

# Electrophysiological characterization of the fast acting antidepressant LuAA21004: key role for the serotonin (5-HT)<sub>3</sub> receptor blockade

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## Background

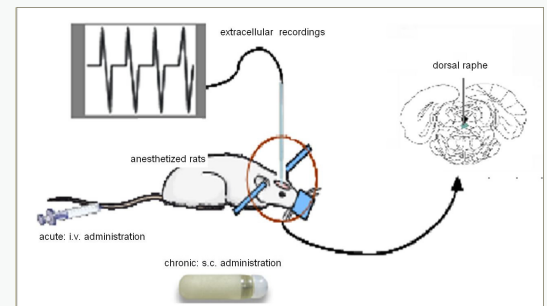
Available antidepressants induce a therapeutic response after a delay of weeks or months.

The novel putative antidepressant **LuAA21004**,

- is a mixed **5-HT<sub>3</sub> receptor antagonist**, a 5-HT<sub>1A</sub> receptor agonist and an **inhibitor of the 5-HT transporter**
- displayed anxiolytic-like and antidepressant-like activities in rodents (Moore et al., 2008).

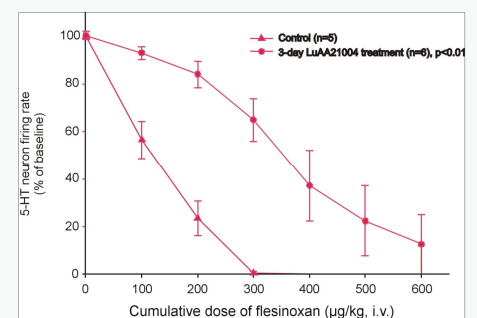
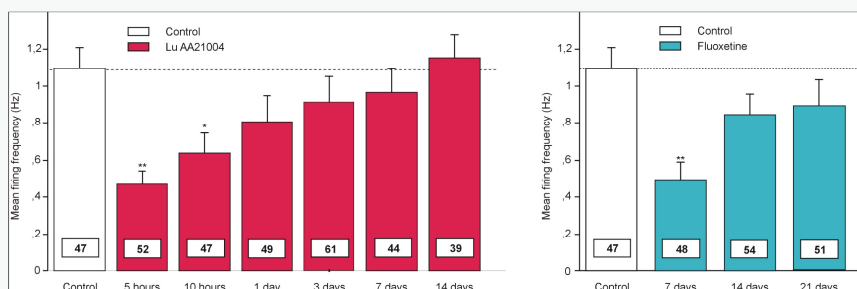
Given its original pharmacological profile, the present study was undertaken to determine whether **LuAA21004** is a putative fast acting antidepressant compared to a classical SSRI like **fluoxetine**.

## Methods

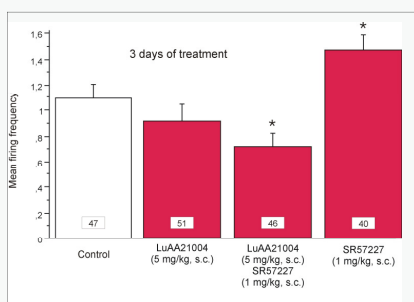
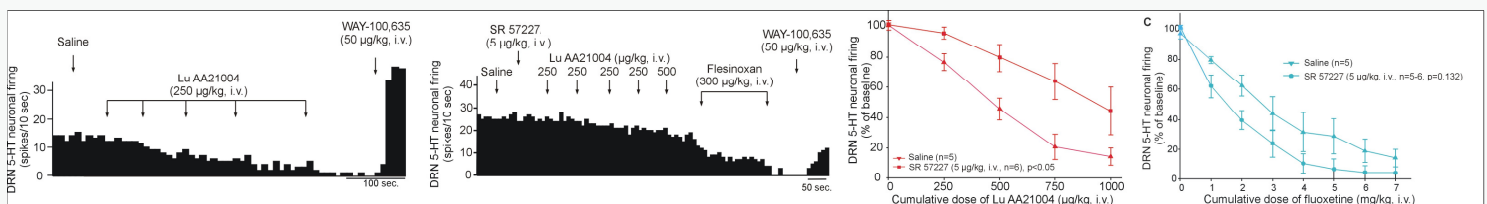


Extracellular recordings of dorsal raphe nuclei 5-HT cells

## Results



The recovery of firing was surprisingly achieved after only **1 day of treatment** with LuAA21004, whereas 14 days of treatment were necessary with fluoxetine. This fast recovery was associated with a **desensitization of 5-HT<sub>1A</sub> receptor**.



Compared to fluoxetine, LuAA21004 has the electrophysiological profile of a **fast acting antidepressant**.

Since, the selective 5-HT<sub>3</sub> receptor agonist SR 57227 seems to counteract the effect of LuAA21004 both after acute and sub-chronic administrations, we suggested that **the 5-HT<sub>3</sub> receptor antagonistic activity** of LuAA21004 might partly explain its fast acting property. This unique preclinical profile may result in a unique antidepressant profile.

Prior administration of the **5-HT<sub>3</sub> receptor agonist SR 57227** prevented the acute suppressant response of LuAA21004, whereas it had no significant effect on the suppressant response induced by fluoxetine.

After sub-chronic treatment, SR 57227 induced an increase of firing activity of 5-HT neurons while **co-administration of LuAA21004 and SR 57227 delayed the recovery of firing** observed previously after 3 days of treatment.

## Conclusion