Trigeminal Nerve Stimulation as a Novel Therapy for Traumatic Brain Injury

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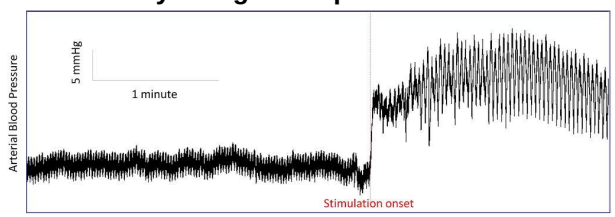
Background

- Traumatic brain injury (TBI) is a major cause of death and disability in both the civilian and military settings. The initial physical damage to the brain includes secondary pathophysiologic consequences, which include, but are not limited to, ischemia, cellular excitotoxicity, inflammation, swelling, and consequent abnormalities of brain function.
- Pharmacological agents have so far yielded disappointing results in modulating these secondary injuries and improving outcomes.
- Recent studies have shown that activation of the parasympathetic nerve system through electrical stimulation of the vagus nerve can have a physiologically beneficial effect in TBI.
- Trigeminal nerve stimulation (TNS) is conceptually allied with vagus nerve stimulation, but has the advantage of being non-invasive.
- TNS can modulate parasympathetic, sympathetic and respiratory activity, which ameliorate the adverse sequelae of TBI.

Methods

- A controlled cortical impact (CCI) model was used to create severe TBI in male Sprague-Dawley rats (n=4-8/group).
- Animals were divided into three groups: sham-animals with opening of the skull but no TBI and TNS, TBI-animals, and TBI-animals with TNS immediately after TBI.
- Electrical stimulation of the trigeminal nerve was performed by introducing two needles (23 GA) subcutaneously bilaterally along an imaginary line connecting the ear and eye.
- Rectangular cathodal pulses (0.5 ms) were delivered by electrical stimulator at 25 Hz, 10 V continuously for 60 minutes.

Physiological Experimental Data



Parameter	TBI	TBI with Trigeminal Nerve Stimulation
Mean arterial pressure (MAP)	81 ± 9 mmHg	102 ± 11 mmHg #
Pulse pressure (PP)	11 ± 6 mmHg	27 ± 8 mmHg #
Respiration rate	43 ± 5 per min	29 ± 7 per min #

Mean arterial blood pressure (MAP), pulse pressure (PP), and respiration rate were measured by using pressure transducer. During the stimulation, MAP (81±9 mmHg vs. 102±11 mmHg) and PP (11±6 mmHg vs. 27±8 mmHg) increased significantly (n=4, p<0.05); while respiration rate (43±5 per min vs. 29±7 per min) significantly decreased (n=4, p<0.05) compared to TBI rats (n=3, # p<0.05 vs TBI).

Edema, BBB Permeability and Lesion Volume Analysis

Parameter	Sham	TBI	TBI with TNS
Edema (%)	77.2 ± 0.6	82.9 ± 0.8 *	80.5 ± 0.5 * #
BBB (µg/g)	0.21 ± 0.02	2.17 ± 0.05 *	0.95 ± 0.08 * #
Lesion volume (mm^3)	0	11.65 ± 1.26 *	7.0 ± 1.03 * #

Mean ± SD; n=3-6/group; one-way ANOVA; * P<0.05 vs. sham, # P<0.05 vs. TBI

Neuropathological Results

Parameter	Sham	TBI	TBI withTNS
Brain tissue TNF-α (pg/mg)	26.5 ± 7.8	200.1 ± 17.6 *	147.8 ± 21.8 * #
Brain tissue IL-1β (pg/mg)	51.2 ± 14.3	947.4 ± 132.4 *	563.3 ± 133.8 * #
Blood plasma IL-6 (pg/ml)	152.7 ±7.1	234.0 ± 49.1 *	177.0 ± 32.7 #
Blood plasma HMGB1 (ng/ml)	0.25 ± 0.1	1.58 ± 0.45 *	0.63 ± 0.14 #
Caspase-3 activity (µM AMC/min/mg)	1.6 ± 0.7	4.2 ± 0.5 *	3.1 ± 0.6 #
Beam balance score	1	5.4 ± 0.54 *	3.6 ± 0.55 * #

Mean ± SD; n=3-6/group; one-way ANOVA; *P<0.05 vs. sham, #P<0.05 vs. TBI

Results

- TBI produced brain lesion accompanied by brain edema and increase of BBB permeability. After TNS treatment, there was a 2.9% decrease in brain edema, 56% decrease in BBB permeability, and 40% decrease in lesion volume (n=6, p<0.05).
- TNS also resulted in attenuation of inflammatory responses (TNF-a 200.1 vs. 147.8 pg/mg; IL-1ß 947.4 vs. 563.3 pg/mg; IL-6 234.0 vs. 177.0 pg/ml; HMGB1 1.58 vs. 0.63 ng/ml). Caspase-3 activity was decreased after TNS treatment (4.2 vs. 3.1 µM AMC/min/mg).

Conclusions

- The data demonstrate that trigeminal nerve stimulation is effective in attenuating traumatic brain injury consequences decreasing lesion volume, suppressing immune response and improving motor behavior.
- TNS may therefore offer a novel therapeutic approach to TBI treatment by the activation of endogenous neuroprotective mechanisms.

Acknowledgement

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Learning Objectives

1. Factors contributing to pathophysiology of severe traumatic brain injury
2. Effects of trigeminal nerve stimulation
3. Understanding the endogenous neuroprotective mechanisms