114. ONDANSETRON IMPROVES P50 AUDITORY SENSORY GATING IN MEDICATED SCHIZOPHRENIC PATIENTS

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P50 auditory sensory gating is impaired in schizophrenic patients. A schizophrenic patient does not show a decrease in the amplitude of the P50 waveform of the auditory evoked potential to the second of two closely paired click stimuli. In contrast, a normal control has a greatly decreased amplitude of the P50 waveform to the second stimulus. Expressed as a percentage (amplitude to the 2nd stimulus/amplitude to the first stimulus × 100), the P50 ratio is significantly higher in schizophrenic patients. This genetic deficit in inhibitory neuronal processing is mediated by the alpha-7 nicotinic receptor, which is rapidly desensitizing to nicotine. Nicotine briefly ameliorates this deficit in schizophrenic patients, but the effect is usually lost after one hour. Clozapine treatment, but not conventional antipsychotic medication, improves P50 auditory gating. We hypothesized that blockade of the S5T3 receptor by clozapine may result in release of acetylcholine which then acts directly at the alpha-7 nicotinic receptor to enhance gating.

To test this hypothesis, we gave 16 mg of oral ondansetron, a selective 5HT3 receptor antagonist, to 7 stable medicated schizophrenic patients in a double-blind placebo design. On two different days, the same subject had baseline auditory evoked responses recorded followed by either oral ondansetron or placebo. ERPs were recorded hourly for the next three hours. Ondansetron, but not placebo, resulted in a significant decrease in P50 ratio in these patients (Repeated measures ANOVA: F = 21.44, d.f. = 1, 12, p = 0.001) that lasted significantly longer than nicotine treatment. These results support a possible role of 5HT3 antagonism in enhancing P50 gating by atypical antipsychotics.

115. CONFIRMATION OF DIFFERING DISTRIBUTION OF P50 RATIOS IN SCHIZOPHRENIC PATIENTS VS CONTROLS

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P50 auditory sensory gating is impaired in schizophrenic patients. A schizophrenic patient does not show a decrease in the amplitude of the P50 waveform of the auditory evoked potential to the second of two closely paired click stimuli. In contrast, a normal control has a greatly decreased amplitude of the P50 waveform to the second stimulus. Expressed as a percentage (amplitude to the 2nd stimulus/amplitude to the first stimulus × 100), the P50 ratio is significantly higher in schizophrenic patients. We studied the distribution of the P50 ratios of 89 schizophrenic patients versus 163 normal controls with no history of psychosis in themselves or first degree relatives. Mean P50 ratio for the schizophrenic patients was 86.4% ± 5.2% s.e.m., with a median of 75.0%. Skewness (G1) was positive (G1SES = 0.83/0.26 = 3.1), whereas kurtosis (G2) was low (G2/SEK = 0.28/0.51 < 1). Coefficient of variation (C.V.) was 0.57. For normal controls, mean CTR was 19.2% ± 1.6% s.e.m. with a median of 15.3%. Skewness (G1) was quite high (G1SES = 1.580.19 > 7.5) Kurtosis (G2) was significantly higher than for the schizophrenics, (G2/SEK = 4.77/0.38 = 12.6) Thus, P50 ratios for schizophrenic patients more closely resemble a slightly skewed normal distribution, whereas the normal controls have a highly kurtotic and skewed distribution- most having P50 ratios under 20% and a significant number with P50 ratios of zero. These data suggest that the commonly applied upper cutoff of 40% or lower for “normal” gating is actually quite conservative, as is the requirement that “impaired” gating have a P50 ratio of >50%.

116. THE EFFECTS OF AGING IN SCHIZOPHRENIA ON AN ANTISACCADE EYE MOVEMENT TASK

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The antisaccade eye movement task, which has been linked to frontal lobe function, presents a target in one visual field and requires subjects to move their eyes to the same location in the opposite field. The task involves inhibition of the reflexive prosaccade to the cue, initiation of an antisaccade to the opposite field and visuo-spatial memory of the cue location. Older normal subjects make more incorrect prosaccadic movements to the cue and have greater processing time to inhibit the incorrect movement to the cue. Forty-nine schizophrenic patients from age 17–64 years of age performed this task and a control task, visually-guided saccades to the cue itself, to determine which functions are affected by aging in schizophrenia. As in normal subjects, aging in schizophrenia increases the rates of prosaccadic movements to the cue and has no effects on visuo-spatial memory. Additionally, latency of the visually-guided saccades increases with aging in schizophrenia. However, the latency of the antisaccade and the processing time show no relation to age in schizophrenia. Thus, the initial deficits in initiation of an antisaccade and inhibition of the incorrect movement to the cue in schizophrenia may be so severe that they may not have the ability to decline further with aging.

117. VULNERABILITY MARKERS IN SCHIZOTYPAL PERSONALITY DISORDER: DEFINING A PHENOTYPE


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Schizotypal personality disordered (SPD) subjects are phenomenologically similar to schizophrenic patients and it is likely that at least a subgroup of individuals who meet the SPD criteria are genotypically linked to schizophrenia. SPD subjects have been shown to have abnormalities of cognition, attention and information processing, similar to those observed in schizophrenic patients, as assessed by specific laboratory measures. Because SPD subjects are typically not medicated, actively psychotic or chronically institutionalized, the attention and information processing paradigms may identify trait-linked deficits that will lead to a better characterization and understanding of the pathophysiology and genetics of the schizophrenia spectrum. To achieve this end, it will be important to first determine whether information processing-defined markers identify the same or different domains of vulnerability to developing schizophrenia. An additional important question is whether a subgroup of individuals with SPD can be identified (based on information processing task performance) who are genotypically

linked to schizophrenia. We will present data from a group of 45 SPD subjects who were assessed on a specific set of information processing tasks including startle prepulse inhibition, P50 event related potential sensory gating, visual backward masking, visual contrast sensitivity, ocular motor measurement, choice, and neuropsychological measures. Preliminary analyses show strong but selective relationships between many of the information processing measures. These results suggest that some of the measures may collectively identify a vulnerability to schizophrenia. In addition, there appear to be subgroups of SPD subjects with deficits across multiple measures. The significance of these findings will be discussed.

118. PPI IN UNMEDICATED AND MEDICATED ACUTELY PSYCHOTIC SCHIZOPHRENIA PATIENTS

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The present study was designed to extend our understanding of sensorimotor gating in acutely psychotic schizophrenia patients and to assess the relationship between gating deficits and neuroleptic treatment. Many studies support the hypothesis of a schizophrenia-linked deficit in sensorimotor gating with an associated vulnerability to psychosis. One way to assess sensorimotor gating in humans is through prepulse inhibition (PPI) of the startle blink reflex. PPI occurs when a weak pre-stimulus presented 30 to 500 milliseconds prior to a startling stimulus results in a dampening of the blink reflex. In animal studies, activation of D2 dopamine function in the limbic forebrain produces deficits in PPI that model the PPI deficits seen in schizophrenia patients. Blockade of the D2 receptors restores prepulse inhibition. Recently, there has been a report that clozapine-treated schizophrenia patients showed normal levels of PPI compared to patients treated with typical neuroleptics. The same group has also found that haloperidol disrupted PPI in normal males leading to the conclusion that hypo and hyperdopaminergic states may lead to PPI deficits. However, it remains unclear if there is an interaction between medication status, acuity and symptom state in the mediation of PPI. The strategy used in this study to address this question was to assess a sample of schizophrenia patients all of whom are within 48 hours of admission to an acute psychiatric hospital.

In this study, PPI was measured in acutely psychotic schizophrenia patients within 48 hours of admission. Sixteen patients were unmedicated while the other 13 were being treated with an antipsychotic medication, eleven patients were treated with atypical antipsychotic medications. Subjects were clinically assessed with the PANSS to quantify symptoms. The medicated versus unmedicated subjects were not significantly different on any of the symptom measures. PPI was measured in a paradigm using three prepulse to pulse intervals (30, 60 and 120 msecs). There were no differences between the two groups for any of the three conditions, nor was there a relationship between symptoms and PPI for either group or when the groups were combined. These findings support the interpretation that symptom acuity is a more powerful mediator of PPI than medication status in schizophrenia patients.

119. SUSTAINED HALOPERIDOL OPPOSES APOMORPHINE AND PHENCYCLIDINE-INDUCED STARTLE GATING DEFICITS

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Both dopamine (DA) agonists and NMDA antagonists produce prepulse inhibition (PPI) deficits in rats that model PPI deficits in schizophrenia patients. While DA agonist effects on PPI are reversed by acute treatment with either “typical” high potency D2 DA antagonists or “atypical” antipsychotics, PPI deficits produced by phencyclidine (PCP) are preferentially reversed by acute treatment with “atypical” antipsychotics. Acute effects of antipsychotics may not accurately model the more clinically relevant effects of these drugs, that emerge after several weeks of continuous treatment. In the present study, sustained treatment with haloperidol via subcutaneous minipumps blocked the PPI-disruptive effects of the DA agonist apomorphine and attenuated the PCP-induced disruption of PPI. Restoration of PPI in apomorphine-treated rats was evident within the first week of sustained haloperidol administration; a partial but statistically significant reversal of PCP effects on PPI did not develop until weeks 2–3 of haloperidol treatment; was not observed for treatment weeks 4–6, then re-emerged in the seventh week of sustained haloperidol treatment. The delayed emergence and re-emergence of anti-PCP effects of haloperidol suggests that the brain substrates responsible for the DAergic and NMDA regulation of PPI are differentially sensitive to acute and chronic effects of antipsychotics.

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120. REGULATION OF SENSORIMOTOR GATING IN RATS BY HIPPOCAMPAL NMDA: ANATOMICAL LOCALIZATION

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Prepulse inhibition (PPI) of the startle reflex is a measure of sensorimotor gating that is reduced in humans with certain neuropsychiatric disorders, including schizophrenia, and in rats after manipulations of limbic cortico-striato-pallido-pontine circuitry. We have reported that PPI is reduced after specific manipulations of the hippocampal complex (HPC) in rats, but the mechanisms for these effects remain poorly understood. For example, dopaminergic substrates clearly regulate PPI, but the PPI-disruptive effects of intra-HPC carbachol or NMDA are not reversed by D2 receptor antagonists. This study examined the anatomical specificity of the PPI-disruptive effects of NMDA infusion. Startle magnitude and PPI were assessed after acute bilateral infusion of NMDA (0, 0.4 or 0.8 μg) into the dorsal subiculum (DS), the ventral subiculum (VS) or the entorhinal cortex (EC), in a within-subject design with order balanced across groups. A dose-dependent disruption of PPI was observed after NMDA infusion into the VS or EC, but not the DS. These findings demonstrate the importance of the ventral, but not the dorsal HPC, in the glutamatergic regulation of PPI. The proximity of the VS and EC preclude simple conclusions regarding the relative role of