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Atypical antipsychotic paliperidone prevents behavioral deficits in mice prenatally challenged with bacterial endotoxin lipopolysaccharide

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ABSTRACT

Studies on animal models provide enough evidences that old age appearance of psychosis on exposures to various insults during critical period of brain development could be prevented by antipsychotic drug treatment. Presently, gestational intervention of the atypical antipsychotic paliperidone (PAL) is done along with the exposure of bacterial endotoxin lipopolysaccharide/LPS hypothesizing that the drug would counteract and/or prevent the immune activation-induced behavioral deficits in mice. Effect of the PAL (0.05 mg/kg; GD 15-PND 28) in preventing reflex, sensorimotor and anxiety deficits in prenatally LPS-challenged (800 μg/kg; GD 15 and GD 17) mice was assessed at three different life stages: neonatal (PND 4–PND 14), adolescence (PND 35) and at adulthood (PND 85). LPS-induced behavioral deficits were recognizable even at neonatal and adolescence stages, though more pronounced at adulthood. In only PAL-treated group few behavioral deficits though observed both at neonatal and adult stages but less prominent than LPS group were found. PAL co-treatment prevented the abnormalities in nest-seeking behavior in neonates, anxiety abnormalities at adolescence and adulthood but not the sensorimotor impairment. The drug might have maintained the stress homeostasis to counteract the behavioral abnormalities as LPS-induced hypercorticosteronemia was prevented on PAL co-treatment. In view of the in utero exposure, comparatively low drug dose was selected. Though efficacy has been predicted, the dose was not effective to prevent all psychopathological impairments. Considering the wider objectives, it was not possible to conduct multi dose study simultaneously. Our ongoing study with higher dose may predict the effective PAL dose in prevention of psychiatric illness.

1. Introduction

Studies on animal models provide compelling support to the growing body of epidemiological evidences that the etiologies of some psychiatric illness in human are of neurodevelopmental origin. Exposure to various insults during critical period of development, including that of prenatal maternal stress and infection/immune activation alter fetal brain structure and function thereby acting as risk factors for appearance of psychosis later in life (Meyer and Feldon, 2010; Bilbo and Schwarz, 2009). Two of the well established animal models are based on prenatal maternal exposure to bacterial endotoxin lipopolysaccharide (LPS) and viral mimic polyriboinosinic–polyribocytidilic acid (polyI:C) (Baharnoori et al., 2012). Gestational immune activation alters cytokine production in the dam which through transplacental effects could affect the fetal brain to cause neuropathology and psychopathology (behavioral abnormalities) characteristics of psychosis (Miller et al., 2012; Romero et al., 2007). The immune activation reflected in neuroendocrine changes as there is a reciprocal interaction between the neuroendocrine and immune system. Cytokines produced under infection stimulate the hypothalamic–pituitary–adrenal (HPA) axis (Haddad et al., 2002; Kanczkowski et al., 2013). Systemic administration of LPS through release of cytokines elicit a prolonged activation of the HPA axis potentially stimulating the corticosterone secretion (Rothwell, 1991; Beishuizen and Thijs, 2003). Inappropriate response of the HPA axis to the cytokines might play a role in the onset of neuropathology/psychopathology. Antipsychotic drugs modulate the immune (Meyer et al., 2011) as well as neuroendocrine axis (Curtis et al., 1995). Atypical antipsychotic drugs (AAPD) such as clozapine, olanzapine and risperidone (RIS) suppressed pro-inflammatory cytokines in LPS-induced mice (Sugino et al., 2009). There are reports of prevention/reversal of behavioral abnormalities on AAPD medication in prenatally immune activated rodents through stress axis modulation (Basta-Kaim et al., 2011; Piontkewitz et al., 2011). Beside these few reports, studies on AAPD modulation of behavioral deficits on maternal immune activation are lacking.

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The present study investigated the efficacy of PAL in prevention/reversal of psychopathology in mice prenatally immune challenged with LPS. Unlike well reported study design where drug treatment was done during the asymptomatic peri-adolescence period, presently gestational intervention of the atypical antipsychotic PAL was done along with LPS exposure hypothesizing that the drug would counteract/prevent the immune activation-induced behavioral deficits in mice. Neuroprotective effect of PAL has been demonstrated in animal model of psychosis (Peng et al., 2013; Gassó et al., 2012). PAL, the 9-hydroxy metabolite of RIS, has a similar pharmacologic profile to RIS (van Beijsterveldt et al., 1994). It is an antagonist at the dopamine D_2, serotonin 5-HT_{2A}, and histaminergic H_1 receptors (Shayegan and Stahl, 2004; Kim et al., 2007). PAL, being mainly excreted via the kidneys, without requiring processing in the liver could be potential candidates for the treatment of schizophrenic patients with serious hepatic disease (Kantrowitz and Citrome, 2008). This study evaluated the effect of the drug in preventing deficits in reflex, sensorimotor and anxiety behavior, the major behavioral biomarkers of psychiatric illness. The behavioral assessment was carried out at three different stages: neonatal, adolescence and at adulthood. Maternal behavior was also assessed.

2. Materials and methods

2.1. Animals and experiment deigns

Swiss albino mice (weight: 29 ± 1 g) purchased from Indian Institute of Toxicology Research, Lucknow, India were kept in polyvinyl chloride cages ($290 \times 320 \times 390$ mm^3) in standard laboratory conditions (12 h light–dark cycle; temperature 21 ± 2 °C and humidity 55 ± 5%) with free access to mice feed and water. After 2 weeks of acclimatization, mice were kept for mating. Females with vaginal plugs were designated as on gestational day (GD) 0 and were divided into four groups (8/group). Group I/Control were given intraperitoneal injection (i.p.) of physiological saline, Group II mice received i.p. injection of LPS (800 μg/kg; *Escherichia coli* serotype 026:B6, L-2654, Sigma-Aldrich, India) at GD 15 and GD 17 and Group III received oral exposure to AAPD PAL (PAL: 0.05 mg/kg; P-0099, Sigma-Aldrich, India) from GD 15 to postnatal day (PND) 28. Group IV received LPS of the same dose as that of Group II along with oral exposure to AAPD PAL (PAL: 0.05 mg/kg; P-0099, Sigma-Aldrich, India) from GD 15 to postnatal day (PND) 28. PAL dose selected was commonly prescribed human oral dose for a 50 kg adolescent (Roenker et al., 2011). Dose was kept low to avoid the risk of fetal development related abnormalities during in utero exposure.

The maintenance and handling of the animals were done according to the guidelines of the Committee for the Purpose of Control and Supervision of Experimental Animals, Ministry of Environment and Forests, Government of India. The experimental protocols were approved by the Institutional Animal Ethical Committee of the University.

2.2. Study of maternal behavior

The maternal behaviors were assessed on PND 4 and PND 5 both in light and dark phases as per the methodology described by Leonhardt et al. (2007). All the behaviors were scored simultaneously. There are two sessions of observations in each phase; each session of 75 min with 25 observations. Mother's behaviors were assessed under two categories: behaviors related to self and behaviors related to the pups. Self-grooming, wandering (active/passive), nest-building and eating/drinking behaviors were studied to relate dam's act to self. Nursing (active or arched back nursing/passive nursing) and pup grooming behavior of dam were analyzed for assessment pup-related behavior.

2.3. Study of neonatal behavior (PND 6–14)

Behaviors were studied daily starting from PND 6 to PND 14 under three categories: reflex action, locomotion and nest-seeking behavior. All testing protocols were performed on both male and female neonates only in the light phase (09.00–16.00) by a single examiner blind to the experimental design. As there were no significant differences in testing scores between males and females, data were pooled for final analysis.

2.3.1. Reflex action

To study the various reflex action protocols developed by Fox (1965) was followed. Q2

2.3.1.1. Forelimb grasp reflex (PND 6–10). The reflex was considered fully developed when the pup was able to grasp the barrel (16-gauge needle) as it was rubbed against the palm of the forepaw.

2.3.1.2. Righting reflex (PND 6–9). The pup was placed on its back on a flat surface and the time required to turn over to original position with all four limbs on the flat surface was noted. The cut-off time was 30 s.

2.3.1.3. Cliff avoidance (PND 6–10). The pup was placed on the edge of the flat surface while its snout and forepaw were placed over the cliff (70 cm height). The time taken by the pup to turn back from the cliff to flat surface was recorded.

2.3.1.4. Negative geotactic reaction (PND 6–11). The pup was placed facing downwards on a 45° inclined surface covered with wired mesh. Each pup was given 3 min and allowed to turn off 180° toward upper end of the surface.

2.3.1.5. Auditory startle (PND 11–14). This response was considered fully developed when a pup showed whole body startle response on a sudden noise of clap occurred from approximately 10 cm distance.

2.3.1.6. Grip strength response (PND 6–13). Mouse was suspended by the forelimbs on a horizontal rod (40 cm above a thick bed of wood shavings) for minimum time of 5 s.

2.3.2. Locomotion (PND 6–10)

The test was performed as described by Altman and Sudarshan (1975). Pups were observed by an examiner blind to experimental design placing them in the center of open field (50 cm × 50 cm plywood surface subdivided into 25 squares for scoring purposes). Scoring was done based on the number of lines crossed by each pup during 3 min.

2.3.3. Nest-seeking behavior or olfactory discrimination (PND 8)

The method was modified from Antonelli et al. (2005). A rectangular polycarbonate cage used as a testing box ($290 \times 320 \times 390$ mm^3) was divided into three equal compartments by a permanent ink marker: a central arena and two side compartments. One of the side compartments had nest bedding from the test pup's home cage and the opposite side contained equal quantity of fresh clean bedding. Each pup was placed in the central arena and allowed for nest seeking. To assess nest-seeking, crossing of the line toward nest compartment with the forepaws and head plus sniffing and exploration of the nest was considered a positive score. Each pup was allowed to two trials

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