
Symposium WA-2
Wednesday, July 26, 2006

Influence of genetic variation in serotonin transporter function on aggression and emotion; evidence from mutant mouse models

Andrew Holmes, PhD



Identifying biological mechanisms through which genes lead to individual differences in aggression and emotion is paramount to our understanding of risk for neuropsychiatric illness. An important finding has been the discovery of a genetic polymorphism in a critical regulatory molecule within the 5-HT system, the serotonin transporter (SERT), and its influence on affective traits. Rodents do not have an orthologue of the human SERT polymorphism. However, by deleting a critical region of the SERT gene via homologous recombination, mice have been engineered with a functionally inactive SERT (SERT knockout, KO). Behaviorally, SERT KO display a phenotype characterized by increased fear-, anxiety- and depression-related behaviors. Isolation-induced aggression towards a conspecific is reduced in male SERT KO and SERT heterozygous mutant mice as compared to WT controls, while non-aggressive social behaviors are normal. The neural basis of these behavioral abnormalities is yet to be fully determined. SERT KO mice have abnormal 5-HT function in brain, including increased extracellular fluid 5-HT and alterations in the density and/or function of 5-HT receptor subtypes implicated in aggression (5-HT1A, 5-HT1B, 5-HT2A, 5-HT2C). SERT KO mice also exhibit significant alterations in the morphology of neurons located in regions of the medial prefrontal cortex (infralimbic) that mediate impulse control, a major feature of aggression. SERT KO mice provide an interesting model system to study the neural and genetic factors influencing the pathophysiology of aggression and impulse control disorders.