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Aripiprazole and haloperidol suppress excessive dopamine release in the amygdala in response to conditioned fear stress, but show contrasting effects on basal dopamine release in methamphetamine-sensitized rats

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ABSTRACT

Although emotional dysfunction in patients with schizophrenia is thought to be associated with poorer outcomes in terms of overall quality of well-being, only a few basic studies have examined the biochemical effect of antipsychotics on emotional function. In this investigation, we examined differences in the effects of aripiprazole and haloperidol on the conditioned fear response in methamphetamine-sensitized and fear-conditioned rats in an *in vivo* microdialysis study. Aripiprazole is the first antipsychotic drug with an action involving partial dopamine D_2 receptor agonism, thus differing from haloperidol, a typical antipsychotic that shows selective dopamine D_2 receptor full antagonism. After exposure to a conditioned stimulus, methamphetamine-sensitized rats exhibited significantly higher dopamine release in the amygdala than unsensitized rats. We considered this hypersensitivity of dopamine release to be a biochemical marker of hypersensitivity and vulnerability to stress in psychosis. In the present study, we found that aripiprazole and haloperidol equally suppressed the marked increase in extracellular dopamine levels in fear-conditioned rats, whereas haloperidol increased and aripiprazole decreased tonic dopamine levels. In conclusion, the effect of an antipsychotic drug is likely to be involved in attenuation of the phasic increase in dopamine associated with the fear response, at least in the amygdala. In addition, the contrasting effects of haloperidol and aripiprazole on tonic dopamine levels in the amygdala are likely due to the difference in their actions (selective dopamine D_2 receptor full antagonist vs. partial agonist, respectively).

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1. Introduction

Although it has been suggested that symptoms of emotional dysfunction in patients with schizophrenia are associated with poorer outcomes in terms of overall quality of well-being (Lysaker and Salyers, 2007; Wetherell et al., 2003), no basic study has examined the biochemical effect of antipsychotics on the fear response of a neurotransmitter (i.e., dopamine).

To examine the reaction to emotional stress, conditioned fear stress has been developed as a form of psychological stress based on classical conditioning theory (Fanselow, 1980). Since this method involves no physical invasiveness for imposition of the conditioned stimulus, response can be directly related to emotional changes, thereby making this model suitable for the study of reactions to psychological stress. The amygdala is known to be one of the most potent modulators of the mechanisms responsible for the emotional memory system (LeDoux, 1993a,b). The central nucleus of the amygdala is integral to the acquisition and expression of emotional memory, whereas the basolateral amygdala leads to conditioned or primary reinforcers (Everitt et al., 1999; Simmons et al., 2007). In addition, the amygdala is a site of dopaminergic innervation (Oades and Halliday, 1987), and dopamine afferents are particularly dense within the intercalated cell masses, basolateral nucleus and central nucleus of the amygdala (Asan, 1998; Brinley and McDonald, 1999; Fallon and Moore, 1978; Marowsky et al., 2005).

Methamphetamine-induced sensitization (reverse tolerance phenomenon) in rats has been widely and successfully used as an animal model of stimulant-induced psychosis and schizophrenia in terms of the paranoid psychotic state and its vulnerability to relapse (Robinson and Becker, 1986; Sato et al., 1992; Seiden et al., 1993). This animal model is analogous to human schizophrenia in that the animals show disruption of prepulse inhibition (Tenn et al., 2005); blocking of sensitization by antipsychotics (Karler et al., 1990); and decreased somal volume, length of spine density, dendrites, and terminals of prefrontal cortical pyramidal neurons in layer II/IIIs (Selemon et al., 2007). Methamphetamine-sensitized animals show significantly higher extracellular dopamine release in the amygdala than unsensitized rats after exposure to a conditioned stimulus (Suzuki et al., 2002). This hypersensitivity of dopamine release is considered to be a biochemical marker of hypersensitivity and vulnerability to stress in psychosis (Suzuki et al., 2002). Interestingly, abnormal responsiveness

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of central dopamine neurons to stress has been proposed to play a role in the expression and exacerbation of symptoms associated with schizophrenia (Finlay and Zigmond, 1997).

Thus, in order to investigate the pharmacological effect of antipsychotics on the emotional component of psychosis, it would be of great value to compare the effect of the selective dopamine D_2 receptor full antagonist haloperidol with that of the D_2 receptor partial agonist aripiprazole on extracellular dopamine level in the amygdala of methamphetamine-sensitized rats after fear stress.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (Japan CLEA, Tokyo, Japan) weighing 180–190 g at the beginning of the experiment and 290–420 g at the time of microdialysis were used. The animals were kept at constant room temperature (26 ± 2 °C with a 12-h light–dark cycle (dark from 20:00 h) and free access to water and food. All procedures were performed in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals and were approved by the Tokyo Women's Medical University School of Medicine Animal Experiments and Ethics Committee.

2.2. Drugs

Methamphetamine hydrochloride was purchased from Dainippon Sumitomo Pharmaceutical (Osaka, Japan); aripiprazole was kindly donated by Otsuka Pharmaceutical Company (Tokushima, Japan); haloperidol was purchased from Wako Pure Chemical Industries (Osaka, Japan). All other chemicals and reagents were the purest available commercially and were purchased from Wako Pure Chemical Industries (Osaka, Japan). Haloperidol was dissolved at 0.5 mg/ml in lactate and physiological saline. Aripiprazole was dissolved at 5 mg/ml in 1 mol/l hydrochloric acid and *N*,*N*-dimethylformamide and physiological saline. The pH of these solutions was controlled to between 5.0 and 6.0 by addition of 1 mol/l sodium hydroxide solution.

2.3. Methamphetamine sensitization and surgical implantation of cannulae (days 1–11)

Methamphetamine was administered to rats using a previously reported method to produce a reverse tolerance model; this method has been confirmed to induce behavioral sensitization upon re-challenge with methamphetamine (Tanaka et al., 1998). Methamphetamine hydrochloride dissolved in saline (2 mg/ml) was injected subcutaneously for 10 days at 2 mg /kg/day (methamphetamine groups; MP). Control groups were given an equivalent volume of physiological saline (saline groups; Sal). Following sensitization on day 11, a guide cannula was inserted using a stereotaxic frame (Model 900, David Kopf Instruments, California, USA) into the left amygdala at a point 2.4 mm posterior and 4.4 mm lateral to the bregma, and at a depth of 7.2 mm from the surface of the bone at the bregma (Paxinos and Watson, 1997). Pentobarbital anesthesia (50 mg/kg, mean body weight at surgery: 330 g) was used during the procedure. For the stereotaxic procedure, an ear bar with dulled tips was used for anchoring to avoid damage to the rats' eardrums. After surgery, the rats were transferred to their individual home cages (opaque sided, 30 cm high, 25 cm wide, 15 cm deep).

2.4. Fear stress conditioning protocol (days 12–14)

Fear conditioning was performed once a day for 3 consecutive days, starting from the day after insertion of the guide cannula. As rats did not show any motor or sensory abnormalities and showed successful fear conditioning, the time course of this method did not influence the study results.

Fear conditioning was performed by transferring the rats from their home cages to stimulation cages (clear sided, height 45 cm, width 22 cm, depth 22 cm) in a soundproof room, and applying an electric foot shock from a floor grid made of stainless steel rods (diameter, 4 mm, at intervals of 8 mm). A continuous sound of 80 dB for 30 s (conditioned stimulus; CS) was emitted before administration of the electric foot shock at 0.8 mA for 0.5 s (unconditioned stimulus) (fear conditioning groups; FC). The electric foot shock was a constant-current stimulus produced by a shock generator/scrambler (Muromachi Kikai, Tokyo, Japan). Animals in the control groups were exposed to audio stimulation under the same conditions but with no foot shock (sham groups; Sham).

2.5. Microdialysis (day 15)

The day after the conditioning session, microdialysis was begun following insertion of a probe into the left amygdala and intraperitoneal injection of a drug (haloperidol 1 mg/kg, aripiprazole 10 mg/kg, or saline 2 ml/kg in the same volumes) while the animals were anesthetized and unrestrained. The dialysis probe had a membrane length of 2.0 mm, an outer diameter of 0.5 mm, and an MW cutoff of 20,000 Da (AI-12-2; Eicom, Kyoto, Japan). Ringer's solution (147 mM Na^+, 4 mM K^+, 2.3 mM Ca^{2+}, 155.6 mM Cl^-) was used as the perfusate for microdialysis, and samples were collected at a flow rate of 2 μl/min.

Acclimation for 180 min was allowed after the beginning of microdialysis. Then, the pre-CS extracellular dopamine level was measured for 80 min between 180 and 260 min after the start of microdialysis. CS (i.e., sound only, with no foot shock) was then applied to rats in all groups at 260 min after the beginning of microdialysis. The duration of freezing behavior was measured during the 20-min CS application period. Time-based changes in the extracellular dopamine level as the post-CS extracellular dopamine level were measured for 80 min following CS application between 260 and 340 min after the start of microdialysis. The total microdialysis run time was 340 min (acclimation 180 min, sampling of pre-CS extracellular dopamine levels 80 min, sampling of post-CS extracellular dopamine levels 80 min). As a preliminary experiment had shown that the effect of haloperidol and aripiprazole on dopamine release in the amygdala was prolonged over 340 min, the extracellular dopamine level during the duration of sampling was that under the effect of the drug.

2.6. Measurement of extracellular dopamine levels

Extracellular dopamine levels were measured by high-performance liquid chromatography every 20 min. Samples were collected with an Auto Injector (ESA-20: Eicom). To quantify dopamine on a real-time basis, the samples were placed in a high-performance liquid chromatograph (HITEC-500: Eicom) every 20 min, using a CA-5ODS column (2.1 × 150 mm; Eicom) with a mobile phase containing 134.49 g/l NaH_2PO_4, 49.40 g/l Na_2HPO_4, 1% methanol, 800 mg/l sodium 1-decanesulfonate, and 50 mg/l EDTA-2 Na. The detector in this system had a graphite working electrode set at + 0.45 V relative to an Ag/AgCl reference electrode. Use of the Auto Injector enabled dopamine levels to be measured without sample decomposition or loss through oxidation.

2.7. Histology

At the end of each experiment, the animals were given an overdose of sodium pentobarbital (100 mg/kg) and perfused transcardially with physiological saline, followed by 10% buffered formalin. The brains were post-fixed in 10% buffered formalin for 1 to 10 days and then cryoprotected by immersion in 25% sucrose for 2 days. The

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