THE ROLE OF SUBPLATE NEURONS AND WHITE MATTER INTERSTITIAL NEURONS IN THE PATHOGENESIS OF EPILEPSY

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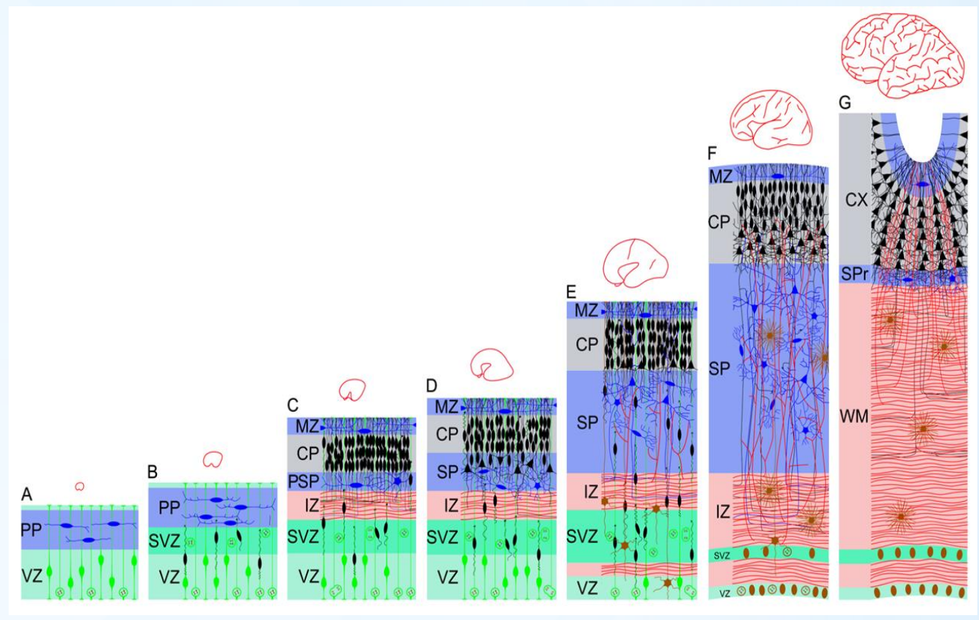
INTRODUCTION

White matter interstitial neurons (WMIC) are a large, but insufficiently explored group of neurons located beneath the cerebral cortex, between the bundles of white matter. Exact role of WMIC in the functioning of the cerebral cortex has not been proven yet. Interestingly, in many neurological and psychiatric disorders the number, distribution and density of WMIC is altered. Epilepsy is one of disorders where alterations of WMIC have been observed. In the brains of people with epilepsy, it is often possible to find an increased number of WMIC. According to classical authors, these neurons are cortical neurons that did not migrate to the correct position during development. Although there is no single evidence that increased number of WMIC in the white matter is the consequence of neuronal migration disorders, with the exception of clearly defined cortical malformations due to similar disorders (e.g. focal cortical dysplasia), the prevailing opinion to date is that those are residual and aberrantly located cortical neurons. In the proposed study, we will analyse molecular phenotype and developmental origin of WMIC in the areas relevant for the pathogenesis of epilepsy .

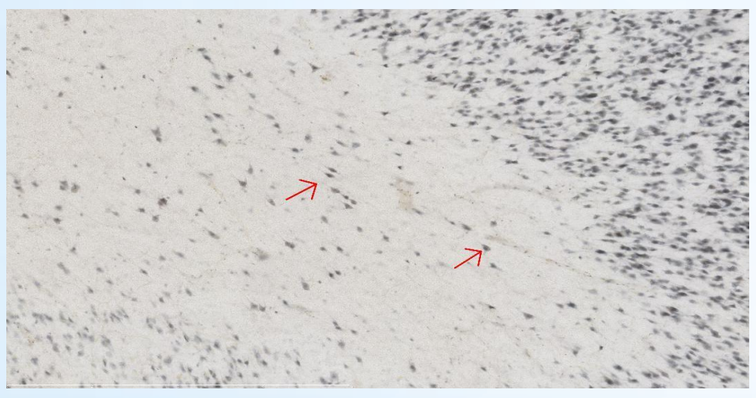
Keywords: subplate, interstitial neurons of white matter, epilepsy, human brain, cerebral cortex

HYPOTHESIS

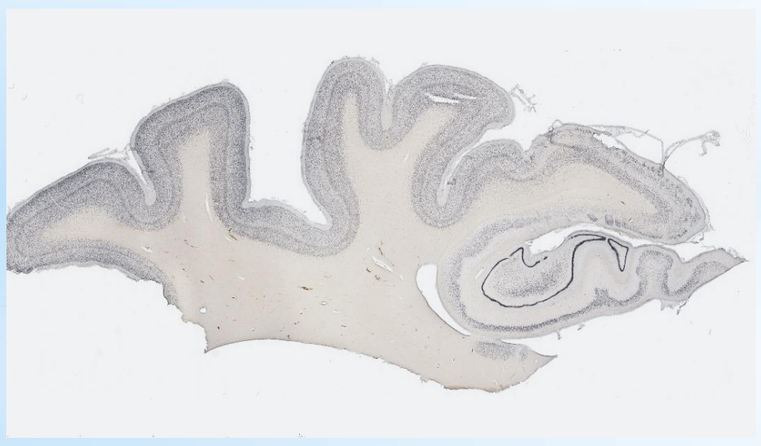
The hypothesis of this research is that increased number of neurons in the white matter of patients with epilepsy is the result of disturbances in the apoptotic elimination of subplate neurons during development rather than migration disorders of cortical neurons



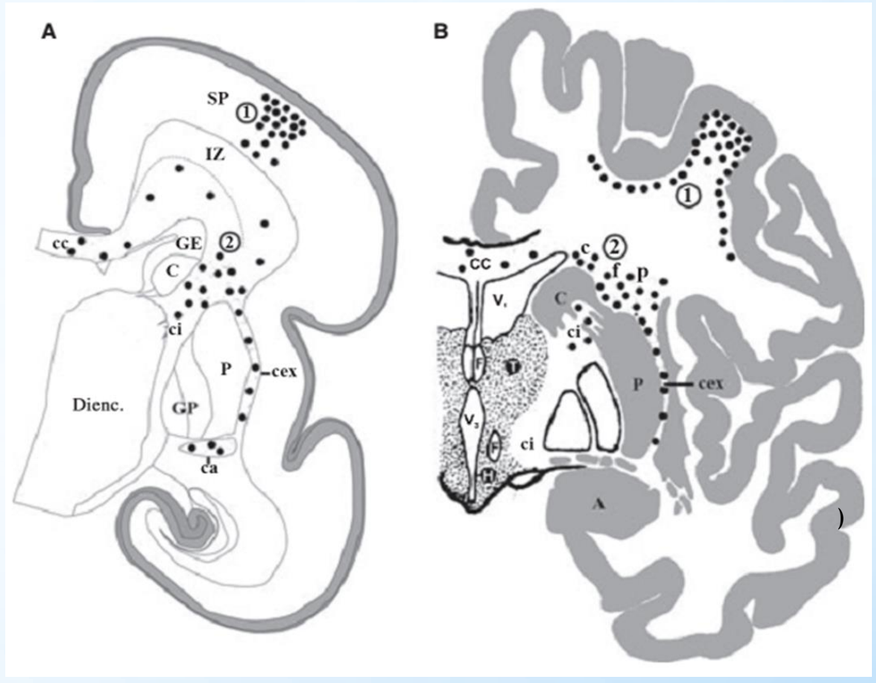
Source: Sedmak, personal data



NeuN histological method, adult brain: Border of cortex and white matter. Arrows point white matter interstitial neurons.
Source: CIBR Neuroembryological collection .



NeuN histological method: Sample of adult brain through hippocampus and following isocortex.
Source: CIBR Neuroembryological collection .



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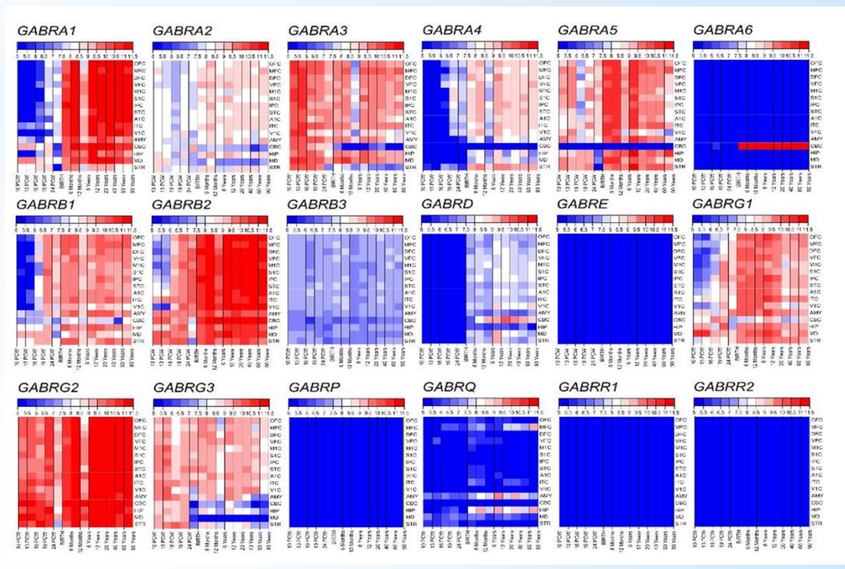

Sedmak, personal source

AIMS

The general aim of this research is to determine the molecular profile of neurons within the white matter during development (i.e. subplate neurons) and in the adulthood (i.e. white matter interstitial neurons) and differences in the composition of white matter interstitial neurons in normal healthy individuals and patients with epilepsy.
Specific aims are: a) to determine the molecular profile and classify subplate neurons in three regions during development; b) to determine the molecular profile and classify white matter interstitial neurons in three regions of adult human brain; c) to determine which classes of subplate neurons survive into adulthood; d) to compare white matter neurons in adult brain between healthy controls and patients with epilepsy; and e) to determine the distribution and differences of different GABA A receptor subunits in white matter interstitial neurons between healthy controls and patients with epilepsy.

METHODS

The proposed research will be conducted using post-mortem samples of normal fetal and adult human brain which are part of versatile Zagreb Neuroembryological collection. All analysed samples will be without known neurological or psychiatric disorders and without history of substance abuse or long-term use of psychoactive medications. Analysis of the epileptic samples will be conducted on the post-operative tissue samples collected during indicated neurosurgical procedures for treatment of pharmacoresistant epilepsy. The samples are part of the University of Zagreb School of Medicine Department of Pathology and Clinical Hospital Centre Zagreb Department of Pathology. All used samples were collected with the prior ethical approval of IRB. We will analyse three fetal brains per stage (15 – 18 PCW; 24 – 28 PCW and 35 PCW – Newborn) and five adult brains (age 30 – 60 years), (hipocampus, picture 2). We will also analyse 10 adult samples from patients with epilepsy (age 30 – 60 years). To elucidate molecular profile of neurons we will use classical histological methods (e.g. Nissl and Golgi), immunocytochemistry, in-situ hybridization and RNAscope for different biochemical markers.

EXPECTED SCIENTIFIC CONTRIBUTION

The expected scientific contribution is better understanding of developmental origin of white matter interstitial neurons and developmental fate of different subplate neuron classes. Furthermore, we will elucidate the role of these neuronal populations in the pathogenesis of epilepsy. We will gather data on location and composition of different GABA A units within defined neuronal population.

White matter interstitial neurons.
Source: CIBR Neuroembryological collection .

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