FOREBRAIN CHOLINERGIC PLASTICITY IN RATS WITH CHRONIC EPILEPSY INDUCED BY STATUS EPILEPTICUS

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INTRODUCTION

- Temporal lobe epilepsy (TLE) is the most common type of symptomatic epilepsy, with around 80% of patients showing drug resistance.
- TLE is frequently associated with an epileptic focus in mesial temporal lobe structures, such as the hippocampal formation (HF).
- The HF has important neuronal projections to the medial septal nucleus/vertical limb of diagonal band of Broca complex (MS/DB), regulating septal activity through GABAergic direct inputs that are originated in the stratum oriens of CA1 and CA3.
- Sprouting of the cholinergic fibers into the molecular layer of the dentate gyrus and their removal from the dentate hilus, would make hippocampal circuits hyperexcitable, a mechanism which has long been implicated in neuropathology of TLE.
- Some studies have demonstrated the existence of GABAergic and cholinergic interconnectivity in MS/DB.

AIM

- Evaluate the GABAergic population in the MS/DB in a chronic epilepsy model of kainic acid (KA)-treated rats.
- Assess the GABAergic and cholinergic interconnectivity in the MS/DB in a chronic epilepsy model of kainic acid (KA)-treated rats.

METHODS

- An intracerebral infusion of 192 IgG-saporin (SAP) at subtoxic levels was used to produce a moderate, but significant loss of septohippocampal cholinergic cells and to suppress their plasticity.
- GABAergic neurons were evaluated with a parvalbumin (PV) staining.
- To assess GABAergic and cholinergic interconnectivity in MS/DB, colocalization was evaluated using immunofluorescence techniques against PV and VACHT.
- To evaluate if GABAergic neuronal loss affected the communication with the cholinergic system, we studied VACHT-immunoreactive fiber varicosities density in MS/DB.

RESULTS

- **Rats with SE**
  - Sham: 90% (9/10)
  - SAP: 90% (9/10)
  - Effect of SAP: n.s. *
- **Latency to SE, min**
  - Sham: 46.8 ± 7.9
  - SAP: 75.7 ± 5.6
  - P (1,16) = 8.83, p=0.009 *
- **Mortality**
  - Sham: 50% (5/10)
  - SAP: 0% (0/10)
  - H(1,20) = 6.33, p=0.024 *
- **Recurrent motor seizures**
  - Sham: 83% (6/7)
  - SAP: 40% (4/10)
  - H(1,16) = 2.68, p=0.101 *
- **Recurrent motor + EEG seizures**
  - Sham: 100% (6/6)
  - SAP: 50% (5/10)
  - H(1,16) = 4.09, p=0.043 *

- *Nonparametric Kruskal-Wallis ANOVA by ranks with SAP pretreatment as independent variables.
- * Parametric ANOVA with SAP pretreatment as independent variable.

- SAP-pretreatment was associated with longer latency to the onset of SE and with reduced mortality rate. Rats in the KA group developed SE almost twice as rapidly as rats in the SAP+KA group.
- A higher percentage of rats with intact septohippocampal cholinergic connections showed spontaneous seizures, when compared to SAP-pretreated rats.
- Treatment with KA lead to a loss of 40–50% of hippocampal neurons and this effect was not ameliorated by prior SAP-treatment.
- KA induced cognitive deficits were detected in both SAP-pretreated and sham-pretreated groups but the rats in the SAP+KA group had higher latency on the retention trial when comparing with the KA group.
- KA-pretreated rats had almost as twice as many VACHT-stained neurons in the MS/DB compared to controls (p<0.001 for post-hoc test).
- The density of cholinergic fiber varicosities in the MS was increased by 45% in epileptic animals.

There was a 35% reduction in the GABAergic neuronal population.

CONCLUSION

- Seizure-induced plasticity of septohippocampal cholinergic cells may enhance seizure susceptibility and contribute to epileptogenic processes.
- KA epilepsy model is related with a decrease of GABAergic PV-stained neurons in MS/DB.
- In MS/DB there is a colocalization of cholinergic and GABAergic populations.
- The number of VACHT-stained varicosities increases in this model, which suggests a compensatory mechanism for the decrease of GABAergic neurons.

REFERENCES