Child Health Research Institute
University of Nebraska Medical Center
Children's Hospital & Medical Center

Shared susceptibility to seizures and depression in selectively bred rats

Joon Won Kang, Department of Pediatrics, University of Nebraska Medical Center and Children's Hospital & Medical Center, Omaha, NE; Department of Pediatrics, Chungnam National University Hospital, Chungnam National University College of Medicine, Daejeon, South Korea
Jaewon Jeong, College of Medicine, University Tennessee Health Science Center, Memphis, TN; Division of Pediatric Neurology, Department of Pediatrics, Emory Children's Center, Emory University School of Medicine, Atlanta, GA
Saeyoon Kim, Department of Pediatrics, Yeungnam University Hospital, Yeungnam University School of Medicine, Daegu, Korea
Jacob White, Division of Pediatric Neurology, Department of Pediatrics, Emory Children's Center, Emory University School of Medicine, Atlanta, GA
Youngjin Jung, Department of Neurosurgery, Yeungnam University Hospital, Yeungnam University School of Medicine, Daegu, Korea
Russell Sanchez, Division of Pediatric Neurology, Department of Pediatrics, Emory Children's Center, Emory University School of Medicine, Atlanta, GA
Sookyong Koh, Division of Pediatric Neurology, Department of Pediatrics, Emory Children's Center, Emory University School of Medicine, Atlanta, GA; Department of Pediatrics, University of Nebraska Medical Center and Children's Hospital & Medical Center, Omaha, NE; Children's Healthcare of Atlanta, Atlanta, GA

Depression is the most common psychiatric comorbidity in epilepsy. There is a bidirectional relationship between epilepsy and depression. A person with epilepsy has a 5-fold higher risk of developing depression, while epilepsy is about 5-fold more frequent in individuals with depression, including a family history of depression. There is a connection between these two diseases, yet the evidence for a shared pathology is unclear. We aim to characterize seizure susceptibility and age-dependent depressive-like behavior in rats selectively bred for over 70 generations for immobility in the forced swim test (FST) while also examining the expression of glia. Sprague Dawley (SD) rats from Charles River Laboratories have been selectively bred since 1987 for low activity scores (AS) in the Porsolt FST. The FST involves an animal placed in a cylindrical plexiglass tank 65 cm tall and 30 cm in diameter for 15 minutes. The amount of time an animal spends struggling/high activity is defined as all four paws vigorously moving. The amount of time an animal is an immobile/low activity is defined as no limb movement. We subtracted the two scores, and a negative activity score reflects an animal's learned helplessness, as it spent more time immobile than struggling to escape. These low-activity animals named swim low (SwLo) exhibit a robust display of learned-helplessness and have reached over 70 generations. We performed 2 experiments: (1) FST at various postnatal (P) ages: P30 (n=11), P35 (n=8), P42 (n=44) and P90-120 (n=16). (2) seizure occurrence to intraperitoneal kainic acid (KA, 20mg/kg) injection at P35. SwLo rats (n=16) were compared to random SD rats (n=16). At P30, SwLo showed positive AS similar to random control SD. At P35, SwLo started to show negative AS and spent more time immobile than active ($p<0.01$). By P90, naïve SwLo rats, without any further treatment, became nearly immobile in the FST as seen previously ($p<0.001$). GFAP stain for astrocytes and IBA-1 stain for microcytes at P37 exhibit significantly higher activation in SwLo animals than control. At P35, 90% (18/20) of SwLo experienced convulsive seizures, whereas only

45% (9/20) of SD control rats had overt seizures ($p<0.05$). Depressive behavior in SwLo rats developed over time, becoming evident by 5 weeks of age (P35). SwLo animals display signs of increased neuroinflammation by P37 in the hippocampus. At P35, these animals also exhibited increased susceptibility to KA-induced seizures.