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The effect of acute aripiprazole treatment on chemically and electrically induced seizures in mice: The role of nitric oxide

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ABSTRACT

Aripiprazole is an antipsychotic drug which acts through dopamine and serotonin receptors. Aripiprazole was noted to have antiseizure effects in a study on mice, while it induced seizures in a few human case reports. Dopaminergic and serotonergic systems relate to nitric oxide, and aripiprazole also has effects on dopamine and serotonin receptors. This study investigated the effects of aripiprazole on seizures and the potential role of nitric oxide in the process. The following three models were examined to explore the role of aripiprazole on seizures in mice: 1 — pentylenetetrazole administered intravenously, 2 — pentylenetetrazole administered intraperitoneally, and 3 — electroshock. Aripiprazole administration delayed clonic seizure in intravenous and intraperitoneal pentylenetetrazole models. In the electroshock-induced seizure model, tonic seizure and mortality protection percent were increased after aripiprazole administration. In intraperitoneal administration of pentylenetetrazole, aripiprazole effects on clonic seizure latency were significantly decreased when L-NAME — a nonselective nitric oxide synthase (NOS) inhibitor, 7-nitroindazole — a selective neuronal NOS (nNOS) inhibitor, or aminoguanidine — a selective inducible NOS (iNOS) inhibitor was injected before aripiprazole administration. In the intravenous pentylenetetrazole method, administration of L-NAME or aminoguanidine inhibited aripiprazole effects on clonic seizure threshold. Aminoguanidine or L-NAME administration decreased aripiprazole-induced protection against tonic seizures and death in the electroshock model. In both intravenous and intraperitoneal seizure models, aripiprazole and L-arginine coadministration delayed the onset of clonic seizures. Moreover, it increased protection against tonic seizures and death in intraperitoneal pentylenetetrazole and electroshock models. In conclusion, the release of nitric oxide via iNOS or nNOS may be involved in anticonvulsant properties of aripiprazole.

1. Introduction

Psychotropic drugs, especially antidepressants and antipsychotics, may give rise to some concern in clinical practice because of their known ability to reduce seizure threshold and to provoke epileptic seizures. Seizures triggered by psychotropic drugs are a dose-dependent adverse effect. Chlorpromazine and clozapine are among antipsychotics showing relatively high seizurogenic potential; while fluphenazine, haloperidol, pimozide, and risperidone are among antipsychotics that exhibit a relatively low risk [1]. According to studies, seizures were reported in 0.3% of patients given risperidone, 0.9% of patients given olanzapine, and 0.8% of patients who received quetiapine [2].

Aripiprazole is the first dopamine D2/D3 receptor partial agonist approved for use in the treatment of psychiatric disorders, including schizophrenia, bipolar disorder, and unipolar depression in the US [3]. Aripiprazole has a unique pharmacologic profile that includes partial agonism at several G-protein coupled receptors (GPCRs) [especially dopamine (D2) and 5-HT1A] and antagonistic action at others (especially 5-HT2A) [4]. The risk of seizures with aripiprazole is reported to be 0.1%, the lowest among atypical antipsychotic agents [5]. A proconvulsant effect of aripiprazole has been found in at least two human cases [6,7]; in contrast, its anticonvulsant effect is reported in a few experimental animal models [8,9].

Nitric oxide (NO) is an unconventional transmitter molecule in the nervous system, which is synthesized from L-arginine by nitric oxide synthase (NOS) [10]. There are three types of NOS: neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS) [11]. Nitric oxide has been implicated in the pathophysiology of epilepsy, but available data are conflicting, and the actual role of NO in epilepsy still remains to be clarified [12]. Some researchers have demonstrated that NO may act as an endogenous anticonvulsant [13–17], while others suggest a proconvulsant role for NO [18,19].

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Some studies have shown that aripiprazole can inhibit NO production [20]. Considering that dopaminergic and serotonergic systems have an interaction with NO [21,22], and aripiprazole also has an effect on dopamine and serotonin receptors, in this study, aripiprazole and NO interaction and their effects on convulsion were investigated.

2. Materials and methods

2.1. Drugs

The following drugs were used in the study: pentylenetetrazole (PTZ) (Sigma, UK), aminoguanidine (a selective iNOS inhibitor) (Sigma, USA), L-arginine (a NO donor) (Sigma, USA), N^G-L-arginine methyl ester (L-NAME) (a nonselective NOS inhibitor) (Sigma, USA), 7-nitroindazole (7-NI) (a selective nNOS inhibitor) (Sigma, Canada), and aripiprazole (Sigma, USA). All of the drugs except PTZ in intravenous method were administered intraperitoneally. Aripiprazole and 7-NI were suspended in a solution of 1% Tween 80 in normal saline. All other drugs were dissolved in normal saline. The doses of NO inhibitors and L-arginine were selected according to the previous studies [23,24].

2.2. Animals

Male NMRI mice weighing 20–30 g were used throughout this study. Animals were housed in groups of four or five and were allowed free access to food and water except for the short time during which animals were removed from their cages for testing. Each group of mice consisted of seven to fifteen animals. All procedures were conducted in accordance with experimental protocols and approved by the local ethics committee at the Medical University of Shiraz. Additionally, efforts were made to minimize animal suffering and to use only the number of animals necessary to produce reliable scientific data.

2.3. Behavioral seizure evaluation

2.3.1. Intraperitoneal PTZ-induced seizure

We examined the effect of different treatment groups on generalized tonic–clonic seizures induced by intraperitoneal injection of high dose PTZ. Generalized tonic–clonic seizure induced by intraperitoneal PTZ is a distinct model related to tonic-clonic seizures in humans [25,26]. In this model, PTZ (85 mg/kg, CD97 for clonic seizures in the current experiment) was administered with a single intraperitoneal injection to evaluate the latency for the onset of clonic seizures and the incidence of tonic seizures and death following seizures [27,28]. Immediately after injection of PTZ, animals were transferred to an open field (50 cm in diameter) and monitored for the appearance of convulsion or death for 30 min. Following the administration of 85 mg/kg of PTZ, time latencies for generalized clonus were measured. Latency was defined as the time between PTZ injections and the onset of clonic seizures. The incidence of tonic seizure and death was also recorded.

2.3.2. Intravenous PTZ-induced seizure

Intravenous PTZ infusion test is an appropriate test for evaluation of the anticonvulsant activities of new compounds [29–31]. Induction of seizures by intravenous infusion of PTZ is a standard experimental model of clinical myoclonic seizures that has both face and construct validities [25,32]. This model has proven to be more sensitive than intraperitoneal PTZ administration and allows better detection of modulatory effects on convulsive tendency [25]. The clonic seizure threshold was determined by inserting a 30-gauge dental needle into the lateral tail vein of the mouse [27]. The needle was then secured to the tail with a narrow piece of adhesive tape. With the mouse moving freely, the PTZ solution (0.5%) was infused into the tail vein at a constant rate of 0.5 ml/min using an infusion pump (Harvard, USA), which was connected to the dental needle by polyethylene tubing. Infusion was halted when forelimb clonus followed by full clonus of the body was observed. The minimum dose of PTZ (mg/kg mouse wt) needed to induce a clonic seizure was measured as an index of clonic seizure threshold.

2.3.3. Electroshock test

To examine the role of aripiprazole in modulation of susceptibility to electroshock-induced seizures, an electroconvulsive therapy apparatus (Model 7800, Ugo Basile, Camerio, Italy) was used. Tonic convulsions of the hind extremities of mice were induced by passing alternating current (50 Hz, 35 mA, and 0.2 s) via ear electrodes. In order to improve electrode contact, the electrodes were moistened with normal saline before being attached to the ears of mice. Electroshock induces a continuum of motor convulsions that are dependent on the intensity of the electrical stimulation current. Maximal electroshock (MES) is typically induced in mice using supramaximal electroshock currents of 50 mA [33]. The current used (35 mA) was predetermined before experimentation and was the current that caused hindlimb extension in a significant number of mice in the trials [33–35]. Data were expressed in terms of percent protection which is the percentage of animals in each group that did not exhibit hindlimb extension or death after electroshock.

2.4. Treatments

In intraperitoneal PTZ experiments, animals received acute intraperitoneal injections of different doses of aripiprazole (0.5, 1, 2, 4, or 8 mg/kg) 60 min before administration of PTZ. In the other 3 experiments, L-NAME (1 or 5 mg/kg), aminoguanidine (50 or 100 mg/kg), or 7-NI (30 or 60 mg/kg) was administered 5 min before aripiprazole (2 mg/kg) and 65 min before PTZ. In experiment 5, L-arginine (30 or 60 mg/kg) was injected 5 min before aripiprazole (1 mg/kg) and 65 min before PTZ injection.

In experiment 1 of intravenous PTZ method, aripiprazole (0.5, 1, or 2 mg/kg) was injected 60 min before PTZ. In experiment 2, aripiprazole (2 mg/kg) was administered 30, 60, and 120 min prior to PTZ to three groups of mice. In the other two experiments, aripiprazole (2 mg/kg) was administrated 5 min after L-NAME (5 mg/kg) or aminoguanidine (100 mg/kg) and 60 min before PTZ injection. In experiment 5, L-arginine (60 mg/kg) was injected 5 min before aripiprazole (0.5 mg/kg) and 65 min before PTZ administration.

In electroshock experiments, aripiprazole (1 or 2 mg/kg) was administered 60 min before electroshock. In the other two experiments, L-NAME (5 mg/kg) or aminoguanidine (100 mg/kg) was administered 5 min before aripiprazole (2 mg/kg) and 65 min before electroshock. In experiment 4, L-arginine (60 mg/kg) was injected 5 min before aripiprazole (1 mg/kg) and 65 min before electroshock.

2.5. Statistical analysis

Data are expressed as means ± SEM of 8–10 mice and analyzed using the SPSS statistical software package (Version 18.0). One-way analyses of variance (ANOVA) and post hoc Tukey's tests were used to analyze data. In order to determine the protective effects against tonic seizures and death, Fisher's exact test was used. Also, $P < 0.05$ was considered statistically significant.

3. Results

3.1. Intraperitoneal PTZ method

3.1.1. Effect of acute treatment with different doses of aripiprazole in intraperitoneal PTZ method

Table 1 shows the effect of acute administration of different doses of aripiprazole (0.5, 1, 2, 4, and 8 mg/kg) on PTZ-induced seizures. One-way ANOVA revealed a significant effect for aripiprazole on clonic