Arachidoyl-2′-chloroethylamide, a selective cannabinoid cb1 receptor agonist combined with valproate stimulates hippocampal neurogenesis in a mouse pilocarpine model of epilepsy

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Abstract

Rational polytherapy in the treatment of refractory epilepsy has been a main therapeutic modality for several years. Considering the treatment with two or more antiepileptic drugs (AEDs) it is of particular importance that the AEDs should be selected based on their high anticonvulsant properties but also high level of neuroprotection as well as minimal side effects.

The aim of the study was in vivo evaluation of the relationship between treatment with synthetic cannabinoid arachidonyl-2′-choloroethylamide (ACEA) in combination with valproate (VPA) and hippocampal neurogenesis in a mouse pilocarpine model of epilepsy.

All experiments were performed on adolescent CB57/BL mice. The following drugs were used: VPA, ACEA, phenylmethylsulfonyl fluoride (PMSF), pilocarpine (PILO), methyloclocapamine. We evaluated long term response to ACEA and VPA administration (BrDU, Neun, GFAP staining). Confocal microscopy and cell counting was done using Zeiss microscope and ImageJ software.

Obtained results indicated clear decrease of neurogenesis in PILO control group compared to the non-PILO control mice. Moreover, ACEA with PMSF administered alone and in combination with VPA had a significant impact on neurogenesis increasing the total number of BrDU, particularly neurons (NeUN) comparing to the control group, whereas VPA administered alone significantly reduces the total number of NeUN/BrDU-positive cells compared to the control group.

ACEA combined with VPA stimulates the process of neurogenesis, while chronic administration of VPA itself decreases neurogenesis in a mouse pilocarpine model of epilepsy. Obtained results make possible in vivo determination of the neurogenesis after antiepileptic drugs treatment.

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