Selective cognitive impairments and alterations of social behavior in an animal model for human X-linked non-specific mental retardation

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Mutations of the GDI1 gene cause one form of X-linked non-specific mental retardation (XLMR). GDI1 encodes alpha-GDI, one of the proteins controlling the cycling of the Rab GTPases, involved in intracellular membrane traffic, and possibly interacting with Rab3A and Rab3C for synaptic vesicle fusion and neurotransmitter release.

To analyze how lack of alpha-GDI 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 revealed as only visible effect a tri-lamination of the infrapyramidal mossy fibers and disorganized CA3 pyramidal cells in the hippocampus of mutants, possibly reflecting developmental effects of Gdi1. Male mutant and wild type littermates were subjected to an extensive battery of behavioral tests. Mutants showed impairments in the radial maze (working memory), 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..

Supported by EMBO, Swiss National Science Foundation, BIO4CT980297/BBW98.0125,
and NCCR "Neural Plasticity and Repair"