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Schizophrenia-like disruptions of sensory gating by serotonin receptor stimulation in rats: Effect of MDMA, DOI and 8-OH-DPAT

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ABSTRACT

Schizophrenia pathophysiology is associated with alterations in several neurotransmitter systems, particularly dopamine, glutamate and serotonin (5-HT). Schizophrenia patients also have disruptions in sensory gating, a brain information filtering mechanism in response to repeated sensory stimuli. Dopamine and glutamate have been implicated in sensory gating; however, little is known about the contribution of serotonin. We therefore investigated the effects of several psychoactive compounds that alter serotonergic neuronal activity on event-related potentials (ERP) to paired auditory pulses. Male Sprague–Dawley rats were implanted with cortical surface electrodes to measure ERPs to 150 presentations of two 85 dB bursts of white noise, 500 ms apart (S1 and S2). Saline-treated animals suppressed the response to S2 to less than 50% of S1. In contrast, treatment with the serotonin releaser, MDMA (ecstasy; 2.0 mg/kg), the 5-HT2A/2C receptor agonist, DOI (0.5 mg/kg), or the 5-HT1A/7 receptor agonist, 8-OH-DPAT (0.5 mg/kg), caused an increase in S2/S1 ratios. Analysis of waveform components suggested that the S2/S1 ratio disruption by MDMA was due to subtle effects on the ERPs to S1 and S2; DOI caused the disruption primarily by reducing the ERP to S1; 8-OH-DPAT-induced disruptions were due to an increase in the ERP to S2. These results show that 5-HT receptor stimulation alters S2/S1 ERP ratios in rats. These results may help to elucidate the sensory gating deficits observed in schizophrenia patients.

1. Introduction

Serotonin has been strongly implicated in the neurobiology of schizophrenia since it was discovered that hallucinogenic 5-HT2A receptor agonist drugs, such as lysergic acid diethylamide (LSD) and psilocybin, are psychotomimetic and can induce psychotic symptoms in healthy individuals (Breier, 1995; Geyer and Vollenweider, 2008; Hollister and Hartman, 1962). The current main treatments for schizophrenia are the class of atypical antipsychotic drugs, which differ from older, typical antipsychotics in that many have antagonist or partial agonist interactions with serotonin receptor subtypes in addition to antagonism of dopamine D2 receptors (Meltzer et al., 1989; Svensson, 2003). Clinical studies have revealed changes in the density of several serotonin receptor subtypes in the brain of patients with schizophrenia (Hurlemann et al., 2008; Ngan et al., 2000). For example, 5-HT2A receptor densities are reduced in the prefrontal cortex of drug-naive schizophrenia patients (Ngan et al., 2000).

Schizophrenia patients have deficiencies in a form of information processing known as sensory gating (Olincy et al., 2010; Patterson et al., 2008). Sensory gating refers to a neural mechanism which allows for repetitive incoming sensory information to be filtered, allowing focusing on novel, relevant environmental information. Deficiencies in the ability to filter irrelevant sensory information may make it difficult for a schizophrenia patient to focus on the most important pieces of information in the environment (Light and Braff, 1999; Venables, 1964). Sensory gating dysfunction in schizophrenia patients is associated with cognitive decline and hallucinations (positive symptoms) (Cadenhead et al., 2000; Light and Braff, 1999). These deficits are familial and represent a core deficiency of central information processing that is observed in schizophrenia symptomatology (Cadenhead et al., 2005; Olincy et al., 2010).

Sensory gating has been investigated in a number of different experimental paradigms, such as suppression of the P50 or N100 event-related potential (ERP) (Boutros et al., 2009; Patterson et al., 2008), mismatch negativity (MMN) (Boutros et al., 2009) and prepulse inhibition of acoustic startle (PPI) (Light and Braff, 1999). Each of these measures investigates different aspects of the inhibitory processes that are deficient in schizophrenia patients (Braff et al., 2007; Brenner et al., 2004). Suppression of the P50 ERP (P50 gating) is measured by presenting two clicks of sound 500 ms apart and measuring the response with electroencephalography (EEG). In healthy people and animals, the ERP that occurs in response to the second click is diminished to 40–50% of the response to the first click (Boutros et al., 1991a; Light et al., 1999). However, schizophrenia patients respond more similarly to both clicks in this paired-

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click paradigm (Adler et al., 1982; Olincy et al., 2010; Patterson et al., 2008). Atypical antipsychotic drugs appear to be more efficacious than typical antipsychotics to reverse P50 sensory gating deficits, indicating that a mechanism beyond dopamine receptor antagonism is involved (Adler et al., 2004; Light et al., 2000; Nagamoto et al., 1996).

In rodent studies of sensory gating, the component that undergoes suppression in the paired-click paradigm occurs at a different latency and polarity (Bickford-Wimer et al., 1990) and is commonly labelled as N40 (Boutros et al., 1997) or N50 sensory gating (Adler et al., 1988, 1986). However the component that undergoes suppression in the paired-click paradigm can occur anywhere from 20 ms to 90 ms, depending on a number of factors including electrode placement and depth (Bickford-Wimer et al., 1990), strain of animal (Breier et al., 2010) and different auditory stimulus parameters (Boutros et al., 1997). Preclinical studies have attempted to delineate the neuronal pathways that mediate N40 gating and have implicated dopamine and glutamate (Adler et al., 1986; Swerdlow et al., 2006), GABA (Ma and Leung, 2011), noradrenaline (Adler et al., 1988; Keedy et al., 2007) and acetylcholine (Luntzleybman et al., 1992; Stevens et al., 1995). For example, drugs that increase dopamine receptor signalling, such as the dopamine releaser, amphetamine, disrupt N40 sensory gating (Adler et al., 1986), an effect which can be attenuated by antipsychotic drugs such as haloperidol and clozapine (Adler et al., 1988, 1986; Joy et al., 2004). Similarly, the glutamate NMDA receptor antagonist, phencyclidine, was shown to cause a disruption of N40 sensory gating (Adler et al., 1986; Swerdlow et al., 2006).

The role of serotonin in sensory gating is less clear. The serotonin releasing drug, MDMA (ecstasy), has not been tested in the paired-click paradigm of sensory gating in humans or animals although it has been reported to disrupt sensorimotor gating in rats and mice, as measured with PPI (Bubenikova et al., 2005; van den Buuse et al., 2011). Treatment with the 5-HT2A/2C receptor agonist, DOI, has produced conflicting results whereby it can reduce (Johnson et al., 1998) as well as increase (Swerdlow et al., 2006) sensory gating ratios in rats. One study has examined the effect of the 5-HT1A/7 receptor agonist, 8-OH-DPAT, on N40 gating (Stevens et al., 2006) and found that a 0.5 mg/kg dose disrupted gating, while 0.1 mg/kg of 8-OH-DPAT had no effect when administered alone. However, this low dose ameliorated an N40 gating disruption caused by amphetamine (Stevens et al., 2006).

The aim of the present study was to further investigate the effect of direct and indirect 5-HT receptor stimulation on sensory gating. Specifically, we tested the effect of different doses of MDMA, DOI and 8-OH-DPAT in the paired-click paradigm of N40 auditory sensory gating in rats.

2. Methods

2.1. Animals

Thirty-nine male Sprague–Dawley rats were obtained from Monash Animal Services, Monash University, Australia, and were housed in groups of 2–3 in standard rat cages. Rats were maintained on a 12-h light/dark cycle (lights on at 7:00 AM) at a constant temperature of 22 ± 2 °C and had free access to standard pellet food and water. All surgical techniques, treatments and experimental protocols were in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (1990) set out by the National Health and Medical Research Council of Australia.

2.2. Electrode implantation

Surgery for electrode implantation was based on methodology as previously described (Breier et al., 2010; Swerdlow et al., 2006). When the rats were 250–350 g, they underwent surgery for implantation of electrodes onto the dura mater. They were anaesthetised with a mixture of 10% isoflurane and oxygen before being transferred to a stereotaxic apparatus (Stoelting Co., Wood Dale, IL, USA). Animals were positioned on a heating pad that was maintained at 37 °C throughout the procedure and blunt stereotaxic ear bars were used to prevent damage to the tympanic membrane. Prior to any incision, rats were administered 5 mg/kg of the non-steroidal anti-inflammatory drug, carprofen (Rimadyl®, Pfizer, Sandwich, Kent, United Kingdom). Through a 2 cm midline incision on the head, the recording electrode hole was drilled 4 mm posterior to bregma and 1 mm lateral to the midline. Drill holes for the earth and reference electrodes were 1 mm anterior to bregma and ±1 mm from the midline, respectively. Three additional holes were drilled for the placement of mounting screws (Plastics One, Roanoke, VA, USA).

Electrodes were made of stainless steel and insulated with polyimide. The recording electrode was 0.125 mm in diameter and 5 mm long (Plastics One). Reference and ground electrodes were 0.25 mm diameter and 2 mm long (Plastics One). Prior to the beginning of surgery, all electrodes and components were sterilised in 70% ethanol for 2–3 min and then rinsed in saline. The proximal parts of the electrodes were inserted into a matching head plug (MS-363, Plastics One) and mounted onto a stereotaxic electrode holder (MH-363, Plastics One). The head plug ensemble could then be lowered down over the drill holes and electrode tips were carefully placed inside the drill holes, on top of the dura mater. Dental cement (Vertex-Dental, Zeist, The Netherlands) was placed around the head plug ensemble and mounting screws to firmly attach the head plug to the rat's skull and the surrounding skin was silk-sutured closed. Antiseptic cream (Betadine®, povidone–iodine 10% w/w, Faulding Consumer, Salisbury, SA, Australia) was applied to the wound and rats were placed individually in a clean, padded and heated recovery box until they were conscious and mobile. All rats were subsequently housed individually.

2.3. ERP testing apparatus

Auditory gating was measured using a modified stimulus and acquisition system (EMG startle reflex testing system, San Diego Instruments, San Diego, CA, USA), which presented all sounds and acquired electrocorticogram (ECoG) data simultaneously. The recording chamber was a purpose-built, ventilated, electromagnetically shielded and sound-attenuating wooden box (44 cm tall × 40 cm wide × 40 cm deep). Three openings covered with fine aluminium mesh allowed air, light and sound to enter the chamber while it remained electromagnetically shielded. During testing, rats were positioned inside a clear, plexiglass cylinder (12.6 cm diameter) in the centre of the chamber and an electronic swivel (Plastics One) was clamped near the ceiling so that rats could move freely. Two electromagnetically shielded speakers (frequency response predominately 55 Hz–21 kHz; 8030A, Genelec, Finland) were positioned on both sides of the recording chamber to present sounds. Amplifier gain was set to 10,000× and analogue high and low pass filters were set to 0.05 Hz and 300 Hz, respectively. Presentation of sounds and the recording of responses were completely automated using SRLab software (San Diego Instruments) on a laptop computer.

2.4. ERP testing

Two weeks after surgery, rats were acclimated to the testing chamber for a full testing session and the functionality of electrodes was verified. Drug trials commenced 2–3 days later. Each rat had a total of 3 test sessions after receiving a high and low dose of one of the drugs and a saline control in a pseudorandomised and repeated-measures design. Test sessions were conducted 2–3 days apart to allow for drug washout between sessions. Each test session began with a 3 minute acclimation period of background noise (65 dB white noise). Following this, 150 trials of paired clicks (each click 85 dB, 1 ms burst of white noise; 500 ms inter-stimulus interval) were presented at random intervals between 10 and 20 s. Each test session went for a total of approximately 45 min. EEG epochs for each trial were recorded 200 ms before