Chronic convection-enhanced muscimol delivery into the subthalamic nucleus produces transient anticonvulsant effects in an acute rat seizure model

Feja, Malte1,2; Deking, Lillian S.1; Gernert, Manuela1,2

1Department of Pharmacology, Toxicology, and Pharmacy, University of Veterinary Medicine, Hannover, Germany; 2Center for Systems Neuroscience (ZNS), Hannover, Germany

Introduction

• Intracerebral drug delivery is an emerging strategy for the treatment of refractory epilepsies.
• Recently, the GABA$A$ receptor agonist muscimol was infused for up to 24 h into the epileptic focus in drug-resistant epilepsy patients.
• In seizure and epilepsy models in rats, muscimol has shown anticonvulsant potential when injected acutely into the subthalamic nucleus (STN).
• However, continuous administration would be required for the clinical setting.

Thus, we hypothesized that chronic convection-enhanced muscimol delivery into the STN produces anticonvulsant effects in an acute rat seizure model.

Methods

Timed intravenous PTZ infusion seizure threshold test in rats

• Pentylenetetrazole (PTZ): GABA$A$R antagonist → proconvulsant
• Two endpoints: 1st myoclonic twitch & 1st clonic seizure
• Increase in seizure threshold indicates anticonvulsant effect

Summary

• Chronic intra-STN muscimol produces transient anticonvulsant effects on iv-PTZ-induced seizures.
• Diminished anticonvulsant effect in the 2nd week indicates tolerance.
• Low doses of muscimol were well tolerated and not associated with sedation and circling observed after infusion of higher doses.
• BODIPY-labeled muscimol revealed that behavioral adverse effects may be attributable to drug spread into adjacent regions of the STN.

Substantiates STN as a key region in seizure control and indicates the potential of chronic muscimol for prolonged anticonvulsant effects.

Acknowledgement

Funded by the Deutsche Forschungsgemeinschaft (DFG) – 390074275 (GE 1103/9-1). 1Heiss et al., 2019 Neurosurgery Jul 1;85(1):E4-E15. We thank Edith Kaczmarek for technical assistance.

Reference

1 Heiss et al., 2019 Neurosurgery Jul 1;85(1):E4-E15.