

# Effects of estrogen and progesterone on biomarkers of neurogenic inflammation underlying migraine headache in rats

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## Aim

Neurogenic inflammation is held responsible for migraine pathophysiology. Calcitonin gene-related peptide (CGRP) and substance P (SP) that are released from trigeminovascular system are crucial triggers of neurogenic inflammation. Migraine is approximately 3 times more frequent in women than in men. Although it seems that estrogen withdrawal during menstrual cycle may be responsible for this gender difference, its mechanisms remained unclear. We investigated effects of female-sex hormones estrogen and progesterone on plasma levels of CGRP and SP in rats of both sexes.

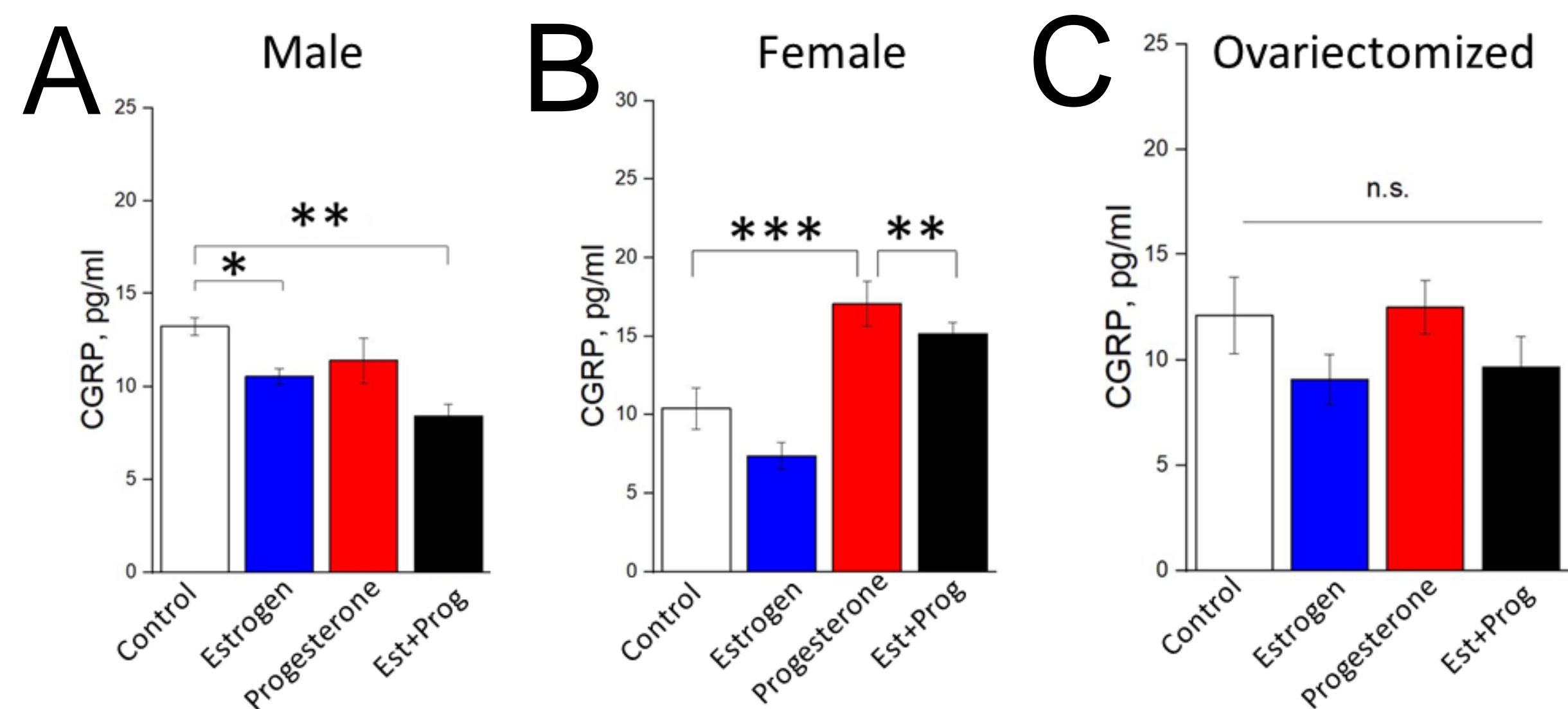
## Methods

Adult Wistar rats were separated to 3 general groups as intact male, female and ovariectomized female. Bilateral ovaries of ovariectomized group were removed. General groups were separated 4 subgroups (n=7) as control, estrogen, progesterone and combination (estrogen+progesterone). Rats received intraperitoneally daily 0.2 ml vehicle, 1mg/kg 17 $\beta$ -estradiol, 8 mg/kg progesterone and 17 $\beta$ -estradiol+progesterone for 5 days, respectively. After 5 days, venous-blood was collected. Plasma CGRP and SP levels were measured using ELISA. Data were compared by one-way ANOVA.

## Results

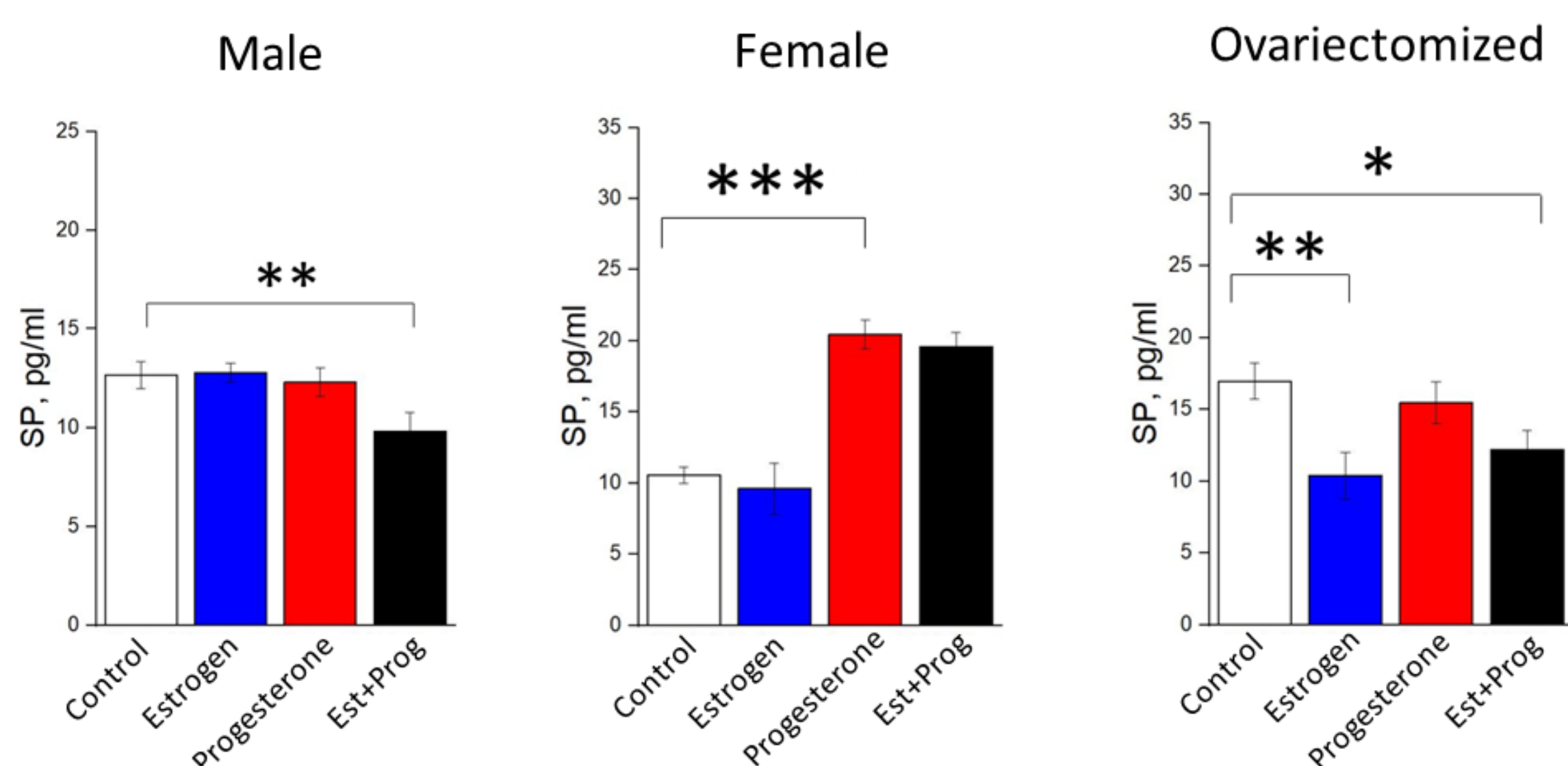
When compared to their control groups, while 17 $\beta$ -estradiol decreased CGRP levels in male-estrogen group (p<0.05, Fig 1A) and SP levels in ovariectomized-estrogen group (p<0.05, Fig 2A), didn't change CGRP and SP levels in female-estrogen group (p>0.05, Fig 1B and Fig 2B). While progesterone increased CGRP and SP levels in female-progesterone group (p<0.001, Fig 1B and 2B), didn't change them in both male and ovariectomized-progesterone group (p>0.05, Fig 1A and C; Fig 2A and C). While the combination decreased CGRP and SP levels in male-combination group (p<0.01, Fig 1A and 2A), increased them in female-combination group (p<0.01, Fig 1B and 2B). While the combination didn't change CGRP levels (p>0.05), it decreased SP levels (p<0.05) in ovariectomized-combination group rats (Fig 1C and 2C).

## Plasma CGRP Levels



**Fig 1.** The effects of estrogen (17 $\beta$ -estradiol), progesterone and their combination on the plasma calcitonin gene-related peptide (CGRP) (A) in intact male rats, (B) in intact female rats and (C) in ovariectomized female rats. \*p<0.05, \*\*p<0.01 and \*\*\*p<0.001.

## Plasma Substance P Levels



**Fig 2.** The effects of estrogen (17 $\beta$ -estradiol), progesterone and their combination on the plasma substance P (SP) (A) in intact male rats, (B) in intact female rats and (C) in ovariectomized female rats. \*p<0.05, \*\*p<0.01 and \*\*\*p<0.001.

## Conclusion

- Estrogen reduces levels of neurogenic inflammation markers including CGRP and SP in both sexes.
- Progesterone induces an increment in CGRP and SP levels in females.
- Our results suggest that estrogen may alleviate neurogenic inflammation underlying migraine via modulation of CGRP and SP release, and progesterone may exacerbate it by inducing CGRP and SP release.

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