Electrophysiological characterization of the fast acting antidepressant LuAA21004: key role for the serotonin (5-HT)₃ 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-HT₃ receptor antagonist, a 5-HT₁A 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 nucleus raphe (5-HT) cells

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-HT₁A receptor.

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

Since, the selective 5-HT₃ receptor agonist SR 57227 seems to counteract the effect of LuAA21004 both after acute and sub-chronic administrations, we suggested that the 5-HT₃ receptor antagonistic activity of LuAA21004 might partly explain its fast acting property. This unique preclinical profile may result in a unique antidepressant profile.

Conclusion

Prior administration of the 5-HT₃ 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.


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