A new relationship between brain derived neurotrophic factor and inflammatory signaling

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In the October 14th edition of Science Signaling researchers at Boston University School of Medicine (BUSM), The Children's Hospital of Philadelphia/University of Pennsylvania School of Medicine and The University of Colorado Denver School of Medicine have shown that the development of epilepsy in adult rats is linked to functional changes in the expression of alpha 1 containing GABA-A receptors, the main inhibitory neurotransmitter receptor in the brain, that may be dependent upon BDNF-induced activation of the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway. Activation of the JAK/STAT pathway has previously been shown to be dependent upon cytokines and is implicated in a large number of inflammatory diseases.

The multiple subunits of the GABA-A receptor show developmental and region specific expression in the brain and produce a diverse set of functional receptor isoforms. Drs. Shelley Russek, a molecular neuroscientist/pharmacologist from Boston University School of Medicine and Dr. Amy Brooks-Kayal, a pediatric neurologist researcher from the University of Colorado Denver School of Medicine, believe that changes in inhibitory receptors in a portion of the brain known as the dentate gyrus may be crtically important to the development of temporal lobe epilepsy, the most common type of epilepsy in children and adults.

Decrease of GABA-A receptors containing alpha 1 subunits at the synapse, and increase of receptors containing alpha 4, has been associated with spontaneous seizures. The senior authors recent publication associates the marked rise in BDNF that accompanies prolonged seizures with a specific decrease in the levels of alpha 1 that is reversed upon in vivo delivery of a JAK/STAT pathway inhibitor. Alpha 1 gene regulation is dependent upon the induction of a transcriptional repressor called inducible cAMP early repressor (ICER) that binds to the alpha 1 gene in coordination with the cAMP regulatory element binding protein (CREB).

Previous research from the laboratories of Russek and Brooks-Kayal reported that BDNF increases the abundance of the alpha 4 subunit of the GABA-A receptor independent of JAK/STAT signaling and dependent upon mitogen activating protein kinases (MAPKs). Taken together with the latest results, BDNF acts through at least two distinct pathways to influence GABA-mediated inhibition in the brain. "Our identification of signaling pathways regulating the most abundant form of synaptic GABA-A receptors in the central nervous system may lead to the development of novel molecular therapies for multiple disorders including epilepsy, given that changes in their expression are also associated with alcoholism, anxiety and stress," states Dr. Russek.

An estimated 400,000 Americans have temporal lobe epilepsy – a neurological impairment that includes both psychopathology and altered brain physiology. Onset of this form of epilepsy in some adults and children can be linked to an initial brain injury or systemic infection. However multiple cases are without such associations and are not treatable by traditional medical therapies.

Source: Boston University