Systemic injection of CGRP increases postural sway and auditory sensitivity in mice

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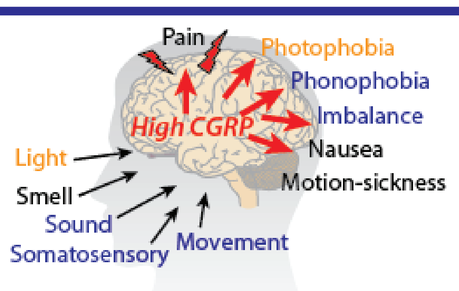
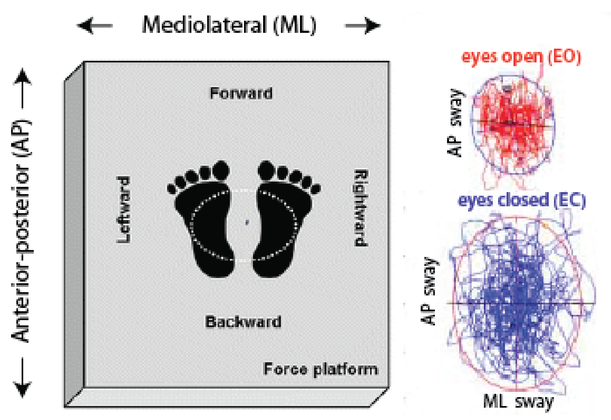


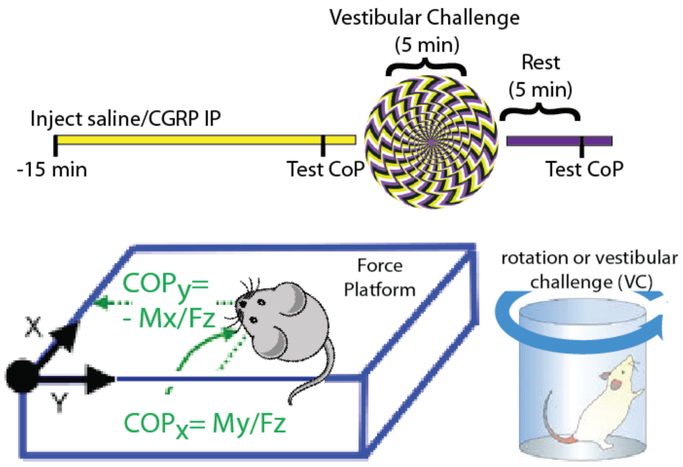
Clinical symptoms / Mouse homologues

Photophobia/ Light-aversion
Phonophobia/ Acoustic Startle and PPI
Imbalance/ Postural sway



About 42% of people with migraine have a vestibular component causing balance problems and dizziness. This form of migraine, termed vestibular migraine (VM), has been recently defined as having at least five episodes of moderate or severe vertigo lasting 5 min-72 hours, history of migraine, either phonophobia, photophobia, or visual aura, and vertigo that cannot be caused by other ear or brain pathologies. In fact, VM is a major cause of vertigo in dizziness clinics and is estimated to affect 1% of the overall population. As migraine increases light, and sound sensitivities, it also increases sensitivities to movement or perceived movement in VM. The most common symptoms of VM were unsteadiness, balance disturbances, and "light headedness". When balance disturbances were quantified, VM patients swayed more than migraine-only or healthy controls when challenged with optic flow, and after optokinetic (OKN) stimulation (with eyes closed) than did either healthy controls or migraine-only patients. In addition postural sway or center of pressure (CoP) testing can be used in mouse models as this test has been used successfully to detect fine tremors in mouse models.

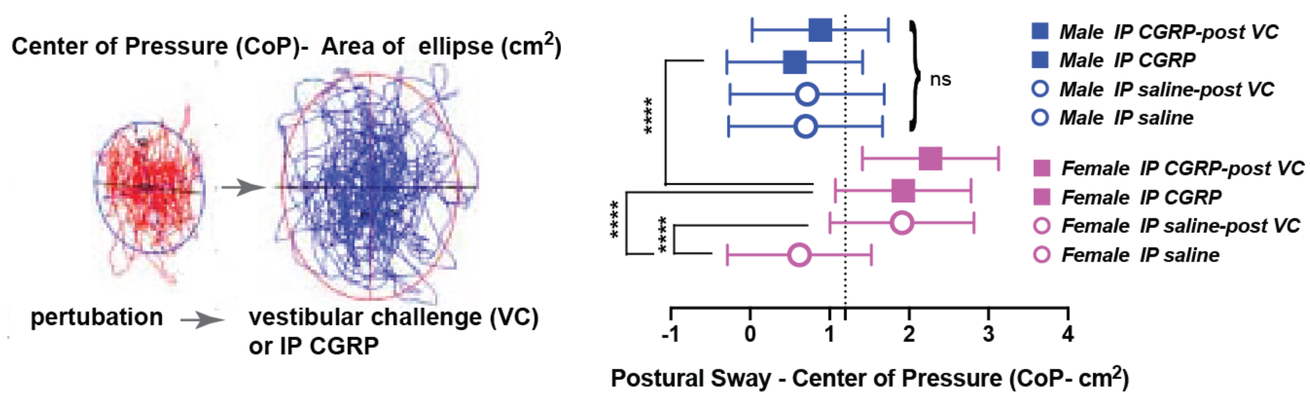
In addition, patients with migraine, and especially VM, exhibit a heightened sense of sound, or phonophobia. Phonophobia is also related to hyperacusis (extreme sensitivity to sound). Behavioral evidence of hyperacusis and phonophobia in mice can be inferred using the acoustic startle reflex (ASR) and pre-pulse inhibition (PPI) of startle testing.



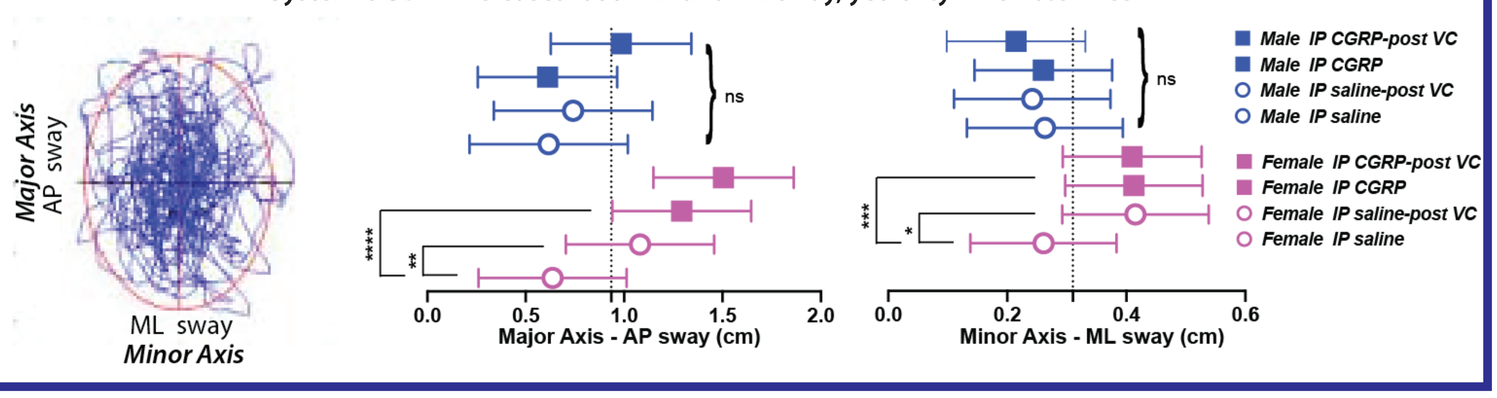
Postural sway or center of pressure (CoP) testing: We studied 20 wildtype C57BL/6J (JAX 664) mice (10F/10 M) for the postural sway testing. Initially the mouse was injected IP with saline and returned to home cage for 15 min. The mouse was then placed on force plate (AMTI Biomechanics) and after acclimatization with the mouse resting still with all feet on platform, we recorded forces and moments for 1 sec, with measurements repeated 10-12 times/mouse. We also obtained CoP measurements after a brief 30-sec vestibular challenge (VC) rotation (125 rpm), and repeated the process. One week after initial testing, the same mice were injected IP with 0.1 mg/kg rat α-CGRP (Sigma), and after 15 min, were subjected to the same postural sway procedure.

We determined that female mice swayed more than male mice after a vestibular rotation as well as after a systemic CGRP injection (2-fold increase in CoP area).

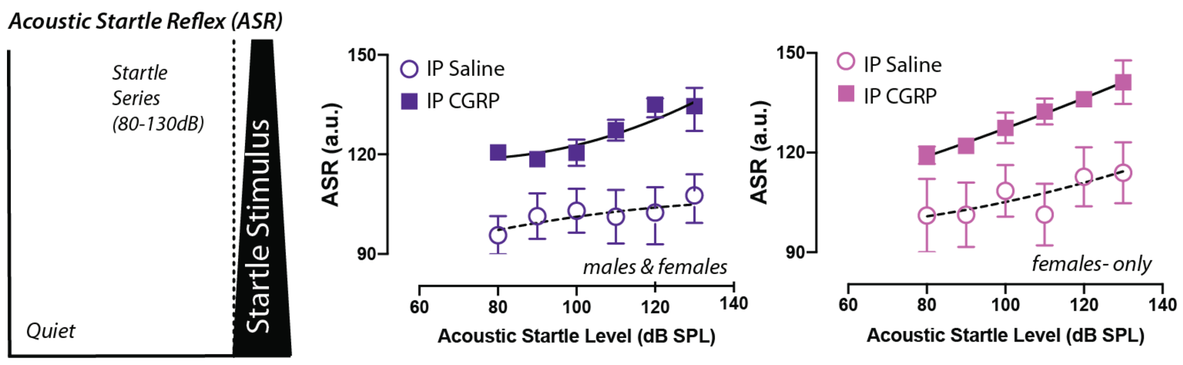
Systemic CGRP increases CoP area only in female mice



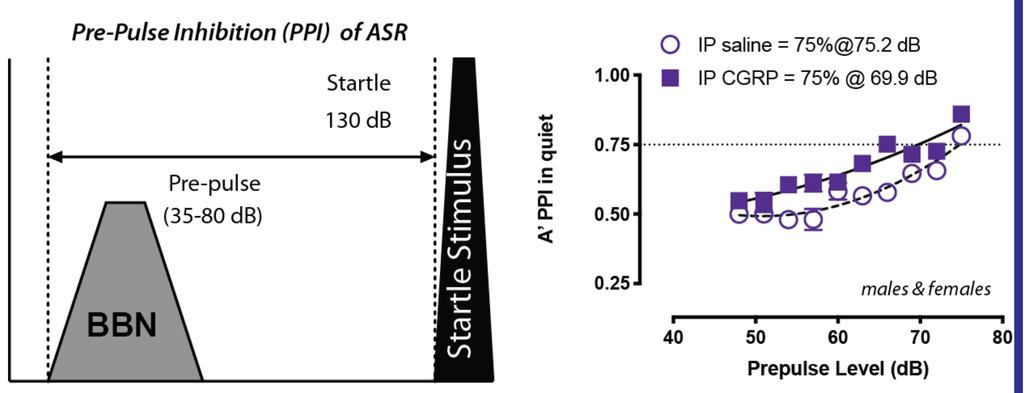
Systemic CGRP increases both AP and ML sway, yet only in female mice



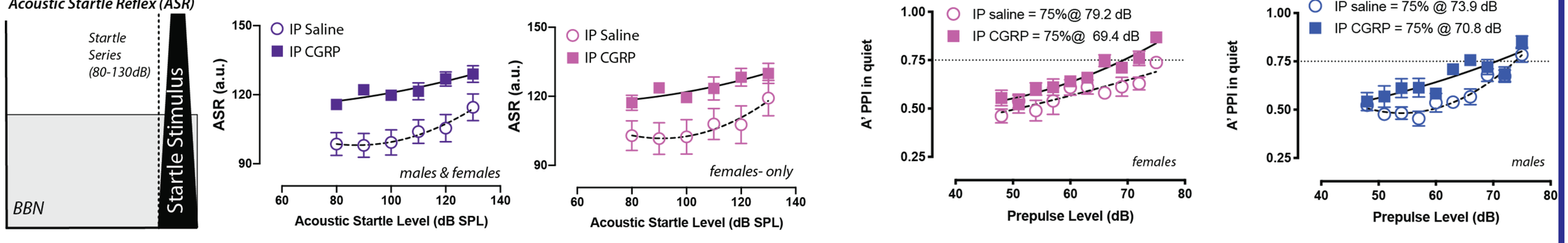
Systemic CGRP increases sound sensitivity to a startle stimulus when in quiet surroundings



Systemic CGRP increases sound sensitivity by PPI assessment



Systemic CGRP increases sound sensitivity to a startle stimulus when embedded in background noise



Acoustic Startle/ Prepulse Inhibition (ASR/PPI) testing: We studied 20 wildtype C57BL/6J (JAX 664) mice (10F/10 M) for ASR/PPI testing. Initially the mouse was injected IP with saline and returned to home cage for 15 min, and then we determined target reception thresholds in dB (that gives A'=. 75 or 50% inhibition) for each animal. Each animal was only tested for 45 min/day (one series of acoustic startle/day; i.e., i) acoustic startle series in quiet and in noise, and ii) PPI in quiet with noise burst (NB) targets of varying loudness. One week after initial testing, the same mice were injected IP with 0.1 mg/kg rat α-CGRP (Sigma), and after 15-20 min, were subjected to the same ASR/PPI procedures over a 2 day period.

We determined that both male and female mice were more sensitive to sounds (5-10 dB SPL) after a single systemic CGRP injection.

In conclusion, systemic CGRP injection increased both motion sensitivity (as measured by postural sway) and sound sensitivity (as measured by ASR/PPI). Experiments are underway to determine what effects systemic-delivered CGRP antagonists and triptans may have on these CGRP-induced sensitivities.

Research supported by NIH R01 DC017261 (AL) and grants from the Kearns Center (UR) and Discovery grants (UR)