

Angelman Syndrome Reviewed from a Neurophysiological Perspective. The UBE3A-GABRB3 Hypothesis

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Abstract

Angelman syndrome is characterised by neurodevelopmental impairment (with or without epileptic seizures) associated with functional deficit of the UBE3A gene. Different mechanisms of UBE3A inactivation correlate with clinical phenotypes of varying severity. However, three distinctive, highly consistent electroencephalographic rhythmic patterns can be observed in almost all patients irrespective of genotype, clinical severity and the presence or severity of a seizure disorder. Pattern I consists of runs of high amplitude 2 - 3/s rhythmic activity predominating over the frontal regions. Pattern II consists of more diffuse runs of 4 - 6/s rhythmic activity. Pattern III consists of bursts or runs of high amplitude 3 - 5/s rhythmic activity, maximal over the occipital region, sometimes containing small spikes and facilitated by eye closure. We review the available neurophysiological evidence from human and animal studies in the light of recent molecular advances. Electroencephalographic features in both patients and various mouse models point to two separable categories: characteristic rhythmic patterns, which are not related to epilepsy, and less specific epilepsy-related discharge activity. These features are consistent with a model of cortical and thalamo-cortical dysfunction resulting from dysregulation of synaptic GABAergic neurotransmission by (1) deficient recruitment of functional GABAA receptors related to reduced UBE3A gene expression in all cases and (2) decreased amount of $\beta 3$ sub-unit in these receptors related to reduced GABRB3 gene expression in deletion cases.

Key words

Angelman syndrome - EEG - UBE3A - GABAA - epilepsy - chromosome 15