Gdi1 knockout mice, an animal model for human X-linked non-specific mental retardation, show selective cognitive impairments and alterations of social behavior

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Mutations of the Gdi1 gene are responsible for one form of X-linked non-specific mental retardation (XLMR). Gdi1 encodes alphaGDI, one of the proteins controlling the cycling of the Rab GTPases, small G proteins involved in intracellular membrane traffic. It was suggested that the main role of alphaGDI in the brain is to interact with Rab3A and Rab3C for synaptic vesicle fusion and neurotransmitter release. However, Gdi1 is expressed early in development and is upregulated during brain development, long before synaptic transmission starts. Thus a role in neuron differentiation and/or migration is likely.
To analyze how lack of alphaGDI causes mental retardation, we generated knockout mice deficient for Gdi1. The mice were viable and fertile and no obvious phenotypic anomalies were detected. Histological analysis of brains by Nissl and Timm staining revealed as only visible effect a trilamination of the infrapyramidal mossy fibers and disorganized CA3 pyramidal cells in the hippocampus of mutants.
Gdi1 male mutant and wild type littermates were subjected to an extensive battery of behavioral tests. Mutants showed cognitive impairments in the radial maze (working memory paradigm), in conditioned taste aversion (CTA) and in trace fear conditioning. In the resident-intruder test, male mutant mice were non-aggressive and were even attacked by the intruder.
We tentatively conclude that Gdi1 deficiency induces subtle malfunctions in many brain areas. These may barely be noticed in sensorimotor systems but are evidenced in associative cortical and limbic structures including hippocampus as a decreased ability to form task-immanent short-term memories, while anomalous social behavior might reflect the same malfunction expressed in subcortical systems. Thus, Gdi1 knockout mice appear to be a relevant model to understand the function of Gdi1 in mental retardation.

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