Journal club title – Role of neurogenesis in autism comorbid with epilepsy

Citation of article being reviewed – Bercum FM, Rodgers KM, Benison AM, Smith ZZ, Taylor J, Kornreich E, Grabenstatter HL, Dudek FE, Barth DS (2015) Maternal Stress Combined with Terbutaline Leads to Comorbid Autistic-Like Behavior and Epilepsy in a Rat Model. J Neurosci 35: 15894-15902

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Investigating neurobiological mechanisms underlying psychiatric disorders comorbid with epilepsy is one of the goals of current epilepsy research. Autism spectrum disorder (ASD) and epilepsy have a close relationship; even in individuals with ASD that do not show overt seizures, epileptiform activity suggestive of hyperexcitabilty has been routinely observed (Spence and Schneider, 2009). Genetic factors underlying ASD have been recognized, but the role of maternal factors is just beginning to be investigated. Knowledge of the latter is important because unlike genetic factors, they could be potentially reversible.

In the current Journal of Neuroscience study (Bercum et al., 2015), the authors asked whether maternal stressors are sufficient to cause ASD comorbid with epilepsy. Pregnant dams were administered foot shocks as the first stressor and terbutaline as the second - this was done to simulate the 'two hits' that together, have been suggested to precipitate the combined neurological condition of ASD and epilepsy. Individually, the stressors have been shown to produce ASD-like symptoms, but neither of them causes epilepsy. There were four groups used in this study– saline and no stress; terbutaline and no stress; saline and stress; terbutaline and stress. Once the rat pups were older, behavior and electrographic seizures were tested. A composite ASD score was used to quantify behavior and pattern recognition was used to quantify interictal spikes. Astrogliosis was also examined by glial fibrillary acidic protein (GFAP) immunohistochemistry.

All experimental animals exhibited ASD-like behavior (http://www.jneurosci.org/content/35/48/15894/F1.expansion.html). Almost one half of the 'stress and terbutaline' mice showed spontaneous recurrent seizures (http://www.jneurosci.org/content/35/48/15894/F2.expansion.html), and all rats in this group had interictal spikes (http://www.jneurosci.org/content/35/48/15894/F4.expansion.html). There was most GFAP-immunoreactivity in rats that were subject to maternal stress + terbutaline (http://www.jneurosci.org/content/35/48/15894/F5.expansion.html). Thus, the study found that when several risk factors are combined, maternal stress alone was necessary and sufficient to cause development of autism with epilepsy. Given the GFAP-immunoreactivity, the authors suggest that a mechanism that possibly could underlie this could be astrogliosis and inflammation.

ASD and epilepsy together are quite commonly seen (Brooks Kayal, 2011); and even if there are no overt seizures, the presence of epileptiform activity in ASD is not rare (Spence and Schneider, 2009). One thought in this field is that instead of ASD causing epilepsy or vice versa, it is more likely that there are common neurobiological mechanisms at play (Besag, 2015). Some mechanisms that have been suggested are abnormal neurogenesis, neural migration, programmed cell death and synapse development. Aberrant GABEergic signaling caused in part due to

abnormal GABAergic receptors (Kang and Barnes, 2013) may underlie the presence of epileptiform spikes when the two neurological conditions appear together. A promising area of research in this field is that of adult neurogenesis which has shown to contribute to the disease phenotype of both, epilepsy and ASD.

Adult born neurons in the dentate gyrus of the hippocampus may contribute to temporal lobe epilepsy. Animal models show that acute seizures can lead to an increase in rate of neurogenesis, but in the chronic phase, the neurogenic niche seems to be reduced (Blumcke et al., 2001). Seizures during the weeks and months following status epilepiticus increase progressively, and there is data that suggests that adult born granule cells might contribute to this progression (Parent et al., 1997). There is a dramatic increase in the number of adult-born neurons in the days and weeks immediately following status epilepticus (SE), and the newborn cells could contribute to epileptogenesis by increasing excitability. Some granule cells born in the days and weeks post SE may migrate to the hilus of the hippocampus instead of the granule cell layer and establish an ectopic population of hilar granule cells (hEGCs; Scharfman et al., 2000) that could create an epileptic or hyperexcitable focus. hEGCs have a pro-epileptogenic effect in a model of febrile seizures as well (Koyama et al., 2012). Another way by which abnormal postnatal neurogenesis may contribute to seizures is by the formation of hilar basal dendrites (Ribak et al., 2012) that promote excitability as these dendrites have more excitatory input. Hypertrophy (Pun et al., 2012) could have pro-epileptogenic effects as well.

There is evidence for the role of abnormal neurogenesis in ASD also. A majority of genes implicated in autism influence induction and maturation of the neuroblasts, neurite and synapse development (Casanova and Casanova, 2014). A gene known as Wdfy3 has recently been recognized as being implicated in ASD – loss of this gene leads to an enlarged cerebral cortex and abnormal neural migration similar to what is seen in children with ASD. Mouse mutants with loss of function of Wdfy3 show defects in cortical migration. (Orosco et al., 2014). Ankrd11 (Ankyrin Repeat Domain 11) is a gene that is implicated in ASD, and its role in development of the human cortex and for embryonic cell development was just revealed (Gallaghar et al., 2015). In another study with human subjects (Pramparo et al., 2015), toddlers without ASD were shown to have their total brain volume correlate with genes necessary for regulating the cell cycle. In toddlers with ASD, however, this correlation was lost suggesting a role of genes implicated in neurogenesis. Specific mice called BTBR mice show behavioral abnormalities that are similar to those found in ASD. Transplantation of mesenchymal stem cells reduced stereotypical behavior, improved social behavior and decreased cognitive rigidity in these mice and this was associated with increased neurogenesis in the hippocampus (Segal-Gavish et al., 2016). Using the same

mice, another study (Fenlon et al., 2015) showed aberrations in size, position and thickness in cortical areas in these mice, which was reminiscent of patients with ASD that can have subtle but clear and transient increases in brain size and cortical thickness.

Given the role of neurogenesis and neural migration in ASD, epilepsy and the comorbidity between these disorders, could it be that agents that increase neurogenesis might alleviate this comorbidity? Certainly, there is evidence that physical activity helps in epilepsy and environmental enrichment helps in ASD, and it is possible that the mechanism underlying is the correction of aberrant neurogenesis.

Exercise such as treadmill running decreased aggressive behavior and improved some measures of learning in autistic rats; this was associated with an increase in neurogenesis (Seo et al., 2013). In children and youth with ASD, a recent review found that exercise comprising of jogging, martial arts and horseback riding, swimming, yoga resulted in an improvement in behavioral outcomes such as cognition and social functioning (Bremer et al., 2016). The effect of exercise and environmental enrichment in epilepsy has also been shown. In a study (Lim et al., 2015), rats that were a chemoconvulsant pilocarpine were forced to run on a motorized treadmill. In contrast to controls (rats that were given pilocarpine and no exercise), it was found that rats that exercised had decreased loss of neurons in area CA1 of the hippocampus and of glutamic acid decarboxylase (GAD67) expression. In addition, it seemed as though the effects on BDNF / TrkB system were also minimized when rats were subject to exercise. Environmental enrichment, which has been shown to increase neurogenesis, has also been shown to be beneficial in animal models of epilepsy (Arida et al., 2009). In both - a model of temporal lobe epilepsy caused by status epilepticus (Zhang et al., 2015) and in a genetic model (Manno et al., 2011), environmental enrichment was shown to improve outcome on seizure frequency.

Hence, the current literature provides ample evidence that aberrant neurogenesis and neural migration may be an underlying factor behind ASD comorbid with epilepsy. Agents like exercise or environmental enrichment that that enhance neurogenesis could be tested in the model presented in the current paper (Bercum et al., 2015) to see if it alleviates ASD-like behavior, spontaneous recurrent seizures, interictal spikes and GFAP-immunoreactivity.

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