Rat Model of Autism Spectrum Disorders

Genetic Background Effects on Borna Disease Virus-Induced Developmental Brain Damage

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During the past ten years we have been characterizing the first virus-induced Autism Spectrum Disorders (ASD) model, based on Lewis rats (Lew) infected with Borna disease virus (BDV) at birth.[1] Infection of newborn rats with this persistent, RNA virus induces characteristic neuroanatomical, neurochemical, neuroimmune, and behavioral deficits without an associated cellular inflammatory response in the brain. These deficits show strong correlation with abnormalities detected in children with ASD, including neuronal cell dropout in the cerebellum and hippocampus, abnormalities in serotonin neurotransmitter systems and social (abnormal play), emotional (chronic anxiety), and cognitive (decreased spatial learning and memory) behaviors.[2–8]

Genes or genetic background influence the development of ASD or the expression of ASD symptoms in the majority of children with these disease syndromes.[9–12] However, only in a subset of patients has ASD been shown to be the result of a purely genetic disease (e.g., Rett's syndrome, Fragile X, and phenylketonuria). Therefore, it is likely that most cases of ASD are due to a complex interaction between environmental insults and the host's genetic background. Thus, we sought to use our virus-induced model of ASD to explore the effects of genetic background on expression of disease.

We studied the effects of genetic background on developmental brain injury by comparing neuroanatomical, neurochemical and behavioral disturbances in inbred Lew, inbred Fisher 344 (Fi), and outbred Sprague-Dawley (SD) rats neonatally infected with BDV. BDV-induced cerebellar hypoplasia and hippocampal dentate gyrus degeneration appeared to be more severe in Fi and was less severe in SD rats, when compared to Lew rats. In all strains, BDV produced locomotor hyperactivity, stereotypies, and disturbed emotionality when tested at postnatal day (PND) 180 in an open field test. At PND 30, infected Fi344 rats demonstrated attenuated non-play and play social activity, whereas infected Lew rats exhibited abnormally increased

non-play interaction and deficient play activity. Neonatal BDV infection differentially altered regional brain monoamine concentrations in three strains of six-month old rats. In hippocampus and cerebellum, 5-HT content was increased in Fi and Lew but not SD-infected rats. In frontal cortex, levels of 5-HT were increased only in infected Lew and remained unaffected in infected Fi and SD rats. BDV increased norepinephrine (NE) content in cerebellum and did not alter NE levels in the cortex of any strain. In the hippocampus, NE was increased in infected Fi rats only. Dopamine content in the caudate-putamen and nucleus accumbens was not changed by neonatal BDV infection in any of the strains. Thus, neonatal BDV infection induces selective neuroanatomical, neurochemical and behavior abnormalities in rats with different genetic backgrounds. These data indicate that neonatal BDV infection of the rat brain can be a valuable animal model for studying the pathogenic mechanisms of developmental brain and behavior damage.

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