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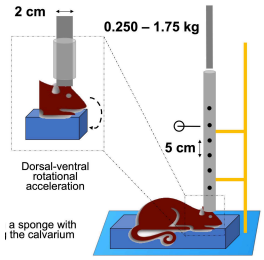
Surgery free rat closed head repetitive mild injury model of traumatic brain injury



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PRECISE-TBI

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We use this protocol and it's working

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Abstract

This is a surgery-free closed head weight drop injury protocol for repetitive mild TBI of adult rats. The model consists, of a guide tube and weight cylinders that deliver an injury to the calvarium of an anesthetized rat in prone position on a sponge causing rotational acceleration.

Rats typically recover without incident with the most common adverse occurrence being a nose bleed. 4 injuries 2 weeks apart with 1.5 kg weight did not result in detectable pathology, but 8 injuries resulted in regional astrogliosis, microgliosis, encephalomalacia, without overt motor deficits.

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Guidelines

Injuries for this protocol were established in male Sprague-Dawley rats 10-12 weeks of age at the time of first injury and all injuries were spaced 10-14 days apart.

It is highly recommended that investigators preform titrations for their specific application, rat strain, sex, and age, with injury ranges 0-1.75kg from 25 cm and 0.250 kg increments.

Materials

weight drop apparatus (see Delic et al 2022 reference for details), sponge, weights, tube, Isoflurane delivery system, recovery cage no bedding with paper towel, heat pad or lamp, timers, decapitation cones, biohazard bags

Troubleshooting

Safety warnings

if performing injuries at the higher end 1.5 - 1.75 kg, mortality is expected. Therefore IACUC approved euthanasia equipment should be on standby. Injury should be titrated down incrementally until tolerable degree of mortality is achieved while still obtaining desired degree of brain pathology. e.g. detectable astrogliosis, microgliosis, tissue damage.

Ethics statement

Male Sprague Dawley (SD) rats 9-10 weeks of age were procured from Charles River and were handled in accordance with the VA New Jersey Health Care System Institutional Animal Care and Use Committee (IACUC). Rats were housed individually in standard polycarbonate 18 quarts tubs with bed-o-cob bedding which was changed once a week. Individual housing was necessary due to planned behavioral experiments, and the unknown effect of r-mTBI together with PFF on the interaction between injured males in the same cage. Rooms were kept at 22°C +/- 4°C and rats were kept on 12 hours on and 12 hours off reverse light cycles such that the behavioral experiments were performed during rat subject active phase. To minimize stress during handling and behavioral experiments rats were acclimated to the experimenter by handling for a week before experiments were performed. All behavioral experiments were performed under red light. Three separate cohorts were used in this study. Cohort 1: 4x r-mTBI and shams for behavior and histology, cohort 2: 8x r-mTBI and shams for behavior and histology, cohort 3: nucleation of PD by injection of PFFs followed by 8x r-mTBI for histology.

Apparatus Setup

1 Ensure that the TBI platform is stable with pin in the 5th hole from the bottom
25 cm height.

2 Load weights. If loading multiple weights into the guide tube, load smaller weights first to ensure proper balance.

3 Turn on Isoflurane system with following settings:

- Open O2 gas tank connected to apparatus
- Turn knob to 4-5% v/v for isoflurane
- Gas delivery rate to 1.5 L/min for O2
- Turn on valve for gas delivery to gas chamber and wait at least 10 seconds for chamber to fill before placing animal in

Delivery of hit

4 Anesthetize the animal for 2 minutes in the gas chamber. Must be full anesthetized as to not respond to toe pinch.

- Good time to weigh the rat

5 Place anesthetized animal carefully into a decap cone and then under the weight-drop apparatus so that the top of the skull completely underneath the guide tube covering the entire calvarium. Arrange body in prone position on sponge. The guide tube should be lightly touching the head while the animal is on the sponge underneath.

* Ensure that the rat forelimbs are folded back and that the tongue is not between incisors.

6 Pull the pin to release weights

7 quickly retract weights up the guide tube using the attached string

8 Place animal in recovery cage on its back, and time for the righting reflex

Recovery observation

9

Full recovery

- Quickening of breath
- rat has righted itself completely with paws underneath he body
- if minor bleeding present, it has rapidly resolved
- Once fully recovered place rat in home cage
- observe rats for 3 days, twice a day for continued signs of recovery

Not recovering

- no breathing for more than 30s (rapid color change in tail, snout, paws)
- very labored breathing that is not improving
- seizures
- profuse bleeding
- rat not woken up and not righted within 10 minutes
- Euthanize rat