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Nicotinic modulation of auditory evoked potential electroencephalography in a rodent neurodevelopmental model of schizophrenia

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ABSTRACT

Schizophrenia is a chronic disease that has been hypothesized to be linked to neurodevelopmental abnormalities. Schizophrenia patients exhibit impairments in basic sensory processing including sensory gating deficits in P50 and mismatch negativity (MMN). Neuronal nicotinic acetylcholine receptor (nAChR) agonists have been reported to attenuate these deficits. Gestational exposure of rats to methylazoxymethanol acetate (MAM) at embryonic day 17 leads to developmental disruption of the limbic-cortical system. MAM exposed offspring show neuropathological and behavioral changes that have similarities with those seen in schizophrenia. In this study, we aimed to assess whether N40 auditory sensory gating (the rodent form of P50 gating) and MMN deficits as measures of auditory evoked potential (AEP) electroencephalography (EEG) are present in MAM rats and whether nAChR agonists could attend the deficit. E17 male MAM and sham rats were implanted with cortical electrodes at 2 months of age. EEG recordings evaluating N40 gating and MMN paradigms were done comparing effects of vehicle (saline), nicotine and the α7 agonist ABT-107. Deficits were seen for MAM rats compared to sham animals in both N40 auditory sensory gating and MMN AEP recordings. There was a strong trend for N40 deficits to be attenuated by both nicotine (0.16 mg/kg i.p. base) and ABT-107 (1.0 mg/kg i.p. base). MMN deficits were significantly attenuated by ABT-107 but not by nicotine. These data support the MAM model as a useful tool for translating pharmacodynamic effects in clinical medicine studies of novel therapeutic treatments for schizophrenia.

1. Introduction

Schizophrenia is a chronic disease that is linked to neurodevelopmental abnormalities [1,2]. Schizophrenia patients exhibit impairments in basic sensory processing and higher cognitive functions, such as language, reasoning, and planning. There is an ever growing interest in the development of animal models that represent impairments found in schizophrenia. Gestational exposure of rats to methylazoxymethanol acetate (MAM) at embryonic day 17 leads to developmental disruption of the limbic-cortical system [3–5]. MAM exposed offspring show neuropathological and behavioral changes including impairment of cognitive tasks such as spatial working memory, attentional set-shifting, and reversal learning that have similarities with those seen in schizophrenia [3,6]. Electroencephalography (EEG) and imaging studies done in MAM rats suggest abnormalities in structure and synchronized oscillatory activity that parallel disruptions of frontotemporal connectivity in schizophrenia [5,7–10]. Similar to schizophrenia patients, MAM rats also demonstrate a deficit in prepulse inhibition (PPI) of the startle response, a form of sensorimotor gating. To date, whether MAM rats also show other forms of sensory gating deficits typically seen in schizophrenia patients such as P50 and mismatch negativity has not been studied.

Sensory gating describes neurological processes for filtering out redundant or unnecessary stimuli in the brain from all possible environmental stimuli [11] by preventing an overload of irrelevant information in the higher cortical centers of the brain. Although sensory gating is largely automatic, it also occurs within the context of attentional processes. Sensory gating is mediated by a network in the brain which involves the auditory cortex, prefrontal cortex and hippocampus. Other areas of the brain associated with sensory gating include the amygdala, striatum, medial prefrontal cortex, and the GABAergic neurons of the midbrain dopamine cell region [12]. Using a paired-click paradigm is a common

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non-invasive technique used to measure sensory gating, a type of event-related potential (ERP). For normal sensory gating, if a person hears a pair of clicks within 500 ms of one another, the person will gate out the second click because it is perceived as being redundant. In humans, evidence of the gating can be seen in the P50 wave, occurring in the brain 50 ms after the click. Low values of the P50 wave indicate that sensory gating has occurred. High values of the P50 wave indicate a lack of sensory gating [11]. Individuals with schizophrenia only reduce the amplitude of the second stimulus by 10–20%, whereas individuals without schizophrenia reduce the amplitude of second stimulus by 80–90%. The P50 auditory gating deficit is one of the best established endophenotypes associated with schizophrenia. Most antipsychotics used clinically do not normalize P50 gating deficits in schizophrenia patients, except clozapine [13,14]. In rodents, a similar paradigm is measured in EEG denoted by amplitude differences between the P20 and N40 waves [15].

Cognitive decline associated with schizophrenia can be indexed by temporofrontal functional deficiency expressed as deficient auditory discrimination and orienting [16]. This functional deficiency can be objectively assessed by means of an electrophysiological measure known as mismatch negativity (MMN). MMN is presumed to reflect the existence of a short-term memory trace of the standard stimulus at the moment of presentation of a deviant stimulus. The MMN is considered an automatic (pre-attentive) response. It can be recorded in the absence of the subject's attention to auditory stimuli and even in unconscious comatose patients [17]. Since MMN is a change–detection response of the brain that can be elicited in the absence of conscious attention or behavioral task, an auditory ERP wave is generated for the responses to both the 'standard' and 'deviant' stimuli. As frequencies become divergent, a normal individual can detect the differences between the standard and the deviant. ERPs identify the mismatch. In the human auditory cortex, a detectable change (deviant stimulus) in the physical parameters of a repeated (standard) stimulus evokes a negative component in the auditory ERP within a 100–200 ms time window from stimulus onset. MMN has traditionally been recorded in the so-called auditory odd-ball paradigm involving randomized presentation of repetitive standard sounds and rare occasional deviant sounds. MMN is best visualized in a subtractive or difference waveform. Attenuated MMN amplitudes are a robust finding in patients with schizophrenia and studies done with either typical or atypical antipsychotic medications do not abolish MMN abnormality in patients with schizophrenia [18–21]. MMN has been demonstrated to be recorded in humans along with various animals, including rats [22,23].

Activation of nicotinic acetylcholine receptors (nAChRs) has been shown to improve attention, learning, and memory. Several subtypes of nAChRs are expressed in the mammalian brain, each with distinct physiological and pharmacological properties. Nicotine, which acts as an agonist at multiple nAChR subtypes, can normalize temporal aspects of sensory processing in patients with schizophrenia. Nicotine has also been demonstrated to normalize P50 [24] and MMN amplitude [25,26] in normal healthy subjects. A series of human and animal investigations has suggested that altered expression and function of the α7 nAChR may be responsible for the P50 auditory sensory gating deficit characterized in schizophrenia patients and their relatives [26,27]. α7 nAChRs are widely expressed in the hippocampus, an area of the brain closely associated with memory [28]. α7 nAChR agonists have been shown to improve performance in preclinical learning and memory tasks including pre-attention as measured by sensory gating [29–32]. They have also been shown to improve attention, working and episodic memory in humans. DMXB-A, a partial α7 nAChR agonist, demonstrated significant improvements in P50 inhibition in schizophrenia patients [33]. Recently, it has also been demonstrated that EVP-6124, a selective and potent α7 nAChR agonist can attenuate P50 and MMN deficits in schizophrenia patients [34]. In this study we evaluate the measures of N40 and MMN in MAM versus control rats and the effects of nicotine and the selective α7 nAChR agonist ABT-107.

2. Methods

2.1. Animals

Sprague Dawley timed pregnant female rats were received at E12 from Charles River Laboratories (Raleigh, NC). On E17 pregnant dams were injected intraperitoneally (i.p.) with either sterile phosphate buffered saline (PBS) or a 25 mg/kg methylazoxymethanol acetate (MAM). Pups were born 5–6 days later. On PD21, pups were weaned and separated by gender and litter into groups of 3–5 rats. Rat pups were maintained in group housing on a 12 h light:dark cycle (home cage and lab lights on 06:00–18:00; off 18:00–06:00) with food and water ad libitum. Pups were allowed to mature until they were 2 months old (PD60) before any behavior evaluation was completed. Based upon knowledge from within our lab, the MAM deficit phenotype can be characterized by spontaneous locomotor hyperactivity in early adulthood and postmortem brain weight. Behavioral profiling identified litters to have a good MAM effect prior to assignment for EEG surgery (data not shown). Male rats from two litters for an inclusive total of eight rats each of MAM exposed or control (PBS exposed) groups were surgically implanted with electrodes for recording EEG signals from both frontal and parietal cortices.

2.2. Surgical procedure

Under isoflurane anesthesia, male rats were implanted with stainless steel recording electrodes in the frontal (AP + 3.0; ML ± 2.0) and parietal (AP − 3.0; ML ± 4.0) cortices. Reference electrodes were implanted over the frontal sinus (AP + 6.0; ML + 1.0) and cerebellum. Recording electrodes were grounded to cerebellar reference. Peri-operatively, rats received 2.5 mg/kg subcutaneously (s.c.) flunixin meglumine (QD dosing; Banamine-S, Merck Animal Health, NJ). Flunixin was given for 2 additional days post-operatively. After surgery, the rats were single housed, maintained on a normal light:dark cycle and on a restricted diet to control weight (4 pellets/day).

2.3. EEG recording

EEG recordings did not begin for 2 week post-surgery to allow sufficient recovery from the surgical procedure. Rats were habituated to recording chambers for 1 week before start of studies. During habituation, spontaneous EEG was recorded for 2 h periods. EEG was recorded between 9:00 a.m. and 3:00 p.m. Freely moving rats were tethered in sound attenuating chambers to electrical swivels to convey EEG biosignals (Plastics One, Roanoke, VA, USA). EEG biosignals were amplified with differential AC amplifiers (A-M Systems, Sequim, WA, USA) and filtered at 1 and 100 Hz. The same rats were tested in both N40 and MMN paradigms. Rats were administered with either vehicle or investigational compound(s) in a within subject randomized Latin square design, allowing for at least 3 days wash out between test sessions. N40 sensory gating was presented as paired auditory white noise stimuli (500 ms interstimulus interval) every 15 s for a total of 120 trials. Mismatch negativity (MMN) potentials were generated by presenting auditory stimuli every 500 ms using an odd-ball paradigm where there were no successive repeats of the deviant stimulus. The MMN sound stimulus set was a white-noise