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Valproic Acid in Parkinson's Disease: A Friend or Foe?

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There have been several reports of Parkinson's disease like symptoms being a side effect of Valproic Acid use. Valproic Acid is a drug prescribed for Epileptic seizures and also as a mood stabilizer. Despite the said reports of Parkinson's like side effects, several other studies had shown it to in fact be neuroprotective and perhaps therapeutic against PD in vivo. This review will center around these few studies, bring their results and ask for more experimentation to solve this issue of whether Valproic Acid triggers Parkinson's or perhaps triggers a healing from it. I would hypothesize in this essay that perhaps the supposed PD-like symptoms from VA use are on the other side of the spectrum, for example that PD tremor is being countered by Valproic Acid stiffness which puts an emphasis on its ideal dosage.

Valproic Acid role in Parkinson's is not yet decided. Initial reports show Parkinson's disease (PD)-like symptoms as a result of Valproic Acid use [1, 2] but other studies, done mostly in vivo show it to actually be neuroprotective against PD with the induced Parkinson's like symptoms perhaps show the other side of the spectrum of PD symptoms, causing stiffness where PD causes tremor and perhaps show a possible therapeutic role for Valproic Acid (VA, VPA) in the pathology of Parkinson's disease.

Valproic acid, formally 2-propylpentanoic acid, is a low–molecular weight branched-chain fatty acid. It is a derivative of valeric (pentanoic) acid1, which occurs naturally in valerian (Valeriana officinalis), an Eastern Hemisphere flowering plant. It's prescribed to seizures and also to montal health issues. Parkinson's disease doesn't include seizures but includes tremors and the death of dopaminergic neurons in the substantia nigra pars compacta, Dopaminergic cell death that could perhaps be combatted by VA, thus also showing its potential as a mental illness drug. "Valproic Acid Protects Primary Dopamine Neurons from MPP+-Induced Neurotoxicity: Involvement of GSK3β Phosphorylation by Akt and ERK through the Mitochondrial Intrinsic Apoptotic Pathway"[3] is the title of the first study we'll review, by Zhang and co. From their abstract; "The goal of the present study was to confirm VPA's dose-dependent neuroprotective propensities in the MPP+ model of PD in primary dopamine (DA) neurons and to investigate the underlying molecular mechanisms using specific mitogen-activated protein kinases (MAPKs) and phosphatidylinositol 3-kinase- (PI3K-) Akt signaling inhibitors." They proceed to their results: "VPA reversed MPP+-induced mitochondrial apoptosis and counteracted MPP+-induced extracellular signal-regulated kinase (ERK) and Akt repression and inhibited glycogen synthase kinase 3β (GSK3β) activation through induction of GSK3β phosphorylation". Their conclusions: "VPA may be a promising therapeutic candidate for clinical treatment of PD.". [3]
"Valproic Acid Neuroprotection in the 6-OHDA Model of Parkinson's Disease Is Possibly Related to Its Anti-Inflammatory and HDAC Inhibitory Properties" report XImenes and co. [4] First, they share their methods: "The objectives were to study the neuroprotective properties of VA in a model of Parkinson's disease, consisting in the unilateral striatal injection of the neurotoxin 6-OHDA. For that, male Wistar rats (250 g) were divided into the groups: sham-operated (SO), untreated 6-OHDA-lesioned, and 6-OHDA-lesioned treated with VA (25 or

50 mg/kg). Oral treatments started 24 h after the stereotaxic surgery and continued daily for 2 weeks, when the animals were subjected to behavioral evaluations (apomorphine-induced rotations and open-field tests). Then, they were sacrificed and had their mesencephalon, striatum, and hippocampus dissected for neurochemical (DA and DOPAC determinations), histological (Fluoro-Jade staining), and immunohistochemistry evaluations (TH, OX-42, GFAP, TNF-alpha, and HDAC)" Then they proceed to the results: "The results showed that VA partly reversed behavioral and neurochemical alterations observed in the untreated 6-OHDA-lesioned rats. Besides, VA also decreased neuron degeneration in the striatum and reversed the TH depletion observed in the mesencephalon of the untreated 6-OHDA groups. This neurotoxin increased the OX-42 and GFAP immunoreactivities in the mesencephalon, indicating increased microglia and astrocyte reactivities, respectively, which were reversed by VA. In addition, the immunostainings for TNF-alpha and HDAC demonstrated in the untreated 6-OHDA-lesioned rats were also decreased after VA treatments. These results were observed not only in the CA1 and CA3 subfields of the hippocampus, but also in the temporal cortex". [4] They conclude by saying their results "strongly suggest that VA is a potential candidate to be included in translational studies for the treatment of neurodegenerative diseases as PD."[4]

Ching Long et al. in their report "Valproate is protective against 6-OHDA-induced dopaminergic neurodegeneration in rodent midbrain: A potential role of BDNF up-regulation" [5] share their results: "6-OHDA injection showed significant and dose-dependent damage of dopaminergic neurons and decrease of striatal dopamine content. Rats in the VPA-treated group were markedly protected from the loss of dopaminergic neurons and showed improvements in motor performance, compared to the control group at the moderate 6-OHDA dose (10 μg). VPA-treated rats also showed significantly increased brain-derived neurotrophic factor (BDNF) levels in the striatum and substantia nigra compared to the levels in control animals."[5]

Another study along the same lines is that of Harrison and co. [6] Their "key results": "Despite producing a distinct pattern of structural re-modelling in the healthy and lactacystin-lesioned brain, delayed-start valproate administration induced dose-dependent neuroprotection/restoration against lactacystin neurotoxicity, characterized by motor deficit alleviation, attenuation of morphological brain changes and restoration of dopaminergic neurons in the substantia nigra." [6]

Kim et al. report: "To address this question, we administered VPA in LRRK2 R1441G transgenic mice to determine whether VPA affects 1) histone acetylation and HDAC expression, 2) dopaminergic neuron survival, 3) inflammatory responses, 4) motor or non-motor symptoms. As results, VPA administration increased histone acetylation level and the number of tyrosine hydroxylase (TH) positive neurons in substantia nigra of LRRK2 R1441G mice. VPA reduced iba-1 positive activated microglia and the mRNA levels of pro-inflammatory marker genes in LRRK2 R1441G mice. In addition, VPA induced the improvement of PD-like motor and non-motor behavior in LRRK2 R1441G mice. These data suggest that the inhibition of HDAC can be further studied as potential future therapeutics for PD". [7]

I therefore found just a few results of studies done in vivo showing VA as neuroprotective against PD. I also started this essay by citing several studies that show VA actually has PD-like symptoms to its consumption therefore undermining the possibility that it's therapeutic against PD. However, it's possible that these symptoms are the opposite side of the spectrum of

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PD symptoms, for example that PD tremor is combatted by VA stiffness and I would still call for further studying of VA in treatment of PD perhaps not just in mice but eventually also in human subjects. Based on just these few studies found, the results could show it to be neuroprotective and therapeutic in PD management.

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