Inhibitory effect of valproate sodium on behavior in diabetic mice involves suppression of spinal histone deacetylase 1 and inflammatory mediators

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Abstract

Anti-epileptic medications are included in the international guidelines for managing neuropathic pain. Valproate sodium (VPS) was recently described as “the forgotten analgesic” and has been reported to relief pain in various models of neuropathic pain. Some studies reported anti-inflammatory and histone deacetylase 1 (HDA1) inhibitory properties for sodium valproate. The aim of the current study was to investigate the modulatory effect of VPS on pain behavior and inflammatory reactions in alloxan-induced diabetic neuropathy focusing on HDA1 inhibition and glia reactivity. 28 Male Swiss albino mice were allocated into four groups, (1) vehicle group, (2) alloxan-diabetic group, (3 & 4) alloxan+VPS (25 or 50 mg/kg) groups. VPS was given daily for 5 weeks by oral gavage. Pain behavior demonstrated increased allodynia (von-Frey filaments) and hyperalgesia (hot-plate test) in alloxan-diabetic mice that was reduced significantly by at least one of VPS doses. Sciatic nerves in diabetic mice showed increased histopathology score, increased silver staining for the nerves-indicating myelopathy- and a decrease in immunostaining for nerve growth factor. Spinal cord of diabetic mice showed greater histopathologic score, increased CD11b and glia fibrillary acidic protein (GFAP) immunostaining than vehicle treated mice. Molecular investigations highlighted greater content of spinal histone deacetylases, tumor necrosis factor-α (TNF-α) and interlukin-1β (IL1β) that were favorably modified by VPS. Overall, the current data confirmed that the pain killing and anti-inflammatory activity of VPS is at least partly mediated through inhibition of spinal HDA1 and glia reactivity. These findings support the view of inviting antiepileptics for treating neuropathies.

International Immunopharmacology 2019, May