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### **Excessive UBE3A dosage impairs retinoic acid signaling and synaptic plasticity in autism spectrum disorders**

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The autism spectrum disorders (ASDs) are a collection of human neurological disorders with heterogeneous etiologies. Hyperactivity of E3 ubiquitin (Ub) ligase UBE3A, stemming from 15q11-q13 copy number variations, accounts for 1%-3% of ASD cases worldwide, but the underlying mechanisms remain incompletely characterized. Here we report that the functionality of ALDH1A2, the rate-limiting enzyme of retinoic acid (RA) synthesis, is negatively regulated by UBE3A in a ubiquitylation-dependent manner. Excessive UBE3A dosage was found to impair RA-mediated neuronal homeostatic synaptic plasticity. ASD-like symptoms were recapitulated in mice by overexpressing UBE3A in the prefrontal cortex or by administration of an ALDH1A antagonist, whereas RA supplements significantly alleviated excessive UBE3A dosage-induced ASD-like phenotypes. By identifying reduced RA signaling as an underlying mechanism in ASD phenotypes linked to UBE3A hyperactivities, our findings introduce a new vista of ASD etiology and facilitate a mode of therapeutic development against this increasingly prevalent disease.

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