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MONOAMINE REUPTAKE INHIBITION AND NICOTINE RECEPTOR ANTAGONISM REDUCE AMPLITUDE AND GATING OF AUDITORY EVOKED POTENTIALS

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Abstract—Background: Sensory encoding deficits have been extensively studied as endophenotypic markers of schizophrenia using auditory evoked potentials. In order to increase understanding of the neurochemical basis of such deficits, we utilized an animal model to test whether monoamine reuptake inhibition and nicotine receptor antagonism reduce the amplitude and gating of the P20 and N40 auditory components.

Methods: C57BL/6J mice received 12 days of chronic vehicle, bupropion, haloperidol or bupropion plus haloperidol. Auditory evoked potentials were then recorded in alert mice to measure the amplitude and gating of evoked components during a paired click paradigm similar to tasks used to measure the P50 and N100 auditory potentials in schizophrenia. Evoked potentials were recorded prior to and following acute nicotine.

Results: Bupropion reduced the amplitude and gating of the N40 evoked potential in mice, similar to the P50 and N100 endophenotypes associated with sensory encoding deficits in schizophrenia. This deficit was fully reversed only by the combination of haloperidol and nicotine, suggesting that dopamine reuptake inhibition and nicotine antagonism both contribute to the observed phenotype. Furthermore, nicotine increased P20 amplitude across all groups supporting a role for nicotine agonists in pre-attentive sensory encoding deficits.

Conclusions: We propose that the combination of monoamine inhibition and nicotine receptor antagonism may serve as a useful model for preclinical screening of pharmaceutical compounds aimed at treating sensory encoding deficits in schizophrenia.

Key words: schizophrenia, animal model, event related potentials.

Impairments of sensory encoding have been extensively studied as endophenotypic markers of schizophrenia using auditory evoked potentials (AEP) (Freedman et al., 1983; Siegel et al., 1984; Boutros et al., 1991; Erwin et al., 1991; Jin et al., 1997; Umbricht et al., 1998; Clementz et al., 2004). In these studies, an auditory stimulus evokes a series of electroencephalographic (EEG) responses corresponding to progression of brain activity throughout the auditory pathway. Early components (below 10 ms) originate in the cochlea and auditory nuclei of the brainstem, while mid-latency components including a positive deflection at approximately 50 ms in humans (P50) reflect activation of auditory thalamus and auditory cortex (Picton and Hillyard, 1974; Picton et al., 1974; Erwin et al., 1991). Longer latency components including a negative deflection at approximately 100 ms in humans (N100) have been localized to the primary auditory cortex and cortical association areas (Gallinat et al., 2002). Abnormalities in the P50 and N100 components are postulated to reflect abnormal neuronal architecture related to the generation and modulation of auditory responses and may be informative about more generalized neurological impairments in schizophrenia (Freedman et al., 1994; Adler et al., 1998).

Many AEP studies in schizophrenia have utilized a series of paired clicks to assess brain mechanisms of sensory processing. In these tasks, the amplitude of the EEG response to the first stimulus is larger than the response to the second. Although this approach has been extensively applied to study the P50, it should be noted that multiple components including the N100 also decrease in amplitude following the second stimulus (Erwin et al., 1991, 1994; Boutros et al., 1999, 2004; Rosburg et al., 2004).

Several studies indicate that unmedicated schizophrenia patients have reduced amplitude of the P50 following the first stimulus in a paired click task with resulting loss in gating of the second (Freedman et al., 1983; Jin et al., 1997). Although this finding has been replicated in some studies of patients treated with antipsychotic medications, other studies indicate that antipsychotic treatment results in an increased amplitude for both the first and second responses, maintaining the loss of gating (Freedman et al., 1983; Clementz et al., 1998, 2004). This profile of equal amplitude of response to the first and second stimuli has been conceptualized as impaired gating (Adler et al., 1998). Importantly, nicotine has been shown to restore gating among medicated schizophrenia patients (Fig. 1). Some studies have attributed this effect to a reduction in the second response, while others indicate that nicotine acts primarily to increase the amplitude of the first (Adler et al., 1993; Crawford et al., 2002).

The observation of improved gating following nicotine has led to an extensive body of research suggesting that sensory encoding deficits in schizophrenia are associated with abnormalities in the low affinity alpha-7 nicotinic ace-

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Abbreviations: AEP, auditory evoked potential; EEG, electroencephalographic.

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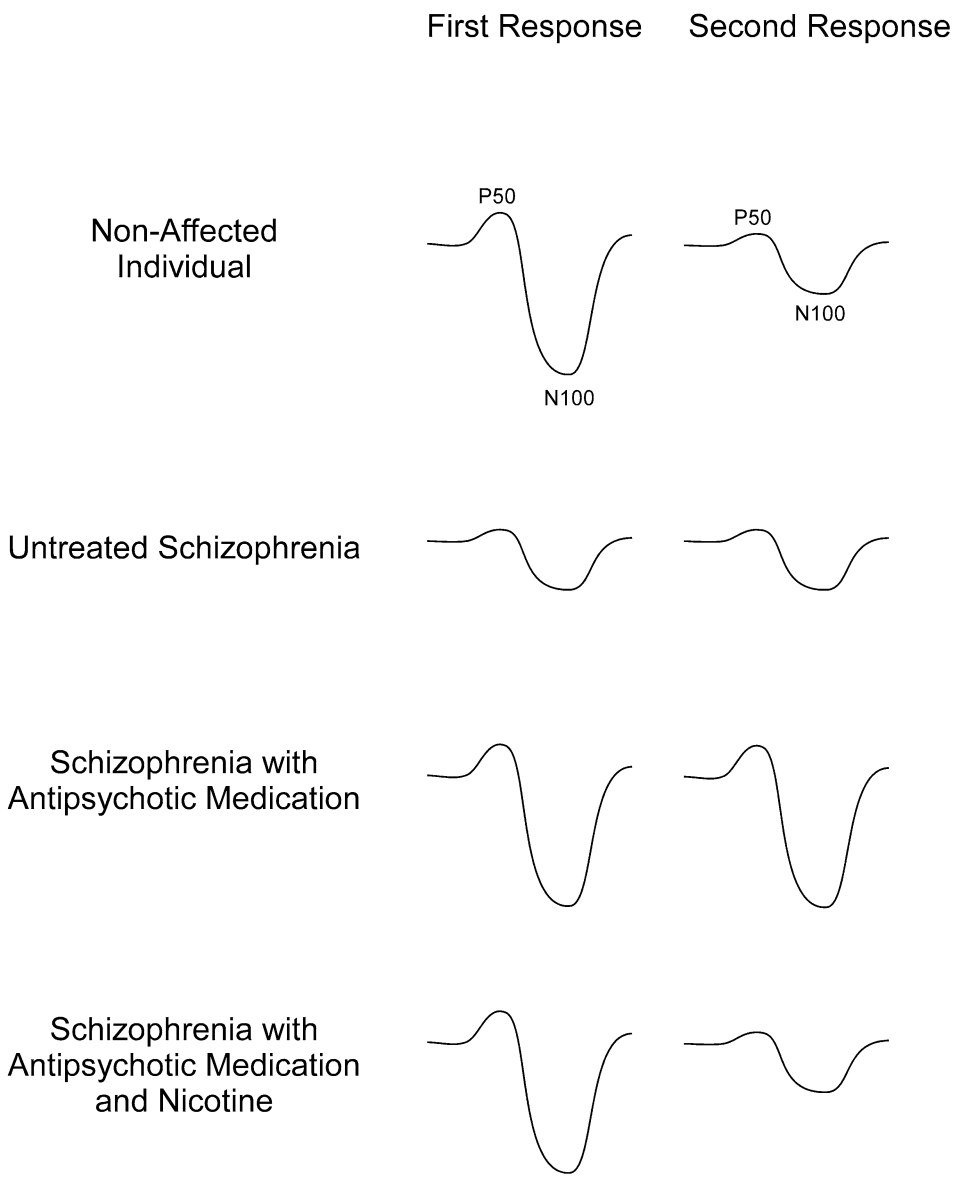

Fig. 1. Schematic representation of schizophrenia phenotypes for the P50 and N100. (A) The normal pattern of P50 and N100 responses in non-affected individuals. Note that the first response is large and the second is decreased. (B) In unmedicated schizophrenia, both the first and second responses are diminished for the P50 and N100. (C) Antipsychotic treatment results in increased amplitude of both the first and second responses for the P50 and N100 among schizophrenia patients, yielding the pattern of normal amplitude with impaired gating often described among medicated patients. (D) Nicotine reduces the amplitude of the second response among medicated schizophrenia patients.

tylcholine receptor (Leonard et al., 1996; Freedman et al., 1997; Adler et al., 1999). As a direct result of these findings, enormous efforts and resources are currently being devoted to the development of selective nicotine agonists to treat the hypothesized nicotine receptor abnormalities and resulting processing deficits (Levin, 2002; Deutsch et al., 2003; O'Neill et al., 2003; Williams, 2003; Hajos et al., 2004; Martin et al., 2004).

Similarly, multiple studies have described reduced amplitude of the cortically generated N100 in schizophrenia (Boutros et al., 1997; Frangou et al., 1997; Clementz and Blumenfeld, 2001). Commonly, the reduction in N100 amplitude occurs primarily at long interstimulus intervals (8 s), suggesting that the disease-specific deficit is manifest as an inability to mount the response rather than a gating deficit (Boutros et al., 2004). However, other studies describe increased amplitude of the N100 at short interstimulus intervals (0.25–0.5 s), suggesting there are also abnormalities in the attenuation of the N100 response to repeated stimuli (Erwin et al., 1991; Boutros et al., 2004). Such deficits in the generation and gating of both the thalamic P50 and cortical N100 support the growing hypothesis that reciprocal thalamocortical circuits are selectively affected in schizophrenia. Therefore, animal models that evaluate these two interrelated components may provide insights to the nature of circuit specific alterations