Temporal and spatial mouse brain expression of cereblon, an ionic channel regulator involved in human intelligence.

Abstract
A mild form of autosomal recessive, nonsyndromal intellectual disability (ARNSID) in humans is caused by a homozygous nonsense mutation in the cereblon gene (mutCRBN). Rodent crbn protein binds to the intracellular C-terminus of the large conductance Ca(2+)-activated K(+) channel (BK(Ca)). An mRNA variant (human SITE 2 INSERT or mouse strex) of the BK(Ca) gene (KCNMA1) that is normally expressed during embryonic development is aberrantly expressed in mutCRBN human lymphoblastoid cell lines (LCLs) as compared to wild-type (wt) LCLs. The present study analyzes the temporal and spatial distribution of crbn and kcnma1 mRNAs in the mouse brain by the quantitative real-time reverse transcriptase-polymerase chain reaction (qPCR). The spatial expression pattern of endogenous and exogenous crbn proteins is characterized by immunostaining. The results show that neocortical (CTX) crbn and kcnma1 mRNA expression increases from embryonic stages to adulthood. The strex mRNA variant is >3.5-fold higher in embryos and decreases rapidly postnatally. Mouse crbn mRNA is abundant in the cerebellum (CRBM), with less expression in the CTX, hippocampus (HC), and striatum (Str) in adult mice. The intracytoplasmic distribution of endogenous crbn protein in the mouse CRBM, CTX, HC, and Str is similar to the immunostaining pattern described previously for the BK(Ca) channel. Exogenous hemagglutinin (HA) epitope-tagged human wt- and mutCRBN proteins using cDNA transfection in HEK293T cell lines showed the same intracellular expression distribution as endogenous mouse crbn protein. The results suggest that mutCRBN may cause ARNSID by disrupting the developmental regulation of BK(Ca) in brain regions that are critical for memory and learning.

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