In this review, we present a clinical case of a women with 55 years old, with suspicion of bipolar disorder, started therapeutic with VPA and after developed a few months a neurological deterioration with lethargy, muscle rigidity, ataxia, distal tremor, and difficulty walking. After withdraw of the VPA, we watched a resolution of the symptoms. Through a basic review of literature, we aim to summarize the current knowledge on VIE, including its clinical presentation, diagnosis, and management. VIE usually occurs within the first few weeks of VPA treatment, although it can also develop after long-term therapy or dose escalation. The clinical manifestations of VIE are variable and depend on the severity of the encephalopathy. Mild cases may present with subtle symptoms, such as irritability, while severe cases may result in coma and death. VIE can occur in patients with no prior history of neurological or psychiatric disorders, and there is no apparent correlation between VIE and VPA serum levels.

The diagnosis of VIE is primarily clinical and based on the presence of characteristic symptoms and signs, as well as the exclusion of other possible causes of encephalopathy. Electroencephalography (EEG) and brain imaging studies, such as magnetic resonance imaging (MRI) and computed tomography (CT), can be helpful in supporting the diagnosis and ruling out other potential etiologies. However, these tests are often non-specific and may not show any abnormalities.

The management of VIE involves the discontinuation of VPA and the supportive treatment of the patient's symptoms. Seizures should be treated with appropriate antiepileptic drugs, and patients with severe encephalopathy may require mechanical ventilation and intensive care support. Although there is no specific antidote for VIE, several pharmacological agents, such as benzodiazepines, barbiturates, and propofol, can be used to control agitation and seizures. Additionally, some studies have suggested the potential benefit of antioxidants and neuroprotective agents in the management of VIE, although further research is needed to confirm these findings.

In conclusion, VIE is a rare but serious adverse event associated with VPA therapy. Clinicians should be aware of the potential risk of VIE and consider it in the differential diagnosis of patients presenting with encephalopathy while on VPA treatment. Early recognition and prompt discontinuation of VPA are essential for the management of VIE, and supportive treatment should be initiated as needed to control seizures and manage the patient's symptoms. Further research is needed to better understand the pathophysiology of VIE and identify effective treatments for this condition.

No conflict of interest

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VORTIOXETINE ATTENUATES NEUROINFLAMMATION BY MODULATING THE NOD-LIKE RECEPTOR FAMILY PYRIN DOMAIN CONTAINING 3 INFLAMMASOME ACTIVATION IN MICROGLIA: IMPLICATIONS FOR COGNITIVE FUNCTION

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BACKGROUND: Vortioxetine (VTX) is a multimodal antidepressant with an extensive pharmacological profile that includes modulation of various neurotransmitter systems, neuroprotective activity, and beneficial effects on cognitive functions. Recent research has revealed a novel aspect of VTX's activity - its anti-inflammatory effects - that suggests an intriguing molecular mechanism may underpin its therapeutic benefits. Neuroinflammation, dysfunctional neurogenesis and neurotransmission, and dysregulation of the hypothalamus–pituitary–adrenal (HPA) axis are all pivotal in the onset and progression of depression. One particular immune-inflammatory pathway overactivated in brain disorders is the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, a multiprotein complex. This complex's activation is mediated by NF-kB and reactive oxygen species (ROS) signalling pathways, leading to caspase-1-dependent release of the proinflammatory cytokines, IL-1β and IL-18. Mounting evidence implicates NLRP3 inflammasome in neuroinflammation-related disorders, with its activation associated with cognitive function impairment. Of note, microglia, the resident immune cells crucial for brain plasticity, express high levels of the NLRP3-inflammasome components. Our initial findings indicate that VTX exerts a region-dependent modulatory effect on the NLRP3-inflammasome system in a LPS-induced memory impairment in vivo model. Furthermore, VTX's ability to modulate immune response suggests that microglia could be a direct target of the drug.

AIM: In light of the compelling evidence surrounding the role of the NLRP3 inflammasome in cognitive dysfunctions and the recent discovery of VTX's anti-inflammatory activity, we aimed to investigate the molecular effects induced by VTX pre-treatment in the presence or absence of the inflammasome-inducer LPS in a well-established in vitro model of mouse microglia: BV2 cells.

METHODS: To dissect the influence of VTX pre-treatment (24h) on the NLRP3 inflammasome signaling pathway and microglial polarization, we analyzed gene and protein expression in BV2 cells stimulated with LPS or vehicle for 6h. We also scrutinized the activation/translocation of NF-kB and ROS release under these conditions. We applied one-way or two-way ANOVA followed by Tukey's post hoc test for statistical analysis based on the experimental design.

RESULTS: Our data demonstrate that short-term exposure to LPS significantly induces the activation/translocation of NF-kB signaling and ROS release in BV2 cells. We observed a time-dependent transcriptional upregulation of the inflammasome complex, IL-1β and IL-18, and microglial pro-inflammatory targets post-LPS stimulation, alongside a downregulation of the anti-inflammatory factors. Interestingly, a pre-treatment with VTX (10 nM) for 24h effectively modulated the LPS-induced NF-kB translocation and ROS production compared to control cells. Cells pre-treated with VTX exhibited lower levels of LPS-induced NLRP3 inflammasome- and microglia pro-inflammatory-related targets. However, VTX did not influence the expression of anti-inflammatory factors in both unstimulated and LPS-stimulated BV2 cells.

CONCLUSIONS: Our findings reinforce the emerging evidence that supports VTX's anti-inflammatory activity. This activity is mediated via modulation of the inflammasome signaling pathway, which plays a pivotal role in the inflammatory response of microglia cells.

Conflict of interest:

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REPEATED, 4-WEEK DOSING OF CPL500036, A NOVEL PHOSPHODIESTERASE 10A INHIBITOR, DOES NOT INDUCE TOLERANCE TO ITS ANTIPSYCHOTIC-LIKE ACTION

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Background: The tolerance to neuroleptics' treatment is a well-established phenomenon and remains a challenge in patient care. Phosphodiesterase 10A (PDE10A) inhibitors are a new class of potential antipsychotics currently undergoing clinical investigation in schizophrenia and L-DOPA induced dyskinesias in course of Parkinson's disease. PDE10A is highly enriched in the striatum, in medium spiny neurons, where it controls intracellular cAMP and cGMP levels that are dependent on dopamine signaling. In the course of preclinical development CPL500036, a novel PDE10A inhibitor, proved to be effective in several animal models of psychotic and neuromotor disorders. However, the tolerance development to its antipsychotic and sedative action remains unknown.

Methods: Behavioral locomotor activity experiments were conducted on male Sprague-Dawley rats (Charles River, Germany). Animals were allocated into four treatment groups (8/group): CPL500036 (0.6 mg/kg), phencyclidine (PCP) (5mg/kg), CPL500036 + PCP and its vehicles. The animals were tested at 1, 7, 14 and 28 days following CPL500036 administration and both spontaneous and PCP-induced locomotor activity was measured. Three hours post the last drug treatment on 1st and 28th day animals were euthanized and total RNA from the striatum and cortex was isolated. Evaluation of immediate early genes expression and D1 and D2 pathways activity was assessed using quantitative Real-time PCR method. Mdh1 and b2m were used as endogenous gene references. Statistical