Double mutant analysis in the mouse

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The cytosolic brain-type creatine kinase (BCK) isoform and the mitochondrial ubiquitous creatine kinase (UbCKmit) isoform are both important for the maintenance and distribution of cellular energy in neurons and astrocytes. Previously, we reported that mice deficient for BCK or UbCKmit each showed a surprisingly mild phenotype, probably due to reciprocal functional compensation by the remaining creatine kinase. Mice lacking both creatine kinase isoforms (referred to as CK--/-- double knockout mice) showed, besides a lower body weight, a more severe behavioural phenotype including impaired spatial learning in both a dry and a wet maze, reduced nestbuilding activity and diminished acoustic startle reflex responses. In contrast, their visual and motor functions, exploration behaviour, prepulse inhibition and anxiety-related responses were not changed, suggesting no global deficit in sensorimotor function, hearing or motivation. Morphological analysis of CK--/-- double knockout brains revealed a reduction of ~ 7% in wet brain weight and hippocampal size, a ~ 15% smaller regio inferior and relatively larger suprapyramidal, and intra-infra-pyramidal mossy fiber areas. These results suggest that lack of both creatine kinase isoforms, that are predominantly expressed in brain, possibly affects brain connectivity during postnatal development and renders the synaptic circuitry in adult brain less efficient in coping with sensory or cognitive activity related challenges.

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