PSG recordings were performed on the pre-dose night and on nights 1 and 3 of dosing in each period and were scored manually by an expert scorer blind to treatment, using standard methods. Blood samples were obtained for pharmacokinetic (PK) analysis. The plasma concentrations of vortioxetine and paroxetine during the PSG measurement were used to estimate SERT occupancies using published relationships between plasma concentration and SERT occupancy in healthy subjects [2,3].

Results: In the pharmacodynamic (PD) analysis both drugs suppressed REM sleep on Day 3. All 3 active treatments statistically significantly ($p < 0.0001$) increased REM onset latency (ROL) and decreased time in REM sleep (TREM). There was no obvious placebo effect on any of the PSG parameters. In the PK/PD analysis using an Emax model, significant relationships were found between REM onset latency (ROL) and vortioxetine/paroxetine exposure, and between time in REM sleep (TREM) and vortioxetine/paroxetine exposure. The relation between REM suppression parameters and SERT occupancy was significantly different between vortioxetine and paroxetine, despite the same SERT occupancy. At a given SERT occupancy, vortioxetine seemed to affect REM sleep to a lesser degree than paroxetine. This indicates that vortioxetine has a different clinical pharmacological profile than an SSRI.

Conclusion: By overlaying the estimated SERT occupancy and the effect on REM onset latency as functions of exposure to vortioxetine or paroxetine, the effects on REM suppression were clearly separated, indicating that vortioxetine and paroxetine have different pharmacological profiles in the human brain.

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P.1.g.014 Vortioxetine, a novel multimodal antidepressant, modulates GABA and glutamate neurotransmission via serotonergic mechanisms

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Purpose: Vortioxetine (Lu AA21004), an investigational multimodal antidepressant, acts as an antagonist at 5-HT$_3$, 5-HT$_7$ and 5-HT$_{1D}$ receptors, a partial agonist at 5-HT$_{1B}$ receptors, an agonist at 5-HT$_{1A}$ receptors and an inhibitor of the 5-HT transporter in recombinant cell lines [1,2].

Previous research demonstrates that vortioxetine has antidepressant activity and improves cognitive function as shown in behavioral models.

Published studies using selective ligands suggest that some of vortioxetine's receptor mechanisms can potentially modulate gamma-aminobutyric acid (GABA)ergic and glutamatergic neurotransmission. 5-HT$_3$ receptors are nearly exclusively expressed on GABA neurons, and 5-HT$_3$ receptor stimulation facilitates GABAergic neurotransmission, which may modulate glutamatergic neurotransmission downstream. 5-HT$_{1A}$ receptors also modulate GABAergic and glutamatergic neurotransmission. Here we examine experiments that suggest a portion of vortioxetine's effects may be mediated by effects on GABAergic and glutamatergic neurotransmission.

Methods: Executive function was evaluated in rats administered the NMDA receptor antagonist phencyclidine (5 mg/kg, b.i.d) for 7 days and acute vortioxetine was tested in the attentional set-shifting test (AST) after a 7-day washout period. The effects of vortioxetine on stress-induced reductions in hippocampal long-term potentiation (LTP) were examined in anesthetized male rats that had been exposed to an elevated platform for 30 min. In female rats, memory function was evaluated using the novel object recognition test (NOR) after serotonin depletion using 4-chloro-DL-phenylalanine methyl ester HCl (PCPA; 86 mg/kg/day, s.c., 4 days). Vortioxetine, the 5-HT$_3$ receptor antagonist ondansetron, or the 5-HT$_{1A}$ receptor agonist flesinoxan was administered 1hr before evaluation in NOR. Depression-like behavior was evaluated using the forced swim test (FST) in a progesterone-withdrawal (PWD) model, where female rats were administered progesterone (30 mg/kg in oil) on a 5d on, 2d off schedule for 3 weeks. Rats were tested 48hr after the final progesterone administration. Subacute vortioxetine, fluoxetine, duloxetine, or amitriptyline dosing and acute administration of ondansetron or flesinoxan were evaluated in the PWD model.

Results: In the AST, subchronic phencyclidine significantly impaired performance during the extradimensional shift (ED) and extradimensional reversal discriminations, and vortioxetine reversed these impairments at 3 and 10 mg/kg. Acute stress due to elevated platform exposure significantly reduced hippocampal LTP, which was reversed by acute 10 mg/kg vortioxetine. PCPA treatment induced profound deficits in NOR performance that were reversed by acute vortioxetine treatment above 0.1 mg/kg, as well as by ondanstron at 3 and 300 ug/kg or flesinoxan at 1 mg/kg. PWD, which induces alterations in GABAergic neurotransmission, caused a depression-like phenotype in the FST that was reversed by subacute vortioxetine or amitripyline but not fluoxetine or duloxetine.

Acute administration of ondansetron or flesinoxan significantly reduced immobility time in PWD rats.

Conclusions: The ability of vortioxetine to reverse phencyclidine-induced impairments in the AST, as well as acute stress-induced impairments in hippocampal LTP, supports the hypothesis that vortioxetine can modulate glutamatergic neurotransmission.

This idea is further supported by a putative role for 5-HT$_3$ and 5-HT$_{1A}$ receptors, both of which can modulate GABAergic and glutamatergic neurotransmission, in vortioxetine's effects in the PCPA and PWD models.

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P.1.g.015 The role of valproic acid and levodopa on oxidative stress in a 6-hydroxydopamine lesioned rat model of Parkinson's disease

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Parkinson's disease is a neurodegenerative disorder characterized by progressive loss of dopaminergic neurons in substantia nigra pars compacta. It affects 1% of the population over 60 years old. Oxidative stress has been strongly implicated in the degeneration of the dopaminergic neurons in Parkinson's disease and numerous studies have been conducted using antioxidants that diminish oxidative stress and decrease neuronal death. Valproic acid (VPA) has been studied for its neuroprotective effects by researchers as well [1]. The aim of this study is to investigate the effects of VPA alone or in combination with classical therapeutic agent levodopa on oxidative stress parameters in a rat model of Parkinson's disease.

Adult male Wistar rats were randomly divided into 7 groups: Sham operated (S), sham operated and VPA treated (SV), sham operated and levodopa treated (SL), nigrally 6-hydroxydopamine (6-OHDA) injected (PD), nigrally 6-OHDA injected and VPA treated (PV), nigrally 6-OHDA injected and levodopa treated (PL), nigrally 6-OHDA injected and VPA and levodopa treated (PVL). They were stereotaxically injected either with 6-OHDA (8μg/2μL) or saline to the substantia nigra using the following coordinates: AP:-4.8 from the bregma, L:-1.8 from the midline, V:-8.2 from the skull. After 10 days, all animals were evaluated for apomorphine (0.5 mg/kg sc) induced rotation test for the verification of the disease model.

Animals were treated with saline, 300 mg/kg VPA or 10 mg/kg levodopa (in combination with 2 mg/kg benserazide hydrochloride) ip for 10 days. After this period, all animals were decapitated and the substantia nigra of their brains were sectioned and analyzed for tyrosine hydroxylase positive neurons. The malondialdehyde levels (MDA) and activities of superoxide dismutase (SOD) [2] and glutathione S-transferase (GST) [3] were measured spectrophotometrically in the left frontoparietal part of the brain tissue including striatum. One way Anova followed by LSD post-hoc test was used for statistical analysis.

MDA level was higher in the PD group compared with the sham operated group. In PV, PL and PVL groups, on the other hand, MDA levels decreased as compared with the PD group ($p < 0.001$, $p < 0.01$, $p < 0.01$ respectively). Both SOD and GST activities decreased in the PD rats compared with the sham operated group ($p < 0.01$ and $p < 0.05$ respectively). The activity of SOD increased in PV, PL and PVL groups as compared with the PD group ($p < 0.01$, $p < 0.05$, $p < 0.05$ respectively).

Furthermore, the GST activity increased in PV group compared with the PD group ($p < 0.01$).

Oxidative stress is a significant component of Parkinson's disease. In our study, we have found that valproic acid and levodopa ameliorated 6-OHDA induced oxidative stress.

This study was approved by the Ethical Committee of Yeditepe University Experimental Research Center and the use of animals was in compliance with US National Institutes of Health Guide for Care and Use of Laboratory Animals.

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P.1.g.016 Effects of tianeptine on mammalian target of rapamycin (mTOR) signaling in rat hippocampal neurons

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Background: Recent studies have demonstrated that antidepressant effect of N-Methyl-D-aspartate (NMDA) antagonist ketamine activates rapidly the mammalian target of rapamycin (mTOR) pathway and increase synaptic proteins. mTOR is a protein kinase involved in the regulation of translation initiation and protein synthesis required for synaptic plasticity. Recent studies suggest that mTOR activation is required for antidepressant action. However, the mTOR signaling underlying antidepressant drugs action has not been investigated. Many studies suggest that tianeptine regulates hippocampal plasticity including neurogenesis and up-regulation of BDNF.

Objectives: The aim of the present study was to determine whether alterations in mTOR signaling were observed following treatment with tianeptine. Additionally, we investigate whether this drug affect the synaptic proteins and neurite outgrowth via mTOR signaling.

Methods: Primary cultures of hippocampal neurons were prepared from fetal brains (embryonic day 17; E17) obtain from Sprague–Dawley rats in a manner similar to that developed by Kaech and Banker. Tianeptine (10 mM) was completely dissolved in dimethyl sulfoxide (DMSO). The solutions were diluted to various concentrations (final concentration of 1% DMSO) with neurobasal medium before use. For purposes of western blotting and neurite assay, cells were cultured for 4 days and 5 days, respectively, with tianeptine (50 and 100 μM). Control cells were cultured without tianeptine under the B27-deprived condition (for western blotting) or normal condition (for dendrite outgrowth aasay). Using Western blotting, we measured changes in the phosphorylation of mTOR, its well-known downstream regulators [eukaryotic initiation factor 4E (eIF4E)-binding protein-1 (4E-BP-1) and p70S6 kinase (p70S6K)], and its upstream regulators [Akt and extracellular signal-regulated kinase (ERK)] under toxic conditions induced by B27 deprivation in rat hippocampal neuronal cultures. Dendritic outgrowth of hippocampal neurons was determined by dendrite outgrowth aasay. Dendrites were