The Relationship between Nicotine and Neurophysiology in Schizophrenia

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Abnormalities of the nicotinic cholinergic system in the brain have been noted 20-50 years ago. The change in amplitude accompanying nicotine administration was significantly larger compared to the placebo 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 evidences 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 “perceptual” 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 nicotine agonists. To assess the effects of nicotine challenge on MMN amplitude and latency, controls and individual 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 placed a series of tones (standard ISI between tones was 500 ms, deviant ISI of 250 ms occurred on average every 25th interval). The average amplitude of MMNs 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<.05). In addition, a significantly greater improvement was noted in the schizophrenia group compared to the controls (p<.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.

Results

• Standard evoked responses were subtracted from deviant evoked responses to obtain 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.

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<.001).

Smokers & Nonsmokers
• Subjects consisted of 10 nonsmoking controls, 10 smoking controls, 9 smoking SZ patients, 3 nonsmoking SZ patients

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

Figure 2: The circle represents changes in individual amplitudes in the nicotine and placebo conditions. The change in amplitude following nicotine administration was significantly larger compared to the placebo condition.