Scientists find seizure drug reverses cellular effects

May 28 2008

In the new research, published in the May 28, 2008 edition of *The Journal of Neuroscience*, the scientists found that gabapentin normalizes the action of certain brain cells altered by chronic alcohol abuse in an area of the brain known as the central amygdala, which plays an important role in fear- and stress-related behaviors, as well as in regulating alcohol drinking. In the study, alcohol-dependent rodents receiving gabapentin drank less alcohol.

“The results are exciting,” said Scripps Research Assistant Professor Marisa Roberto, Ph.D., who was first author of the study. “Our research shows that gabapentin not only changes the alcohol-consumption patterns of addicted rats (and not of the control group), but also may reverse some of the effects of addiction on a specific neurotransmitter in the brain.”

"This is an example of the strength of the translational approach of the Pearson Center, where the clinical uses of gabapentin led us to hypothesize that gabapentin may act to restore homeostatic dysregulation of the GABAergic system," said George Koob, Ph.D., chair of the Scripps Research Committee on the Neurobiology of Addictive Disorders and co-director of the Pearson Center for Alcoholism and Addiction Research at Scripps Research.

"Cellular and behavioral studies converged to suggest that indeed gabapentin could normalize GABAergic tone in a specific brain region known to be dysregulated in dependent animals. Such results provide a

strong rationale for translating these observations back to the clinical setting for the treatment of alcoholism."

In previous studies, gabapentin has been shown to effectively treat alcohol withdrawal and reduce alcohol consumption and cravings following detoxification in alcoholics. However, how gabapentin could act to combat alcohol dependence in the brain has been unclear. The new study sheds light on this question by detailing the action of gabapentin (known commercially as Neurontin)—a structural analogue of the inhibitory synaptic transmitter gamma aminobutyric acid (GABA)—on neural signaling in the brain.

In the new study, the scientists first tested the effects of gabapentin on the behavior of alcohol-dependent and non-dependent rats. The researchers found that alcohol-dependent rats that received gabapentin drank significantly less alcohol and demonstrated fewer anxiety-like behaviors in the face of alcohol abstinence than those who did not receive the drug. The behavior of non-dependent rats receiving gabapentin remained unaffected. These results were observed both when the rats received gabapentin systemically and when the medication was infused directly into the central amygdala region of the brain.

At the cellular level, dependence on alcohol has been associated with increased strength of inhibitory synapses (junctions between two nerve cells) in the central amygdala. In the new study, the scientists found gabapentin, like alcohol, increased the strength of these central amygdala inhibitory synapse cells from non-dependent rats, but decreased their strength in cells from alcohol-dependent rats.

Interestingly, these effects of gabapentin disappeared in the presence of a specific inhibitor of so-called GABAB receptors, indicating that gabapentin's cellular mechanisms likely involve changes in release of the transmitter GABA at the inhibitory synapses. The scientists also found

that the sensitivity of GABAB receptors decreased with alcohol dependence, suggesting a biological mechanism for the development of alcohol dependence in general and for gabapentin's contrasting effects before and after long-term alcohol exposure in particular.

The scientists plan to further explore the mechanism of action of gabapentin in the brain. In addition, clinical trials on the effectiveness of gabapentin as a treatment for alcohol dependence are currently under way at The Scripps Research Institute.

Source: Scripps Research Institute