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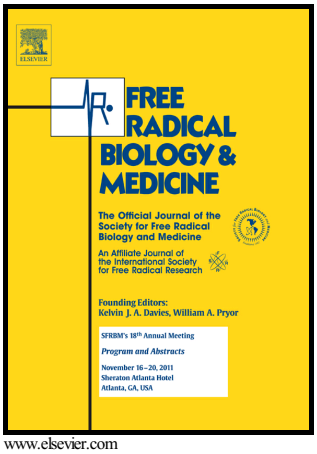

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PII: S0891-5849(17)30785-2
DOI: https://doi.org/10.1016/j.freeradbiomed.2017.10.002
Reference: FRB13470

To appear in: *Free Radical Biology and Medicine*

Received date: 31 July 2017
Revised date: 1 October 2017
Accepted date: 4 October 2017

Cite this article as: Javier Zorrilla de San Martin, Jean-Maurice Delabar, Alberto Bacci and Marie-Claude Potier, GABAergic over-inhibition, a promising hypothesis for cognitive deficits in Down syndrome, *Free Radical Biology and Medicine,* https://doi.org/10.1016/j.freeradbiomed.2017.10.002

GABAergic over-inhibition, a promising hypothesis for cognitive deficits in Down syndrome.

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Abstract

Down syndrome (DS), also known as trisomy 21, is the most common genetic cause of intellectual disability. It is also a model human disease for exploring consequences of gene dosage imbalance on complex phenotypes. Learning and memory impairments linked to intellectual disabilities in DS could result from synaptic plasticity deficits and excitatory-inhibitory alterations leading to changes in neuronal circuitry in the brain of affected individuals. Increasing number of studies in mouse and cellular models converge towards the assumption that excitatory-inhibitory imbalance occurs in DS, likely early during development. Thus increased inhibition appears to be a common trend that could explain synaptic and circuit disorganization. Interestingly using several potent pharmacological tools, preclinical studies strongly demonstrated that cognitive deficits could be restored in mouse models of DS. Clinical trials have not yet provided robust data for therapeutic application and additional studies are needed. Here we review the literature and our own published work emphasizing the over-inhibition hypothesis in DS and their links with gene dosage imbalance paving the way for future basic and clinical research.