The Relationship between Nicotine and Neurophysiology in Schizophrenia

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Introduction

Abnormalities of the nicotinic cholinergic system in the brain have been noted in a number of clinical disorders. The higher than average rate of smoking in clinical populations has been theorized as being related to abnormalities in this system. In schizophrenia, the rate of smoking surpasses that of other clinical populations (approximately 80-90% compared to 45-70%). The high rate of smoking, evidence of genetic linkage of schizophrenia to specific nicotinic receptors, and evidence for positive neuropsychological effects of nicotine, all suggest that nicotinic cholinergic mechanisms may play a pathophysiological role in schizophrenia. To assess whether nicotine could normalize early neurophysiological processing in schizophrenia, we studied a measure that has repeatedly been shown to be impaired in this population. The mismatch negativity (MMN) paradigm is an electrophysiological index that has gained interest in recent years as an endophenotype of schizophrenia. MMN measures "preattentive" physiological processes and is elicited by an infrequent change in a repetitive sound. The utility of MMN to assess change in response to pharmacological challenge has been identified by other researchers. However, MMN deficits do not appear to improve with the use of either conventional or atypical medications. Improvements associated with nicotine would suggest a novel change in physiological processing that is unique to nicotinic agonists. To assess the effects of nicotine challenge on MMN amplitude and latency, controls and individuals diagnosed with schizophrenia were administered nicotine gum versus placebo gum during two visits. Subjects underwent a baseline recording on each of the two visits and an additional recording following administration of either nicotine or placebo. Participants were played a series of tones (standard ISI between tones was 500 ms, deviant ISI of 250 ms occurred on average every 20th interval). The average amplitude of MMN waveform elicited by the deviant interval was significantly larger following nicotine administration compared to placebo condition in both the controls and the schizophrenia patients ($p \leq .02$). In addition, a significantly greater improvement was noted in the schizophrenia group compared to the controls ($p \leq .05$). Finally, symptom checklists suggest that nicotine may alter certain mood states. These results are consistent with the idea that pharmacological agents targeting nicotinic receptors may provide unique physiological benefits that are not addressed by current medications.

Method

Participants

Subjects consisted of 20 normal controls (13 males, 7 females; age range 23-58 years) and 12 subjects (8 males, 4 females; age range = 20-50 years) who met DSM-IV criteria for schizophrenia via a structured interview.

Procedure

- To assess the effects of nicotine on MMN amplitude and latency, controls and SZ patients were administered nicotine gum versus placebo gum during two visits.
- The visit consisted of a diagnostic interview, inventories assessing mood state and psychiatric symptoms, a medical history, and a brief physical exam including cardiac, pulmonary, and neurological systems.
- Carbon monoxide levels were assessed in smoking subjects prior to administration of nicotine to ensure abstinence

Electrophysiological Recordings

- Electrodes were attached to the following 10-20 scalp locations: Fz, Cz, Pz, LM, RM
- Brain activity evoked by auditory stimuli was referenced to an electrode attached to the nose, bandpass filtered from .05 to 30 Hz, and digitally sampled at 1000 Hz. A ground electrode was attached to the forehead.
- Eye movements were monitored with electrodes attached above and directly lateral to the left eye.
- Insert-earphones were used to binaurally present pure tones (1000 Hz, 50 msec in duration) to the subjects.
- Brain evoked responses were collected in a "passive" condition. Participants were administered a total of 2800 tones (per condition) while watching a silent, close-captioned movie. The standard interval between tones was 500 msec, and a deviant interval of 250 ms occurred on average every 16th interval.

Results

- Standard evoked responses were subtracted from deviant evoked response and the largest negativity between 140 and 210 msec post-stimulus was measured
- Controls and patients with schizophrenia exhibited significantly larger amplitudes following nicotine administration compared to placebo

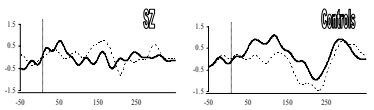

Figure 1: Solid lines represent grand average waveforms in response to placebo. Dotted lines represent grand average waveforms in response to nicotine. Schizophrenia patients are on the left and controls on the right.

Controls

- The change in amplitude accompanying nicotine administration was significantly larger compared to the placebo condition

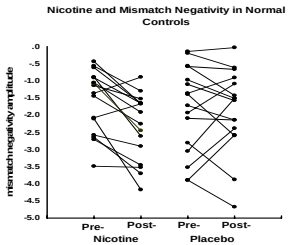

Figure 2. The circles represent changes in individual amplitudes in the nicotine and placebo conditions. The change in amplitude following nicotine administration was significantly larger than the change following placebo.
Nicotine: **0.78 μV ± 0.69** versus placebo: **0.03 μV ± 0.86; t = 2.67, p = 0.01**

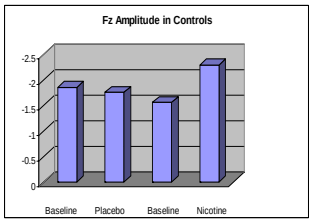

Figure 3. The larger the negative value for the amplitude, the larger the response to the deviant interval duration. The difference in amplitude was not significantly different between baseline and placebo conditions. The difference between the baseline and nicotine conditions were significantly different ($p \leq .01$).

Schizophrenia Group

- Subjects consisted of 12 subjects (8 males, 4 females; age range = 20-50 years) The change in amplitude accompanying nicotine administration was significantly larger compared to the placebo condition ($p \leq .001$)

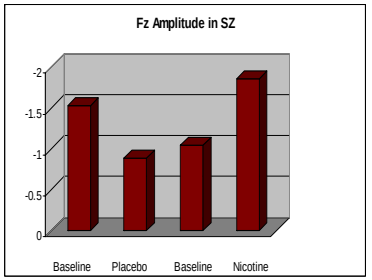

Figure 4: The larger the negative value for the amplitude, the larger the response to the deviant interval duration. The difference in amplitude was not significantly different between baseline and placebo conditions. The difference between the baseline and nicotine conditions were significantly different.
Nicotine: **0.81 μV ± 0.64** versus placebo: **-.64 μV ± 1.13; t = 3.90, p ≤ 0.001**

Nicotine Changes > Placebo Changes in Schizophrenia

- Fz & Cz Amplitude (greater amplitude)
- Fz & Cz Latency (quicker response)

Smokers & Nonsmokers

- Subjects consisted of 10 nonsmoking controls, 10 smoking controls, 9 smoking SZ patients, 3 nonsmoking SZ patients

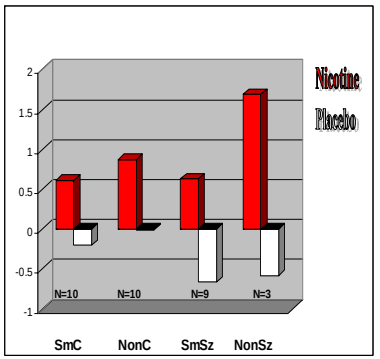

Figure 5: Positive numbers represent greater ***change*** in amplitude with each condition. Negative numbers represent change suggesting a decrease in amplitude.
SmC= Smoking Controls; NonC = Nonsmoking controls; SmSz= Smoking SZ, NonSz=Nonsmoking SZ

Summary of Findings

- Unlike traditional and atypical neuroleptics, nicotinic agonists appear to improve MMN amplitude and latency
- Improvements were noted in both the control group and the patients with schizophrenia. The change in amplitude associated with nicotine was greater in the patients than the controls.
- Preliminary results suggest that schizophrenia patients, both smoking and non-smoking may exhibit the greatest improvement in amplitude and latency following nicotine administration.
- Assessment of symptom changes accompanying nicotine administration suggests a reduction in feelings of being "on edge", excited, and feeling active with nicotine
- While preliminary data suggests positive physiological changes, more information is needed regarding:
  - Long term effects
  - Whether changes lead to improvement in outcome?
  - What is happening in the brain as a result of nicotine administration?

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Acknowledgments

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