Investigating the Increased Prevalence of Migraines in Females Due to Estrogen

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Background

Migraines are two to three times more prevalent in females than in males, but the mechanisms that lead to this significant difference between the sexes is not well understood. While hormones such as estrogen have been implicated in this issue, the underlying mechanisms and neuronal pathways are still unclear. Through this research project, new light is shed on the relationship between the specific hormone estrogen and migraine prevalence during various phases of the menstrual cycle.

The widely understood explanation for the increased migraine prevalence in women compared to men regarding estrogen is the estrogen withdrawal theory. A study conducted in 1996 concluded that migraines in the participants of the study were due to a drop in estrogen levels, which is the premise of the estrogen withdrawal theory (Lichten et al., 1996). The main idea is that the fall of estrogen levels causes an imbalance of the brain's gene activity and increases nerve excitability that triggers migraines (Welch et al., 2006). A study from 2006 aimed to understand the relationship between the various menstrual cycle phases and the rise and fall of estrogen levels with menstrually related migraines. They found that there was a significantly higher number of migraines during the late luteal phase when estrogen levels were declining and a significantly lower number of migraines during the phases when estrogen levels were climbing (MacGregor et al., 2006). A study conducted in 2016 corroborated these findings; this study aimed to compare the daily sex hormone levels between women who had a history of migraines and a control group. They found that women more prone to migraines had a faster estrogen decline during their late luteal (premenstrual) phase than the control group did. This study proposed another aspect to support the finding from the previous study, that women prone to migraines experience a faster rate of estrogen decline, compared to what is most widely accepted, that the rate of estrogen withdrawal following the periovulatory peak is the cause of migraines (Pavlović et al., 2016). A more recent study from 2020 investigated the effects of estrogen and progesterone, and their combination, on the release of calcitonin gene-related peptide (CGRP) and substance P (SP), two neuropeptides that cause neurogenic inflammation and therefore migraines. They concluded that the presence of estrogen has protective effects against inflammation (Ayhan Cetinkaya et al., 2020).

Research Question & Hypothesis

What is the role of estrogen in the impairment of cortical activity in the brain following migraine? We hypothesize that higher estrogen levels attenuate the level of cortical dysfunction induced by migraine.

Experimental Design

Measure estrogen levels in rats using estradiol enzyme-linked immunosorbent assay (ELISA) kit using methods similar to the one described in a prior study (Haisenleder et al., 2011). Use estrogen levels to determine estrous cycle phase, map out estrous cycle of each rat, and plan experiments for rates on a high estrogen day and a low estrogen day.

Experimental work flow: Induce migraines in rats (n=10) during high estrogen levels and during low estrogen levels and use cortical EEG biomarkers identified earlier and behavioral assessments to assess the degree of impairment in cortical function and behavior. Cortical experiments (n=10) involve injection of equal volumes of saline in animals with random levels of estrogen and assessing cortical activity and behavior. Each experiment takes approximately 5 hours. The rats are placed in EEG cage for a 30 minute baseline EEG recording, but allowed to acclimatize to the EEG recording cage for 10 minutes prior. After induction of migraine using an intraperitoneal injection of nitroglycerine (NTG) or saline (in control experiments) as assigned, the rats are returned to the EEG recording cage and EEG is monitored continuously for 4 hours. EEG recording is paused intermittently for 10 minutes of behavioral assessment in open exploration behavioral test. EEG data is sampled, visualized, and saved at 1 kHz per channel using Scout Grapevine processor. Night vision USB camera with infrared light to capture animal behavior in the dark. Behavioral measurements done at 30 minutes, 2 hours, and 4 hours following drug injection. The following measurements are quantified - distance traveled, average speed of rodent, freezing episodes (freezings of whole body for at least 2 seconds), immobility episodes (rodent not moving from place to place for at least 5 seconds), amount of time spent in center zone of the cage, rearing and grooming behaviors (quantified manually).

EEG analysis - EEG data will be analyzed using Matlab, multitapered spectral analyses using Chronux toolbox for generation of spectrograms spanning the full duration of the experiment. Matlab codes for analysis of EEG data already exist in the Neural Microsystems laboratory and will be modified for use, if necessary. Energy in the different frequency bands will be quantified throughout the 4 hours of recovery after migraine induction in all the rodents.

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