Genetic and non-genetic animal models for Autism Spectrum Disorders

Autism spectrum disorder (ASD) is a heterogeneous group of neurobehavioral problems with genetic and environmental origins. The major neurobehavioral changes are manifested by persistent deficits in social and communication interaction, deficits in developing, understanding and maintaining relationships, as well as abnormal and fixed interests and repetitive behavior, with various degrees of severity. Symptoms must be present at early childhood and interfere with daily function. The prevalence is over 1% of children, with higher rates in males. The etiology seems to be the result of genetic and environmental interactions and may be related to epigenetic changes.

Epigenetics deals with heritable changes in gene expression (active versus inactive genes), that do not involve changes to the underlying DNA sequence. It is responsible for changes in the function/behavior of cells or organs without any change in DNA structure. In ASD, as in several other psychiatric disorders, epigenetic changes were found to be an important causative factor.

There are many human genetic diseases with autistic like behavior: i.e. fragile X, Rett syndrome ext. In addition, prenatal and early postnatal environmental exposure to drugs (i.e. valproic acid), maternal infections or chronic diseases during pregnancy (i.e.rubella, diabetes) are associated with a higher rate of ASD.

Animal models of diseases are used to understand better the etiology and the pathogenesis and help in the development of effective treatments. During the last 20 years, many genetic and non-genetic animal models with autistic like behaviors have been developed. Most models are in mice and rats, where genetic or environmental manipulations are relatively easy.

In our review (see title above), we discussed the known animal models of ASD, mostly in mice and rats, that help us to understand the etiology, pathogenesis and treatment of human ASD. Some genetic models mimic known human syndromes like fragile X, where ASD is part of the clinical picture, Rett syndrome with typical change in the gene encoding for the methyl-CpG binding protein 2 (*MECP2*) that binds to methylated-CpG dinucleotides and influences gene expression. In some models treatment abolished the ASD like symptoms. For example, knock out of the FMR1 gene in mice, which is similar to human Fragile X, causes reduced GABA ergic transmission and results in autistic like behavior. Enhancing GABAergic transmission by the GABA A receptor agonist THIP (gaboxadol) corrected many of the abnormal behavioral features of these mice.

Animal models of infection and inflammation during pregnancy may also induce autistic like behavior in the offspring. For example, infection of pregnant mice with human influenza virus may result in autistic like behavior in the offspring. Maternal prenatal immune activation was associated with changes in various interleukins in the fetal brain and autistic like behavior in the offspring.

The most common "chemical" model in rodents is the one induced by the antiepileptic drug valproic acid (VPA) administered either prenatally or early postnatally. VPA induces autism-like behaviors following exposure during different phases of fetal brain development. Various mechanisms of action of VPA have been found, and specific treatments were sometimes developed that reduced the ASD like symptoms. We have recently developed a mouse model where injection of VPA to 4 day old mouse offspring causes autism like behavior. At adulthood, the brain shows increased oxidative stress (i.e. increased free oxygen radicals that may damage lipids, proteins and DNA) and changes in the expression of some genes that are responsible for the neutralization of the excessive free oxygen radicals. As these are typical epigenetic changes, we treated the mice with the methyl donor S adenosine methionine that, as an accepted food additive is in clinical trial for several psychiatric diseases, and the autistic like behavior was almost completely abolished.

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