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GABA inverse agonist restores cognitive function in Down's syndrome

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A selective GABA inverse agonist has restored cognitive function in a mouse model of Down's syndrome (DS) and has the potential to benefit humans, French researchers have revealed.

"The drug we used is a specific GABA-A ?5 inverse agonist (?5IA) that hypothetically could combat the abnormal neuronal excitation/inhibition balance associated with DS", explained lead researcher Dr Benoit Delatour from the Research Centre of the Institute of Brain and Spinal Cord (Centre de Recherche de l'Institut du Cerveau et de Moelle Epinière) at the University Pierre and Marie Curie, Paris.

"We observed that repeated and even single administrations of the ?5IA molecule can potentiate learning and memory performances in cognitively-impaired DS mice, underlying the potency of this therapeutic approach," he added.

An imbalance between inhibitory and excitatory neurotransmission has recently been proposed as a factor in the altered brain function of individuals with DS. While several studies have suggested GABA-A antagonists for restoring learning and memory performances in DS mouse models, many tend to cause seizures in animal models as well as in humans.

To investigate safer agents, the researchers used a GABA-A inverse agonist (?5IA) to specifically target the ?5 subunit of GABA-A receptors in Ts65Dn mice, a classical animal model of DS.

They found that the drug had no convulsant effects and did not promote any side effects on sensory-motor and anxiety-related behaviours. They also found no evidence of histological changes in various organ tissues following chronic administration.

To investigate what impact ?5IA had on learning and memory function, the team trained the mice in a spatial navigation (Morris water maze) task. They found that Ts65Dn mice showed a clear learning impairment that was reversed following daily treatment with ?5IA. Furthermore, an acute injection of ?5IA before acquisition was enough to alleviate recognition memory impairments in the Ts65Dn mice.

"?5IA enhanced behaviourally-evoked immediate early gene products (as markers of neuronal activation) in specific brain regions and also restored normal levels of gene expression in several disregulated pathways", explained Dr Delatour.

"Such stimulation of neuronal activity and normalisation of gene expression combined with the known effects of ?5IA on synaptic plasticity, might support the promnestic [memory enhancing] and therapeutic effects of the drug," he added.

With future human trials planned, Dr Delatour is optimistic about the impact his research could have on cognitive impairment in individuals with DS. "The results obtained by us and by others are very encouraging ... it appears that several targets in DS have been identified and can be the source of new pharmaceutical interventions. It is very likely that the combination of different emerging therapies will provide significant clinical outcomes for people with DS."

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