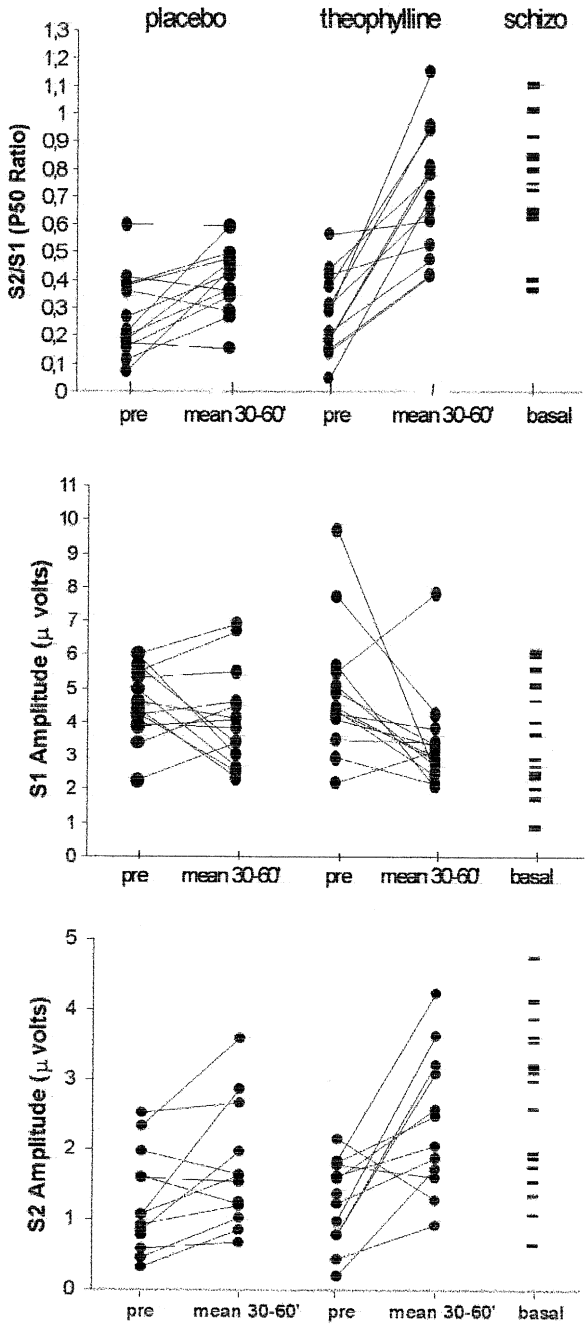

Figure 3. Scattergram of the P50 test/conditioning ratios (S2/S1) (upper panel), S1 (middle panel) and S2 (lower panel) amplitudes in healthy subjects (●) before and after placebo or theophylline treatment, and baseline P50 ratio of schizophrenic patients (−). Pre = pretreatment or baseline measures; mean 30-60′ = mean of P50 ratios at 30 min and 60 min time points for each volunteer; basal = baseline measure from schizophrenic patients.

DISCUSSION

In this study, theophylline increased P50 ratio in healthy subjects from a normal suppression level to a level that could not be distinguished from the P50 suppression deficit of schizophrenic patients. This effect was obtained both by decreasing S1 amplitude and by increasing S2 amplitude. The deficit in P50 suppression (increased S2 amplitude) has been extensively reported in schizophrenia and is not altered by typical antipsy-

Table 1. P50 Latency during Treatments.

	Baseline	5 min	30 min	60 min	90 min
Theophylline	54.5 ± 5.5	55.5 ± 3.4	55.4 ± 3.4	53.3 ± 4.3	54.3 ± 3.0
Placebo	54.5 ± 3.0	55.0 ± 4.5	55.7 ± 4.2	55.7 ± 3.8	55.3 ± 2.9

Values are in ms, mean ± S.D.

chotics (Adler et al. 1998; Light et al. 2000). However, in unmedicated schizophrenic patients reduced S1 amplitude has also been reported (Freedman et al. 1983; Patterson et al. 2000). This may indicate that theophylline-induced alterations in the P50 paradigm more closely resemble the findings in unmedicated schizophrenic patients, but as such subgroup of patients was not included in our study, this hypothesis should be taken cautiously. Nevertheless, our study replicates the well-documented lack of P50 suppression in medicated schizophrenic patients (Figure 1), with fairly normal amplitude of the S1 wave compared with controls, although a relatively small S1 amplitude was observed in some of our patients (see Figure 3, middle panel). Limitations to this study include lack of theophylline blood levels control and toxicology screenings for both volunteers and patients, as well as differences between volunteers and patients, such as age, gender distribution, smoking status and use of antipsychotics, which limit their comparison.

The magnitude of the impairment produced by theophylline on P50 ratio at 30 and 60 min is in the same order of magnitude of the P50 suppression deficit found in schizophrenia. Interestingly, although not systematically evaluated, six subjects after theophylline treatment spontaneously reported to be disturbed by or became aware of stimuli which were previously considered irrelevant, such as the air conditioning noise, a phenomenon related to reduced sensory gating (Adler et al. 1998).

Sensory gating differences by gender have been discussed in previous works. Using the P50 paradigm, Hetrick et al. (1996) found a trend for diminished suppression in women ($p < .08$), whereas other studies found no difference (Rasco et al. 2000). In pre-pulse inhibition (PPI), another paradigm to access sensory gating, women showed less inhibition than men (Swerdlow et al. 1993). The present experiment was not specifically designed to compare gender differences, but there was a trend ($p = .06$) for poorer suppression at 5 min after theophylline treatment in women even in this small sample. The hypothesis that gender affects the P50 response to theophylline treatment should be further investigated.

Since theophylline is a non-selective A1 and A2A receptor blocker, it is unclear which one, or if both receptors have to be blocked in order to produce inhibition of sensory gating. A2A receptors are mostly found in dopaminergic regions, where they closely interact with D2 receptors, decreasing their affinity for dopamine (Ferre et al. 1991; Ferre 1997). If adenosinergic deficit is present in schizophrenia, this mechanism could account for increased basal occupancy of D2 receptors by dopamine recently reported in schizophrenia (Abi-Dargham et al. 2000), but dopaminergic involvement is unlikely to account for the P50 suppression deficits in schizophrenic patients (Adler et al. 1998; Freedman et al. 2000). Moreover, amphetamine, which robustly enhances dopaminergic activity, increased P50 ratio (S2/S1) in humans from 0.24 to 0.48 (Light et al. 1999), which is apparently less pronounced than the alteration induced by theophylline. We therefore hypothesize that blockade of A1 receptors is more likely to account for the diminished P50 suppression induced by theophylline, since: (1) A1 receptors are abundant in the hippocampus, a region probably implicated in P50 suppression and sensory gating (Adler et al. 1998); (2) when activated by adenosine, presynaptic A1 receptors inhibit glutamate release, an event previously suggested to be crucial in the sensory gating mechanism (Adler et al. 1998); (3) in vitro, a selective A1 antagonist mimicked the effect of theophylline in a paired pulse paradigm (Mitchell et al. 1993) and blocked the heterosynaptic inhibition evoked by NMDA administration and tetanic stimulation (Manzoni et al. 1994); and (4) adenosine A1 receptors also potentiated the effect of the dopamine agonist apomorphine in the reduction of prepulse inhibition, another index of sensory gating (Koch and Hauber 1998).

Freedman and colleagues have shown that the P50 suppression deficit in schizophrenic patients are tran-

Table 2. P50 Ratios before and after Theophylline Treatment by Gender.

	Baseline	5 min	30 min	60 min	90 min
Males	0.25 ± 0.04	0.30 ± 0.05	0.75 ± 0.13	0.60 ± 0.07	0.50 ± 0.07
Females	0.32 ± 0.08	0.71 ± 0.18	0.94 ± 0.23	0.62 ± 0.15	0.38 ± 0.12

Values are in percentage, mean ± SEM.

siently normalized immediately after a short period of non-REM sleep (10 min) but not after longer periods (with REM sleep), which can be explained by a resensitization of nicotinic receptors (Adler et al. 1998; Freedman et al. 2000). These data may also be related to the sleep modulating role of adenosine, which reaches higher levels in the initiation of sleep, gradually decreasing to very low levels during REM sleep (Strecker et al. 2000). Indeed, the effect of xanthines (caffeine and theophylline) in delaying sleep onset (Landolt et al. 1995) is due to the antagonism of adenosinergic inhibitory activity via A1 receptors in forebrain and mesopontine cholinergic neurons (Strecker et al. 2000). Interestingly, the sleep pattern of schizophrenic subjects, particularly slow-wave sleep deficit at 1-2 Hz (Keshavan et al. 1998), is similar to the pattern induced by caffeine in healthy volunteers (Landlolt et al. 1995), and refractory schizophrenic patients clearly improved sleep after treatment with allopurinol, an inhibitor of purine degradation devoid of sedative effects in non-schizophrenic patients (Lara et al. 2001b).

Cholinergic modulation of the P50 response has been demonstrated with the impairment of sensory gating produced by the α7-nicotinic receptor antagonist α-bungarotoxin (Luntz-Leybman et al. 1992) and the linkage between the chromosomal locus of the α7-nicotinic acetylcholine receptor gene and schizophrenia (Freedman et al. 1997; Leonard et al. 1998; Riley et al. 2000), although lack of this association has also been reported (Neves-Pereira et al. 1998; Curtis et al. 1999). Moreover, nicotine administration has also been shown to transiently correct the P50 suppression deficit in schizophrenia (Adler et al. 1998), probably by enhancing excitatory transmission at α7-nicotinic receptors in interneurons (Alkondon et al. 1998), which would then be inhibitory by releasing GABA (or adenosine). It is possible that altered sensory gating in schizophrenic patients is not only related to dysfunctional nicotinic input to interneurons, but may also be at the level of its inhibitory mediator, which is not necessarily GABA. Although a GABA-B antagonist moderately increased S2/S1 ratio from 0.25 to 0.55 in the animal model of the evoked potential paradigm (Hershman et al. 1995), it is noteworthy that activation of α7-nicotinic receptors from human brain interneurons failed to trigger GABAergic postsynaptic currents (Alkondon et al. 2000). Moreover, GABA-A and GABA-B agonists have not been shown to be clinically effective or to improve P50 suppression in schizophrenia despite being available and largely used as psychotropic agents for decades. In contrast, the adenosine reuptake inhibitor dipyridamole, which prolonged activity-dependent inhibition in a paired-pulse paradigm in hippocampal slices (Mitchell et al. 1993), was recently reported as a beneficial adjunctive treatment for schizophrenia (Akhondzadeh et al. 2000), probably through a non-dopaminergic mechanism, since patients were already at haloperidol 20 mg a day (Brunstein et al. 2001). Of note, chronic caffeine intake doubles the consumption of nicotine and facilitates the acquisition of self-administration behavior in rats (Shoaib et al. 1999), resembling the excessive smoking behavior of schizophrenic patients and supporting the notion of adenosine receptor blockade as a model of schizophrenia. Finally, adenosine A1 receptor blockade by caffeine in rats increases extracellular acetylcholine levels in the hippocampus over fourfold (Carter et al. 1995), which could stimulate low affinity nicotinic receptors such as the α7. This finding suggests that P50 suppression might be disrupted despite increased cholinergic activity, assuming that caffeine also affects P50 ratio as theophylline, which is likely, since their pharmacological profiles are quite similar and theophylline is an active metabolite of caffeine (Fredholm et al. 1999)

In summary, the P50 suppression deficit induced by theophylline in healthy subjects suggest the involvement of the inhibitory neuromodulator adenosine in sensory gating, which is in line with a hypoadenosinergic model of schizophrenia (Lara and Souza 2000). Moreover, adenosine may be the inhibitory mediator of interneurons activated by α7 nicotinic receptors. Finally, intake of xanthines (caffeine and theophylline) prior to the recording session should be considered as a potential bias in the P50 suppression paradigm.

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