# Systemic injection of CGRP prolongs a nausea-like state in mice

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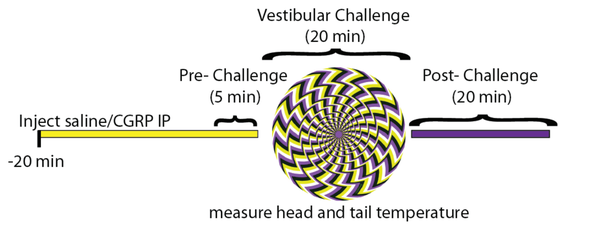
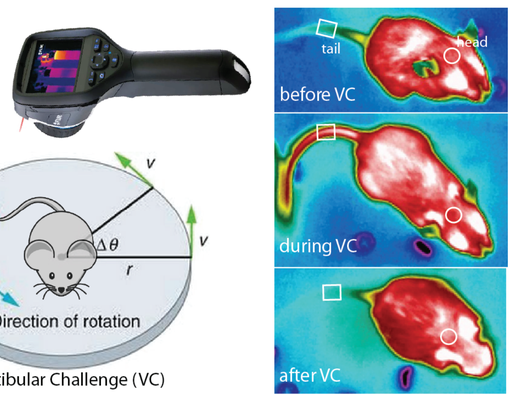
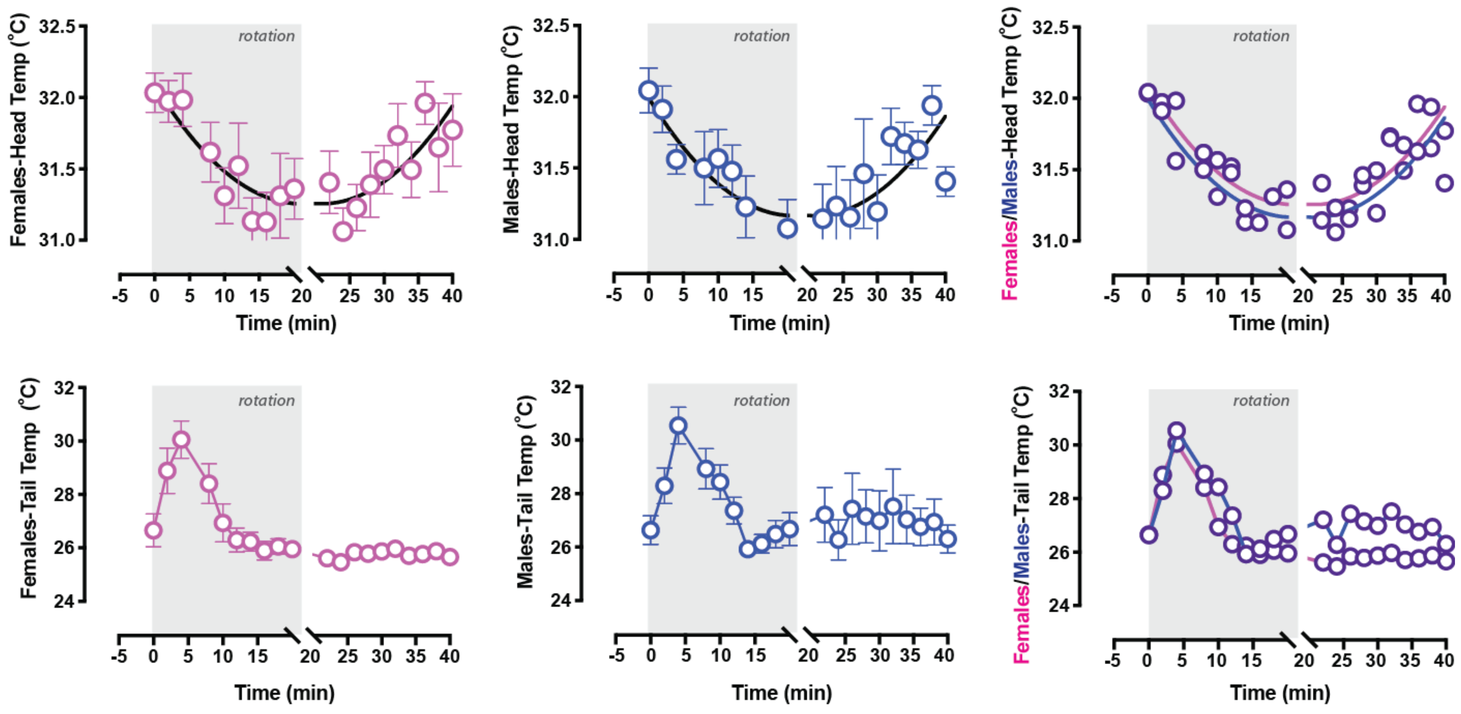



Nausea is a prominent symptom and major cause of complaint for patients with migraine and specifically vestibular migraine (VM). As a readout of a nausea-like state present in migraine and VM, we will assessed hypothermic responses to provocative motion. Recent studies have demonstrated that provocative motion causes robust and prominent hypothermic responses in rats, humans, house musk shrews, and mice that there is a clear parallel in hypothermic responses between animals and humans in underlying physiological mechanism - cutaneous vasodilatation that favors heat loss. Additionally, because systemic CGRP injection has been shown to cause light-aversion (photosensitivity) in mice, we wondered what effect systemic CGRP injection would have on these nausea-like states in wildtype mice.

We carried out these studies on 20 wildtype C57BL/6J (JAX 664) mice (10F/10M). Head and tail temperatures were measured using an FLIR E60 IR camera before, during, and after a 20 min orbital rotation (0.75 Hz to 4 cm displacement) - vestibular challenge (VC) after being injected systemically with saline. One week later, the same mice were injected systemically with 0.1 mg/kg rat α-CGRP (Sigma), and were retested.

## *Pre-condition (Saline IP)*

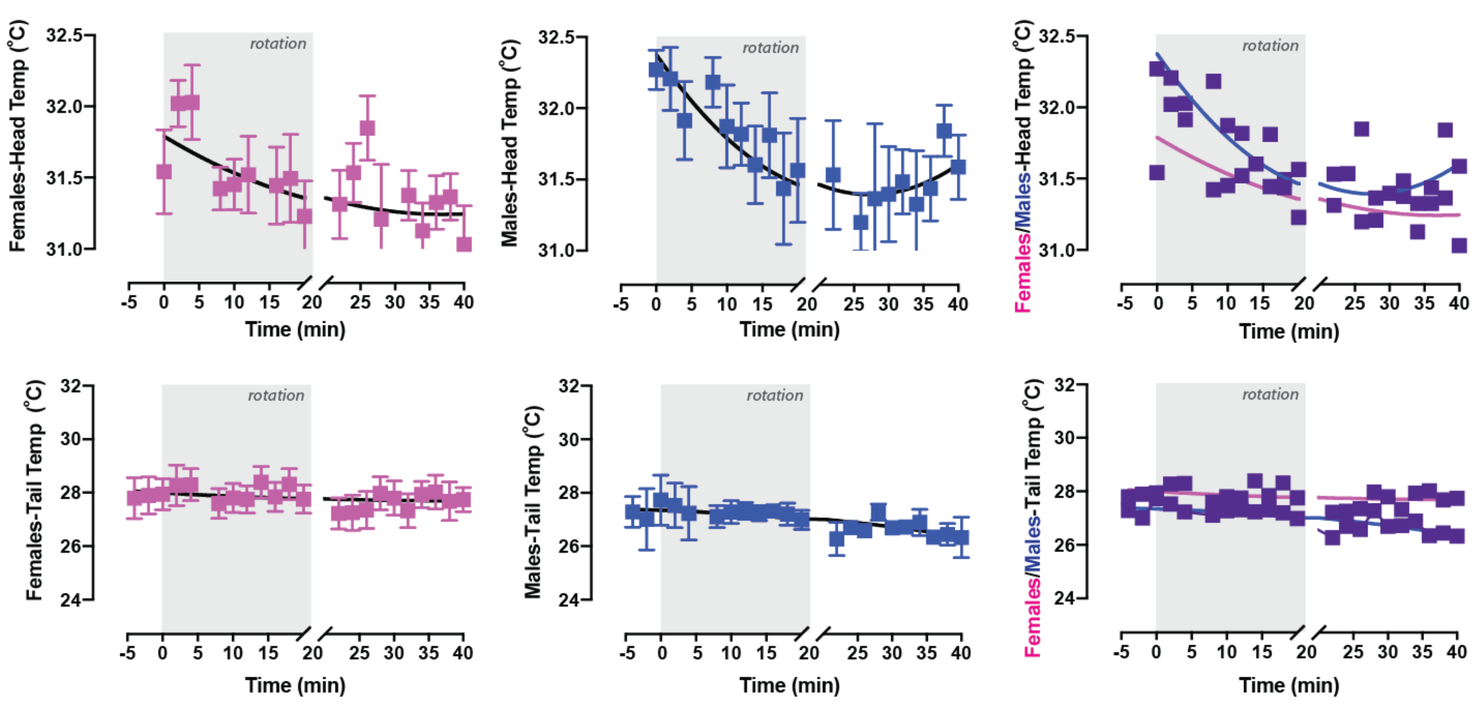



**Top panel:** Head temperatures before, during, and after a 20 minute orbital rotation (vestibular challenge-VC), shown in open circles (pink females; blue males; purple both sexes). Note, there was no sex differences in the head temperature response and recovery is complete at 20 minutes post-rotation.

**Bottom panel:** Tail temperatures before, during, and after a 20 minute orbital rotation (vestibular challenge-VC), shown in open circles. Again, no sex differences in the transient tail temperature responses were observed; and the transient tail temperature increase recovers ~ 15 min into the rotation.

We confirmed in both female and male C57BL/6J mice during provocative motion there is a decrease in head temperature (hypothermia) of ~1.5 degrees C which recovers, and is associated with a short-lasting tail-skin vasodilation (tail skin temperature increase of ~4 degrees C).

## *Post-treatment (CGRP IP)*




**Top panel:** Head temperatures before, during, and after a 20 minute orbital rotation (vestibular challenge-VC) after a systemic injection of CGRP, shown in closed squares (pink females; blue males; purple both sexes). Note, again there were no sex differences in the head temperature response, yet unlike the saline IP condition, there was no recovery in this response post-rotation.

**Bottom panel:** Tail temperatures before, during, and after a 20 minute orbital rotation (vestibular challenge-VC) after a systemic injection of CGRP, shown in closed squares. Note, after CGRP injection, no transient tail temperature responses were observed.

In summary, systemic CGRP injection caused a similar reduction in head temperature to provocative motion, yet the hypothermia did not recover. Moreover, there was no associated tail-skin vasodilation in CGRP-injected mice.

In conclusion, provocative motion in wildtype mice is accompanied by hypothermia that involves both autonomic and thermoeffector mechanisms. Moreover, a systemic CGRP injection prolongs the hypothermia and eliminates the tail-skin vasodilation. Experiments are underway to determine what effects CGRP antagonists and triptans may have on these physiological correlates of nausea and motion-sickness induced nausea.

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