The Alpha5 GABAA inverse agonist treatment alleviates cognitive impairments in a Down syndrome mouse model

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Résumé

Down syndrome (DS) is a major cause of intellectual disability (ID) with a genetic origin. One of the leading hypotheses concerning ID in DS is a shift in the excitatory/inhibitory balance towards inhibition in the central nervous system. Indeed, several molecular markers specific to inhibitory neurons are increased in rodent models. Thus, modulating GABAergic activity could be a potential therapeutic approach with promising results on rodent models using a complete blocker of GABA receptors (PTZ). However, PTZ is known to increase seizure risk. To reduce this risk, we repurposed the a5IA drug developed by Merck, which is a negative allosteric modulator of GABAa5 receptors located post-synaptically after Martinotti cells. Acute injection of the molecule rescued long-term, working and spatial memory without any sign of adverse effects in our previous study in Ts65Dn mice. In this project, we explored the cognitive and motor effects of chronic administration of a5IA on the Dp(16)1Yey mice (a more complete Down syndrome model).
We evaluated working memory, learning capacity, spatial memory and motor function using the Y-maze test, the pattern dissociation paradigm, the Barnes maze and the Rotarod, respectively. Dp(16)1Yey (Dp16) mice and control (WT) littermates were injected with either a5IA or vehicle two times a week throughout the pipeline starting at 8 weeks of age and lasting 7 weeks. We evaluated the effects of a5IA on both males and females, but we did not identify significant sex-related variations.

The treatment restored the working memory in the Y-maze of Dp16-treated mice. These mice showed functioning memory with significantly more spontaneous alternations than random exploration, which was also observed in WT vehicle and WT treated but not in Dp16 vehicle mice. The molecule modulated motor performance. Dp16-vehicle mice performed significantly worse on the rotarod than WT-vehicle mice, whereas Dp16-treated mice displayed intermediate performances. WT-treated mice also displayed a slight improvement compared to WT vehicle mice. Surprisingly, the deficits observed in Dp16 vehicle mice regarding learning in the pattern dissociation task and spatial memory were not rescued by a5IA.
Altogether, a5IA restored working memory but not memory anchoring and spatial learning, despite the localisation of the a5IA targets, the GABAa5 receptors, in the hippocampus. This partial restoration of cognitive abilities might be explained by the fact that the a5IA treatment does not affect all steps in a circuit. For instance, electrophysiological dysregulation

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in Martinotti cells and parvalbumin interneurons were detected, and both cell populations modulate pyramidal neurons. Hence targeting only GABA receptors specific to Martinotti cells could be insufficient to restore all cognitive functions. Future studies will explore the activity modification of these two cell populations to understand the ID linked to DS further.

Mots-Clés: Down Syndrome, Cognition, Mouse model, GABA, Therapy