UK scientists pave the way to tackling anxiety disorders

May 9 2011

Anxiety disorders are severely debilitating, the commonest cause of disability in the US workplace, and a source of great anguish to individuals and their families. Although fear and anxiety are part of our natural response to stress, the causes of chronic and inappropriate levels of anxiety are complex and treatments unsatisfactory.

A study by Bristol researchers, published this week in the prestigious Journal of Neuroscience, has identified a specific protein that appears to be critically important in the manifestation of anxiety-like symptoms.

Professor David Lodge, Dr Laura Ceolin, Dr Zuner Bortolotto and collaborators in the MRC Centre for Synaptic Plasticity, based in the

School of Physiology and Pharmacology, have identified a specific protein that appears to be critically important in the manifestation of anxiety-like symptoms. This could pave the way to finding new treatments for anxiety disorders.

The protein's normal function is to detect and respond to the neurotransmitter L-glutamate, one of the most important mammalian neurotransmitters - the chemicals that mediate communication between nerve cells in the brain and nervous system. There are a number of subtypes of glutamate receptor proteins. Researchers found an animal model that lacked one particular subtype, the mGlu2 receptor. Those that lacked this receptor displayed anxiety-like behaviours echoing symptoms of human anxiety disorders.

Drugs that affect several types of mGlu receptors have demonstrated some success in clinical trials of treating anxiety. These new findings are important as they allow future drug development to selectively target the mGlu2 receptor subtype, potentially increasing treatment efficacy and limiting unwanted side effects.

Moreover, mGlu receptors are also implicated in other brain diseases. Being now able to study animal models specifically lacking the mGlu2 receptor thus opens up a valuable test-bed for treatments for disorders including schizophrenia, stress, epilepsy and neuropathic pain.

David Lodge and Laura Ceolin are now collaborating with colleagues in Bristol Neuroscience to further understand the molecular biology underlying this lack of mGlu2 receptors and investigate the behavioural and therapeutic implications.

More information: Laura Ceolin, Sriharsha Kantamneni, Gareth R. I. Barker, Lydia Hanna, Laura Murray, E. Clea Warburton, Emma S. J. Robinson, James A. Monn, Stephen M. Fitzjohn, Graham L.

Collingridge, Zuner A. Bortolotto, and David Lodge (2011) The Journal of Neuroscience, 4 May 2011, 31(18):6721-6731; doi:10.1523/JNEUROSCI.0418-11.2011

Abstract

Group II metabotropic receptors (mGluRs) regulate central synaptic transmission by modulating neurotransmitter release. However, the lack of pharmacological tools differentiating between mGlu2 and mGlu3 receptors has hampered identification of the roles of these two receptor subtypes. We have used LY395756 [(1SR,2SR,4RS,5RS,6SR)-2-amino-4-methylbicyclo[3.1.0]-hexane2,6-dicarboxylic], an agonist at mGlu2 receptors and an antagonist at mGlu3 receptors in cell lines, to investigate the roles of these receptors in the temporo-ammonic path from entorhinal cortex to CA1–stratum lacunosum moleculare in rat hippocampal slices. Surprisingly, the degree of inhibition of the field EPSP induced by LY395756 fell into two distinct groups, with EC50 values of 100 μM. In “sensitive” slices, LY395756 had additive actions with a mixed mGlu2/mGlu3 agonist, DCG-IV [(2S,2′R,3′R)-2-(2′,3′-dicarboxycyclopropyl)glycine], whereas in “insensitive” slices, LY395756 reduced the effect of DCG-IV, with an IC50 of ~1 μM. This separation into sensitive and insensitive slices could be explained by LY395756 acting as an mGlu2 agonist and mGlu3 antagonist, respectively, a finding supported by data from mice lacking these receptors. The heterogeneity was correlated with differences in expression levels of mGlu2 receptors within our Wistar colony and other Wistar substrains. The initial search for a behavioral correlate indicated that rats lacking mGlu2 receptors showed anxiety-like behavior in open-field and elevated plus maze assays. These findings have implications for rat models of psychiatric disease and are especially pertinent given that mGlu2 receptors are targets for compounds under development for anxiety.

Provided by University of Bristol