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Attenuation of neurobehavioural abnormalities by papaverine in prenatal valproic acid rat model of ASD

Kanishk Luhach [a], Giriraj T. Kulkarni [b], Vijay P. Singh [c], Bhupesh Sharma [a,d,*]

[a] Department of Pharmacology, Amity Institute of Pharmacy, Amity University Uttar Pradesh, Noida, India
[b] Amity Institute of Pharmacy, Amity University Uttar Pradesh, Noida, India
[c] CSIR-Institute of Genomics & Integrative Biology, Academy of Scientific and Innovative Research, New Delhi, India
[d] CNS and CVS Pharmacology, Conscience Research, Delhi, India

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ABSTRACT

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with complex aetiology and phenotypes. Phosphodiesterase-10A (PDE10A) inhibition has shown to provide benefits in various brain conditions. We investigated the role of a PDE10A inhibitor, papaverine on core phenotypes in prenatal-valproic acid (Pre-VPA) model of ASD. In order to identify probable mechanisms involved, the effects on several protein markers of neuronal function such as, neurogenesis-DCX, neuronal survival-BDNF, synaptic transmission-synapsin-IIa, neuronal transcription factor-pCREB, neuronal inflammation (IL-6, IL-10 and TNF-α) and neuronal oxidative stress (TBARS and GSH) were studied in frontal cortex, cerebellum, hippocampus and striatum. Pre-VPA induced impairments in social behaviour, presence of repetitive behaviour, hyper-locomotion, anxiety, and diminished nociception were studied in male Albino Wistar rats. Administration of papaverine to Pre-VPA animals resulted in improvements of social behaviour, corrected repetitive behaviour, anxiety, locomotor, and nociceptive changes. Also, papaverine resulted in a significant increase in the levels of BDNF, synapsin-IIa, DCX, pCREB, IL-10 and GSH along with significant decrease in TNF-α, IL-6 and TBARS in different brain areas of Pre-VPA group. Finally, high association between behavioural parameters and biochemical parameters was observed upon Pearson's correlation analysis. Papaverine, administration rectified core behavioural phenotype of ASD, possibly by altering protein markers associated with neuronal survival, neurogenesis, neuronal transcription factor, neuronal transmission, neuronal inflammation, and neuronal oxidative stress. Implicating PDE10A as a possible target for furthering our understanding of ASD phenotypes.

1. Introduction

Autism spectrum disorder (ASD) is a cluster of neurodevelopmental disorders. ASD is characterised by dysfunctional social interaction, communication deficits and occurrence of stereotypical or repetitive behaviour (Lai et al., 2014). Several co-morbid traits, including anxiety, seizure activity, motor abnormalities, aggressive behaviour and sleep disturbances occur with ASD (Matson and Cervantes, 2014). Pre-natal exposure towards valproic acid (VPA), results in development of core ASD like symptoms and to some extent secondary symptoms, in the male offspring by causing neural tube defects (Kumar and Sharma, 2016a; Schneider and Przewłocki, 2005). The VPA rat model is known to reduce the levels of phosphorylated – cAMP response element binding protein (pCREB), brain derived neurotropic factor (BDNF) and doublecortin (DCX) in the brains of exposed animals (Lee et al., 2016; Wu et al., 2017). Also, recent studies from our lab have indicated a significant alteration in levels of brain inflammatory cytokines (Interleukin-6 (IL-6), IL-10 and tumour necrosis factor-alpha: TNF-α) and brain oxidative stress markers (TBARS, GSH-Glutathione) in various brain regions of the VPA model of ASD (Mirza and Sharma, 2019a, 2019bbib_Mirza_and_Sharma_2019abib_Mirza_and_Sharma_2019b). So, the prenatal VPA model is a robust and validated model for induction of ASD like condition in rats (Kumar et al., 2015; Kumar and Sharma, 2016a, 2016bbib_Kumar_and_Sharma_2016bbib_Kumar_and_Sharma_2016a).

Cyclic nucleotide phosphodiesterase (PDE) are a family of enzymes responsible for degradation of cyclic nucleotides i.e. cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP)

* Corresponding author. Department of Pharmacology, Amity Institute of Pharmacy, Amity University Uttar Pradesh, Sector-125, Noida, Uttar Pradesh, India.
E-mail addresses: drbhupeshresearch@gmail.com, bsharma5@amity.edu (B. Sharma).

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