Chronic **co-modulation** of **5-HT$_4$** and **5-HT$_6$** serotonergic receptors: a new hope to treat **cognitive deficits**?

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Introduction

Current treatments for **Alzheimer's disease** only have symptomatic effects. Moreover, they often focus on a single targeted drug. Both **5-HT$_4$ and 5-HT$_6$ serotonergic receptors** (5-HT$_4$R and 5-HT$_6$R) are located in brain structures involved in memory processes, and therefore are among potent **targets of interest**. Neurochemical and behavioural studies have showed that activation of 5-HT$_4$R[1,2] and blockade of 5-HT$_6$R[3,4] improve memory processes. A therapeutic approach combining a **simultaneous modulation of these two receptors** could be an interesting and **innovative strategy**. We investigated in mice the effects of **chronic 5-HT$_4$R activation** or **chronic 5-HT$_6$R blockade** on **episodic-like memory**.

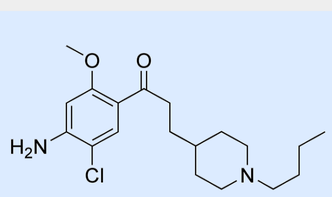
Methods

Animals

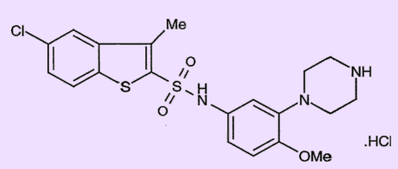
NMRI male mice

6 weeks old

Pharmacological agents



RS 67333
5-HT$_4$R partial agonist

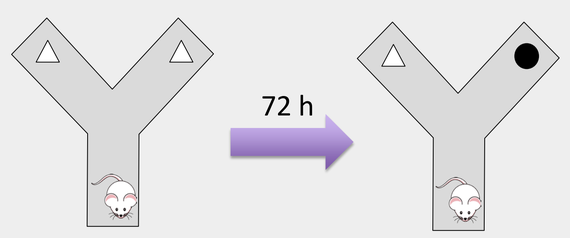


SB-271046
5-HT$_6$R antagonist

Chronic administration (1 per day, 14d)

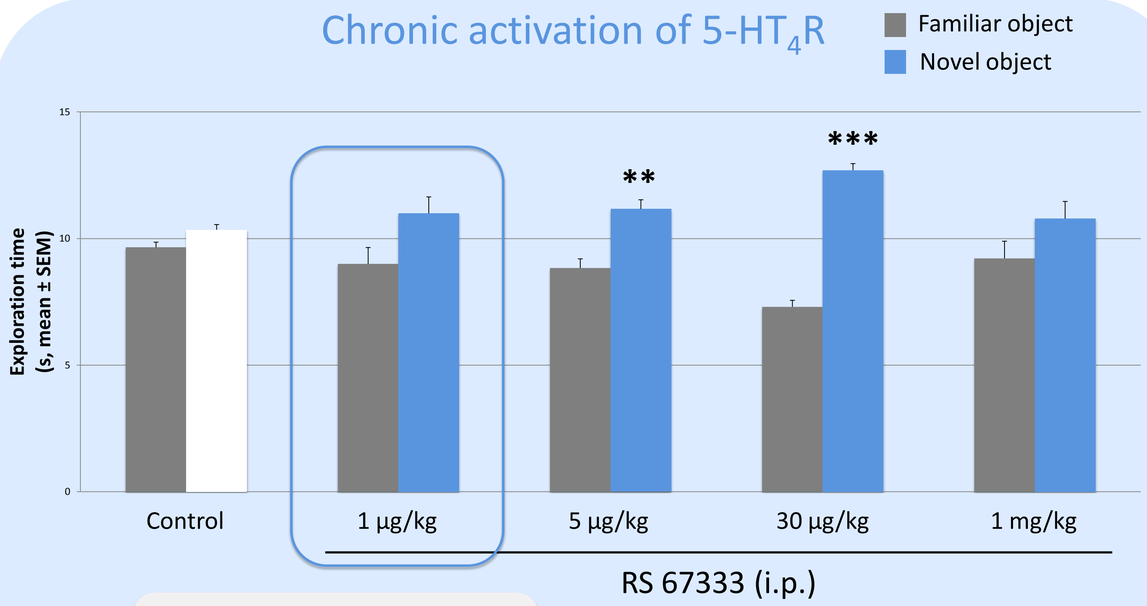
Novel object recognition test in Y-maze[5]

Criterion of exploration of both objects : 20s



Beginning the day after the last injection

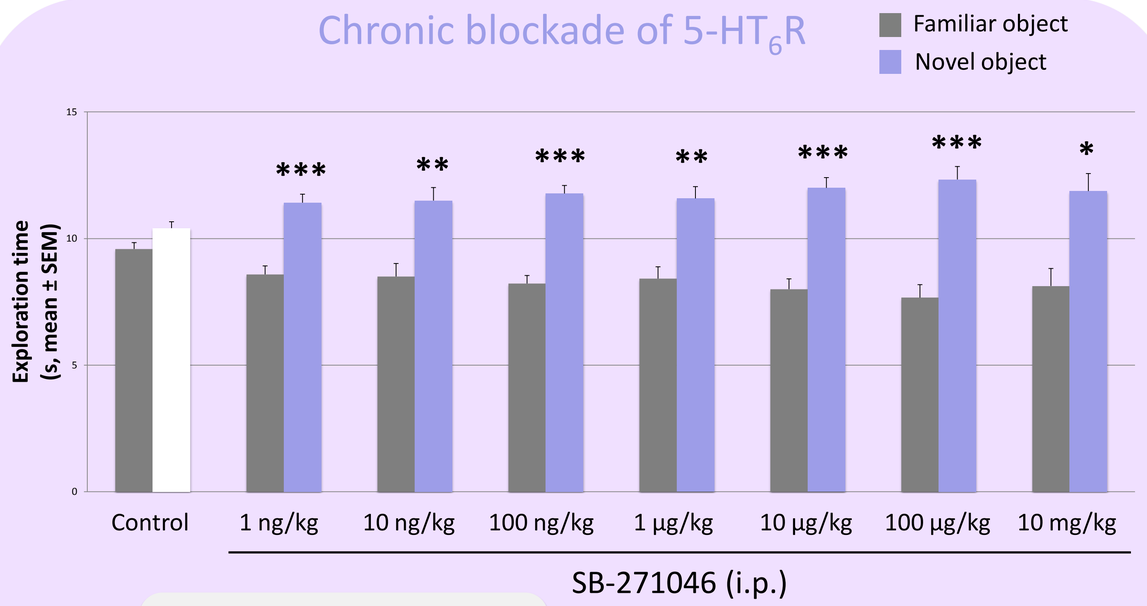
Chronic activation of 5-HT$_4$R



RS 67333 effective at 5 µg/kg
Sub-active dose = 1µg/kg

(n=12 per treatment group)
different from 10 (absence of discrimination) : ** p<0.01; *** p<0.001

Chronic blockade of 5-HT$_6$R



SB-271046 effective at 1 ng/kg
No sub-active dose

(n=12 per treatment group)
different from 10 (absence of discrimination) : * p<0.05; ** p<0.01; *** p<0.001

Discussion

We showed that **chronic activation of 5-HT$_4$R** and **chronic blockade of 5-HT$_6$R improve episodic-like memory performances at very low doses**. Along with the research of a sub-active dose of SB-271046 to perform co-modulation experiments, we will shed light on mechanisms involved in the efficiency of this chronic modulation at very low doses. To this end, we will assess the effects of a chronic modulation on the **expression of 5-HT$_4$R and 5-HT$_6$R**, on **neurogenesis** and on the liberation of **neurotransmitters,** particularly acetylcholine and glutamate. Although these further experiments are required to conclude, our findings showed that the **co-modulation of 5-HT$_4$R and 5-HT$_6$R** could represent a **novel therapeutic approach in the treatment of Alzheimer's disease**. The efficiency of very low doses used herein let foresee **very low adverse effects**, hopefully transposable to clinics.

No potential conflict of interest

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