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

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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 patients¹.
- 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 receptor antagonist → proconvulsant
- Two endpoints:** 1st myoclonic twitch & 1st clonic seizure
- Increase in seizure threshold indicates anticonvulsant effect

Acute microinjection of muscimol into the STN

Chronic microinfusion of muscimol into the STN

Acute microinjection of muscimol into the STN

Acute intra-STN muscimol increases PTZ seizure thresholds compared to vehicle-injected animals.

The majority of rats is responsive (> 25 % increased seizure threshold) to acute intra-STN muscimol.

Fluorophore-conjugated muscimol shows an asymmetrical diffusion extent beyond the STN.

Chronic continuous microinfusion of muscimol into the STN

The anticonvulsant effect persisted in the first week and diminished in the second week during chronic STN inhibition.

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.

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Reference

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