THE EFFECTS OF TONGUE INJECTION OF CTB-SAP ON VENTRAL HYPOGLOSSAL MOTOR NEURONS: A NOVEL MODEL OF ALS

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Introduction and Rationale

- Amyotrophic lateral sclerosis (ALS) is a progressive disorder in which the death of motor neurons leads to a loss of voluntary muscle control.
- Most patients lose the ability to breathe and have to be placed on a ventilator, while many experience dysphagia (swallowing deficits) which often leads to aspiration pneumonia and/or placement of a feeding tube.
- SOD1 transgenic rodents are available for research but take months to develop ALS and are highly variable in the impairment shown (bulbar vs. spinal onset). Can we mimic aspects of the ALS model?

Nichols et al. showed intrapleural injections of cholera toxin B conjugated to saporin (CTB-SAP) resulted in the targeted death of phrenic motor neurons (~60%; Fig. 1) 7 days later, recapitulating what is observed in SOD1(G93A) rats.

Lever et al. has shown that end-stage SOD1(G93A) mice have a decreased lick rate and swallow rate relative to wild type mice (Fig. 2), likely as a result of hypoglossal motor neuron degeneration—Lever et al. has noted vacuolation in the hypoglossal motor nucleus of end-stage mice.

- However, as noted above, SOD1 models take months to reach end-stage and are not always consistent in the impairment they exhibit. Thus, an inducible model that mimics swallowing deficits would be advantageous.

Hypothesis

Following genioglossal injection of CTB-SAP, we hypothesize that CTB-SAP will produce a targeted cell death in the ventral hypoglossal nucleus.

Experimental Methods

1. Genioglossal injection of CTB-SAP or CTB+SAP (control)

2. Location of the hypoglossal nucleus

3. IHC Protocol

4. Quantification of hypoglossal neurons

Expected Results

- Rats receiving tongue injections of CTB-SAP will have fewer surviving hypoglossal motor neurons compared to control treated rats.
- Others members of our team will be conducting lick rate and swallowing studies to determine if CTB-SAP tongue injected rats show a similar deficit as that observed in ALS mice.
- In addition, in vivo neurophysiology will be used to measure hypoglossal and phrenic motor output to show that hypoglossal, not phrenic, motor output is decreased following CTB-SAP tongue injections.

Implications

- We hope this model will aid researchers studying dysphagia associated with ALS by enabling them to rapidly produce test subjects with predictable deficits.
- This model should produce animals with none of the other clinical signs associated with ALS, which makes it ideal to study treatments aimed specifically at dysphagia.

References


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