Citalopram given to stressed and control pregnant rats causes sex-dependent changes in behaviour and gene expression of the CRH family of their offspring

Inbar Zohar, Marta Weinstock
Institute of Drug Research, Hebrew University of Jerusalem, Israel

Background

An increased incidence of anxiety, depression and exposure to stressful life events during pregnancy increases the likelihood of anxiety and depression in the young and adult offspring of humans and experimental animals.

An increasing number of pregnant women exposed to stress and/or suffering from depression are being treated with antidepressant drugs that are selective serotonin reuptake inhibitors (SSRIs) but it is not clear whether any benefits of treatment outweigh the potential adverse effects on the offspring.

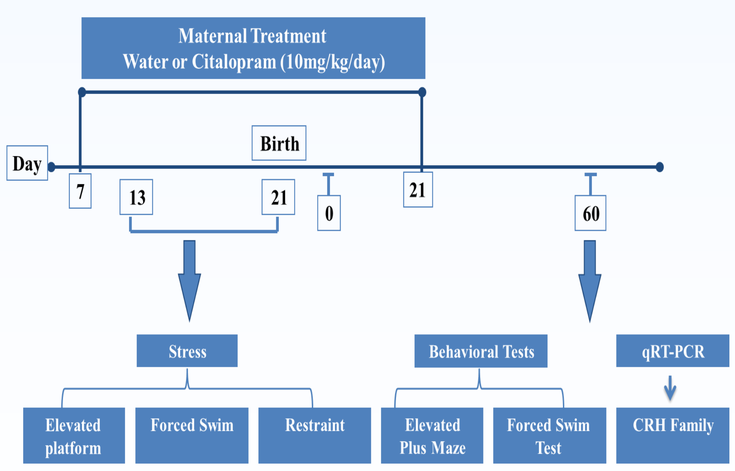
This study compared the effect of maternal treatment with citalopram, a frequently prescribed SSRI, on behaviour and gene expression of the corticotropin releasing hormone (CRH) family in prenatally-stressed (PS) and control rats of both sexes.

Methods

Citalopram (10 mg/kg/day) or water were administered to 40 pregnant rats in their drinking fluid from day 7 of gestation until after their pups were weaned.

Half of each group was subjected to once-daily varied stress from day 14-21 of gestation.

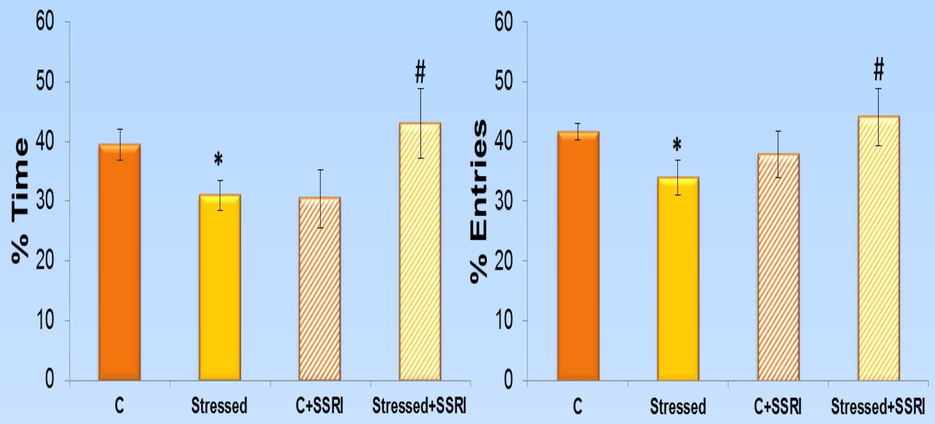
Offspring behaviour and gene expression of the CRH family in the amygdala and hypothalamus was evaluated in adulthood.



Results

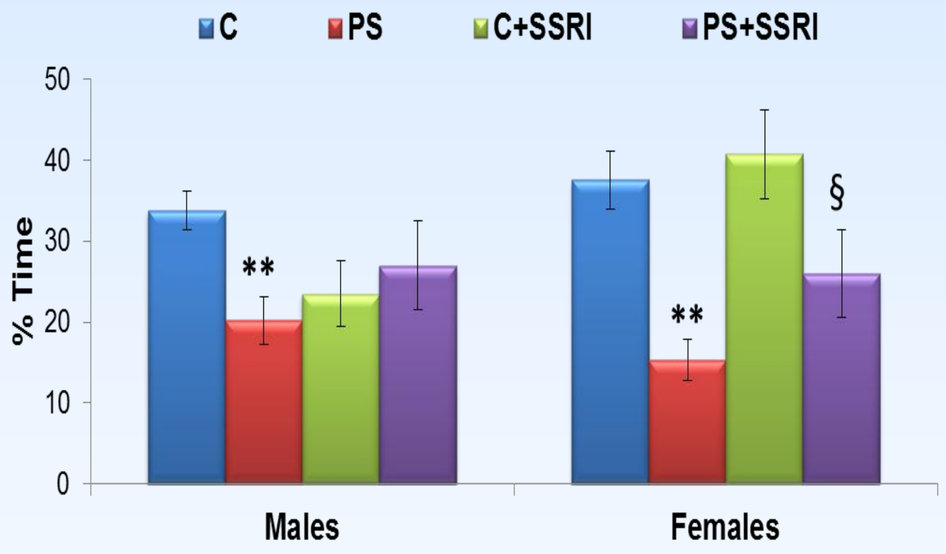
Fig 1. The effect of stress and citalopram administration on a measure of anxiety in the mothers 2 days after their pups were weaned by exposing them to the **elevated plus maze (EPM).**

Stressed mothers were more anxious than controls and citalopram prevented their increased anxiety, but had no effect on the behaviour of control mothers.



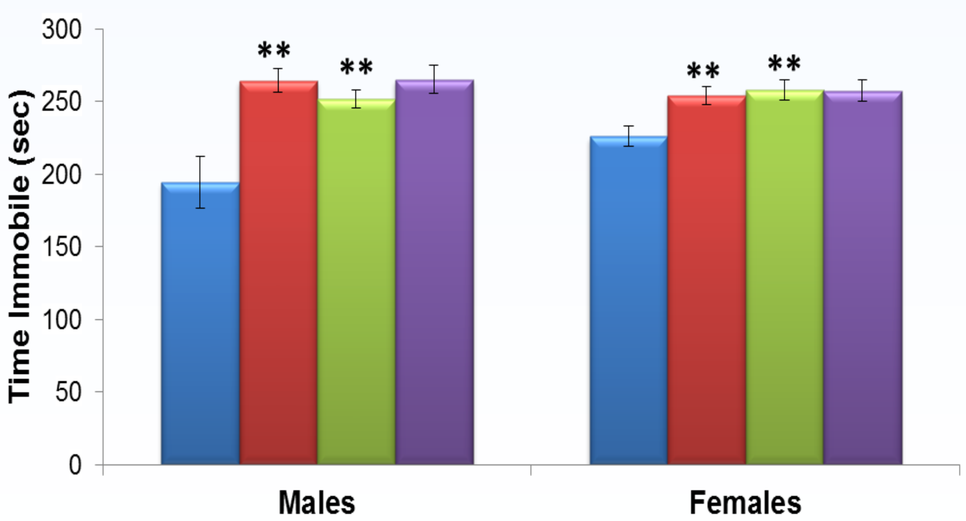
% time spent in open/closed arms; % entries into open/total entries into open + closed arms.
Significantly different from C (*$p < 0.05$); from stressed (#$p < 0.05$).

Fig 2. Prenatal stress heightened anxiety in **offspring** of both sexes in the **EPM.** Citalopram treatment had no effect on PS males and its effect in PS females did not quite reach statistical significance



Significantly different from C group (**$p<0.01$); from PS §$p = 0.06$.

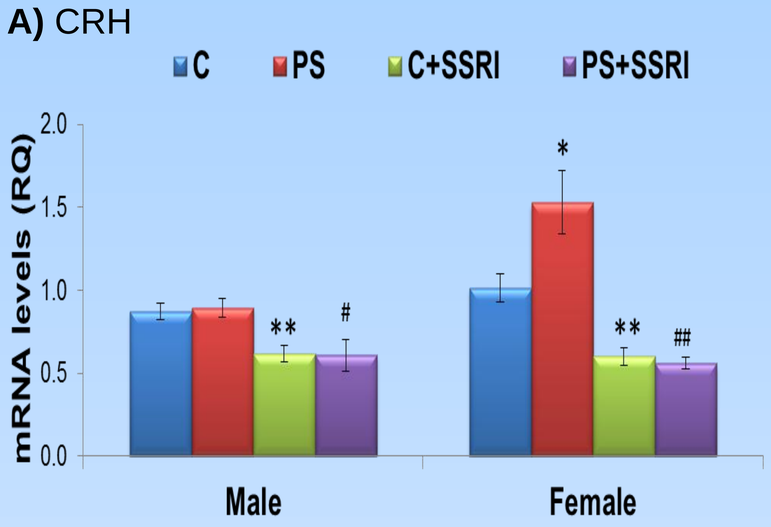
Fig 3. The effect of prenatal stress on depressive-like behaviour in the **forced swim test** of male and female **offspring** was not prevented by maternal treatment with citalopram.



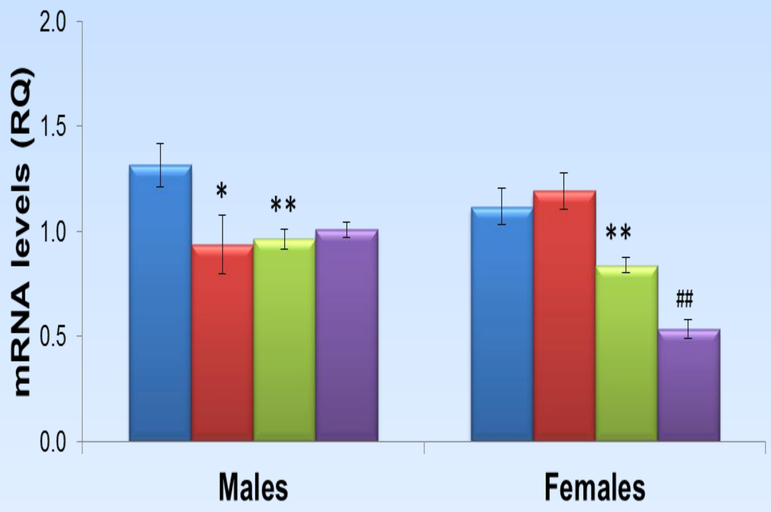
Significantly different from C (**$p < 0.01$).

Fig 4. Prenatal stress and maternal citalopram treatment altered the expression of members of the CRH family measured by **qRT-PCR** in a sex dependent manner.

A) CRH



B) CRH-BP



RQ = relative quantification.
Significantly different from C (*$p < 0.05$; **$p<0.01$);
Significantly different from PS (#$p < 0.05$; ##$p < 0.01$).

Conclusion

- Citalopram administered during gestation prevented anxiety in stressed rat mothers.
- However maternal citalopram treatment did not prevent heightened anxiety and depressive-like behaviour in the offspring of both sexes.
- Citalopram treatment of control mothers induced depressive-like behaviour in the offspring of both sexes possibly because it decreased CRH-BP mRNA in both sexes.
- It is possible that blockade of the 5HT transporter by citalopram at a critical time during development could induce anxiety by causing reduced activation of postsynaptic 5HT1A receptors in the hippocampus and amygdala and thereby also affect CRH and CRH-BP.