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Invited review

Ameliorating effects of aripiprazole on cognitive functions and depressive-like behavior in a genetic rat model of absence epilepsy and mild-depression comorbidity

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ABSTRACT

Aripiprazole (APZ) is regarded as a first-line atypical antipsychotic used for the treatment of first and multiple episodes of schizophrenia to improve positive- and negative-symptoms. Its therapeutic indications were extended to acute manic and mixed episodes associated with bipolar disorder. In addition, APZ was approved as an adjunct therapy for major depressive disorder in 2007. Compared to other antipsychotic drugs, APZ has a unique pharmacological profile. It is a partial agonist at D_2 dopamine receptors and serotonin **5-HT$_{1A}$** and 5-HT$_7$ receptors, whereas it is an antagonist at serotonin **5-HT$_{2A}$** and 5-HT$_6$ receptors. Since epilepsy is often accompanied with neurological comorbidities such as depression, anxiety and cognitive deficits caused by both the disease and/or drug treatment, we wished to examine the effects of a sub-chronic treatment (>14 consecutive days) with APZ (0.3, 1 and 3 mg/kg; i.p.) on both absence seizures and WAG/Rij rat's behavior using different standard paradigms: Open field (OF) test, elevated plus maze (EPM) test, forced swimming (FS) test, sucrose consumption (SC) test and Morris water maze (MWM). WAG/Rij rats represent a validated genetic animal model of absence epilepsy with mild-depression comorbidity, also including other behavioral alterations. APZ treatment showed some anti-absence properties and regarding the behavioral comorbidity in this rat strain, we observed that APZ possesses clear antidepressant effects in the FS and SC tests also increasing memory/learning function in the Morris water maze test. In the two anxiety models used, APZ showed only minor effects. In conclusion, our results indicate that APZ might actually have a potential in treating absence seizures or as add-on therapy but more interestingly, these effect might be accompanied by positive modulatory actions on depression, anxiety and memory which might be also beneficial in other epileptic syndromes.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.

1. Introduction

WAG/Rij rats represent a validated genetic animal model of absence epilepsy with mild-depression comorbidity, also including other behavioral alterations (Sarkisova and van Luijtelaar, 2011). WAG/Rij rats were originally developed and subsequently validated as a genetic animal model of absence epilepsy (Coenen and van Luijtelaar, 2003). Behavioral studies have accumulated evidences in favor of the view that WAG/Rij rats are a model of a chronic low-grade depression (dysthymia) accompanying absence epilepsy: decreased investigative activity in the open field test, increased immobility in the forced swimming test, and decreased sucrose consumption and preference (anhedonia) (Sarkisova and van Luijtelaar, 2011; Sarkisova et al., 2008). These depression-like behavioral symptoms are evident in WAG/Rij rats starting around 3 months of age, with a tendency to aggravate in parallel with the increase in seizure number and duration (Sarkisova et al., 2010). In addition, WAG/Rij rats adopt passive strategies in stressful situations, express some cognitive disturbances (reduced long-term memory), helplessness, and submissiveness, inability to make choice and overcome obstacles, which are typical for depressed patients (Sarkisova and van Luijtelaar, 2011; van Luijtelaar et al., 2007). It is known that depressive symptoms are associated with changes in the tonus of monoamines such as serotonin (5-HT) and catecholamines (dopamine, noradrenaline) and with changes in the

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level of cortisol (corticosterone in rats) (Sarkisova and van Luijtelaar, 2011). Behavioral and electrophysiological studies have demonstrated functional deficits in the brain dopaminergic system in WAG/Rij rats (Sarkisova et al., 2008; Sarkisova and van Luijtelaar, 2011). It is significant that dysfunction of the brain dopaminergic system led to the appearance of a complex of symptoms of depressive behavior with possible involvement of dopamine D_2 receptors in mediating the antidepressant effect of imipramine on genetically determined depression-like behavior in WAG/Rij rats (Sarkisova et al., 2007, 2008; van Luijtelaar et al., 2007). The validity of the model, as a model for mild depression (dysthymia), has been proven experimentally by symptomatology (features of behavior), sensitivity to antidepressant treatment and neurochemical alterations in the brain, fulfilling criteria for face, predictive and construct validity (Sarkisova et al., 2007; Sarkisova and van Luijtelaar, 2011; van Luijtelaar et al., 2007).

Aripiprazole (APZ) is regarded as a first-line atypical antipsychotic used for the treatment of first and multiple episodes of schizophrenia to improve positive- and/or negative-symptoms (Kane et al., 2003). Its therapeutic indications were extended to acute manic and mixed episodes associated with bipolar disorder. In addition, APZ was approved as an adjunct therapy for major depressive disorder in 2007. Compared to other antipsychotic drugs, APZ has a unique pharmacological profile. It is a partial agonist at D_2 dopamine receptors and serotonin **5-HT$_{1A}$** and 5-HT$_7$ receptors, whereas it is an antagonist at serotonin **5-HT$_{2A}$** and 5-HT$_6$ receptors (Zhang et al., 2006). Furthermore, APZ has moderate affinity to histamine receptors, α-adrenergic receptors and the serotonin transporter, which contribute to APZ's improved tolerability profile. In view of its peculiar pharmacological profile, APZ has been described as a dopamine/serotonin system stabilizer. In an animal study, APZ inhibits marble-burying behavior, which is considered as an animal model of obsessive–compulsive disorder (Egashira et al., 2008). Other results obtained in the two-compartment exploratory test showed that APZ improves spatial memory in rats and has antidepressant and anxiolytic effects (Bourin et al., 2009; Burda et al., 2011). It has also been showed that APZ ameliorate phencyclidine-induced impairment of recognition memory through dopamine D_1 and serotonin **5-HT$_{1A}$** receptors (Nagai et al., 2009) and anxiety-like behavior in ethanol physical dependent mice (Shibasaki et al., 2012). However, it has also been demonstrated that both first- and second-generation antipsychotic medications can lower seizure threshold, increasing the chances of seizure induction (Hedges et al., 2003). Aripiprazole, has only 0.1% seizure-inducing potential (Abilify [package insert], 2004), much lower than other antipsychotics. There are only three reported cases of APZ-associated seizures (Malik and Ravasia, 2005; Tsai, 2006; Li et al., 2010).

Based on this background, in the present paper, we wished to examine the effects of a sub-chronic treatment (14 consecutive days) with APZ on both absence seizures and WAG/Rij rat's behavior using different standard paradigms: Open field (OF) test, elevated plus maze (EPM) test, forced swimming (FS) test, sucrose consumption (SC) test and Morris water maze (MWM). The obtained results might elucidate the efficacy and safety of APZ on an epileptic brain which is often accompanied with neurological comorbidities such as depression, anxiety and cognitive deficits caused by both the disease and/or drug treatments (Canevini et al., 2010; Luoni et al., 2011; Turky et al., 2011).

2. Experimental procedures

2.1. Animals

Male WAG/Rij rats only were used. Rat progenitors were purchased from Charles River Laboratories s.r.l. (Calco, Lecco, Italia) at a body weight of ~60 g (4 weeks old). Following arrival, animals were housed three/four per cage and kept under controlled environmental conditions (60 ± 5% humidity; 22 ± 2 °C; 12/12 h reversed light/dark cycle; lights on at 20.00). Female rats at 10 weeks of age were placed with same-age group males for mating for 16 h in the ratio 1:1 and examined the next morning for the presence of a vaginal plug, a sign of successful copulation. Dams were housed 2 per cage up to offspring weaning (P21), and then the newborns were housed three/four per cage. Animals were allowed free access to standard laboratory chow and water until the time of experiments. Procedures involving animals and their care were conducted in conformity with the international and national law and policies (European Communities Council Directive of 24th November 1986, 86/609EEC). All efforts were made to minimize animal suffering and to reduce the number of animal used.

2.2. Sub-chronic treatment procedure

Aripiprazole (APZ) was dispersed in a 1% aqueous solution (physiological saline) of Tween 80. Rats were treated intraperitoneally (i.p.) with APZ at the doses of 0.3, 1 and 3 mg/kg in a volume of 1 ml/kg injected every day at 5 p.m. until the end of the experiments. To evaluate the effects of a short-term APZ treatment (sub-chronic) on absence seizures, different groups of rats, around 6 months of age, were treated for 14 consecutive days, starting treatment one week after surgery for electrode implantation (see Section 2.3). Starting on the 15th day, rats of the sub-chronic treatment group (absence seizure evaluation) underwent three recording periods as described in Section 2.3; treatment was continued up to the last day of recordings. Control group received equal volumes of vehicle (1% Tween 80 in physiological saline). Relative to behavioral tests, no surgery was performed and treatment was continued as above reported for the entire duration of the tests without discontinuation. Therefore, the drug was always present in the system at the moment of the test. Total duration of the treatment in every test should be considered as 14 days added to day of testing; i.e. in the Morris water maze test, on day 5 recordings animals were treated for 19 consecutive days (14 + 5). In any case, APZ blood concentration can be considered stable being at the steady-state already before testing being its half-life in rats is about 1 h (Abilify [package insert], 2004).

2.3. Animal surgery and EEG recording

WAG/Rij rats ($N = 6$ per dose) around the age of 6 months were chronically implanted, under anesthesia obtained by administration of a mixture of tiletamine/zolazepam (1:1; Zoletil 100®; 50 mg/kg i.p.; VIRBAC Srl, Milan, Italy), using a Kopf stereotaxic instrument, with five cortical electrodes for EEG recordings (Russo et al., 2004). Stainless-steel screw electrodes were implanted on the dura mater over the cortex: two in the frontal region (AP = 2 mm; L = ±2.5 mm) and two in the parietal region (AP = −6 mm; L = ±2.5 mm) according to the atlas coordinates of Paxinos and Watson (1998). The ground electrode was placed over the cerebellum. All animals were allowed at least 1 week of recovery and handled twice a day before drug administration. In order to habituate the animals to the recording conditions, the rats were connected to the recording cables, for at least 3 days before the experiments. Every EEG recording was always performed starting at 9.00 am in order to avoid circadian alterations within groups. The animals were attached to a multichannel amplifier (Stellate Harmonie Electroencephalograph; Montreal, Quebec, Canada) by a flexible recording cable and an electric swivel, fixed above the cages, permitting free movements for the animals. All EEG signals were amplified and conditioned by analog filters