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# P.2.e. Mood disorders and treatment – Treatment (basic)

## P.2.e.001 Single dose vortioxetine or ketamine but not fluoxetine increases expression of neuroplasticity related genes in the rat prefrontal cortex

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**Rationale:** Vortioxetine (Lu AA21004) and ketamine are two investigational drugs with antidepressant and pharmacological characteristics that may differentiate them from current antidepressants.

The investigational antidepressant vortioxetine has a multimodal mechanism of action, modulating two protein classes: 5-hydroxytryptamine (5-HT; serotonin) receptors and the 5-HT transporter (SERT). In cell studies, vortioxetine is a 5-$HT_3$, 5-$HT_7$ and 5-$HT_{1D}$ receptor antagonist, 5-$HT_{1B}$ receptor partial agonist, 5-$HT_{1A}$ receptor agonist, and SERT inhibitor. In clinical trials, vortioxetine has been shown to significantly improve depression symptoms and is generally well-tolerated [1]. Furthermore, preclinical data suggests that vortioxetine's activity at receptors may enhance memory function [2]. Ketamine, a non-competitive NMDA receptor antagonist, has been shown to induce a rapid (within 2 hours) and sustained (1 week) antidepressant effect in treatment-resistant patients and in preclinical models [3]. Major depressive disorder is associated with a smaller size and density of neurons and loss of glial cells, dendritic spines, and dendrites in the prefrontal cortex and hippocampus. The clinical efficacy of antidepressants may involve modulation of dendritic spine density and synaptic contacts, as well as neurogenesis in the hippocampus and prefrontal cortex, as the basis for the restoration of behavioral homeostasis. Furthermore, glutamatergic signaling has a central role in the regulation of neuroplasticity in these brain areas. Here we investigate the effect of ketamine and vortioxetine on neuroplasticity at the gene expression level.

**Methods:** Male Sprague-Dawley rats received one i.p. injection with fluoxetine (10 mg/kg), ketamine (15 mg/kg), or vortioxetine (10 mg/kg) 2, 8, 12, or 27 hours prior to euthanasia and collection of the prefrontal cortex and hippocampus. The messenger RNA (mRNA) levels of genes involved in dendritic spine density regulation and glutamatergic signaling were measured by quantitative real-time polymerase chain reaction.

**Results:** No differences between treatment groups were detected 2 hours after treatment. 8 hours after treatment, vortioxetine increased prefrontal cortical mRNA levels of the mammalian target of rapamycin (mTOR, mediator of synaptic plasticity; 131±4.8%), spinophilin (dendritic spine density marker; 180±25%), metabotropic glutamate receptor 1 (mGluR1; 217±20%), HOMER3 (postsynaptic density scaffolding protein family anchoring mGluR1/5; 193±15%), and protein kinase C α (intracellular effector activated by mGluR1/5; 140±12%) significantly compared to vehicle controls. At the same post-treatment time, ketamine produced a significant increase of mGluR1 (175±20%) and HOMER1 (127±5%) transcript expression compared to vehicle controls. Acute fluoxetine treatment did not produce any differences for any of the investigated genes. mRNA levels had returned to baseline for all treatments 12 and 27 hours following injection. No changes were found for the above-mentioned genes in the hippocampus.

**Conclusions:** Acute vortioxetine and ketamine induced a transient increase in the expression of genes involved in neuroplasticity in the prefrontal cortex. These data indicate modulation of dendritic spine density and metabotropic glutamatergic signaling. This may play a role in the therapeutic effects of these investigational antidepressants. The fact that the SSRI fluoxetine did not produce any changes suggests that vortioxetine's effect on gene expression may be mediated by its direct pharmacological actions at serotonergic receptors, rather than by inhibition of serotonin re-uptake.

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## P.2.e.002 Vortioxetine (Lu AA21004), a multimodal antidepressant: differentiation from current antidepressants in animal models of depression

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**Purpose:** Whereas the majority of currently used antidepressants mediate their therapeutic effects through inhibition of monoamine transporters, vortioxetine mediates its effects through modulation of 5-HT receptors and inhibition of the 5-HT transporter (SERT). Vortioxetine (Lu AA21004) is a 5-$HT_3$, 5-$HT_7$ and 5-$HT_{1D}$ receptor antagonist, 5-$HT_{1B}$ receptor partial agonist, 5-$HT_{1A}$ receptor agonist and inhibitor of the SERT in vitro [1,2]. Analyses of ex vivo autoradiography studies of target vs. dose relation in rodents and SERT occupancy studies from human PET studies support a dose dependent occupancy of these targets at therapeutic doses of vortioxetine [1,2].

Here we compare vortioxetine to SSRI (selective serotonin reuptake inhibitor) and SNRI (serotonin norepinephrine [NE]