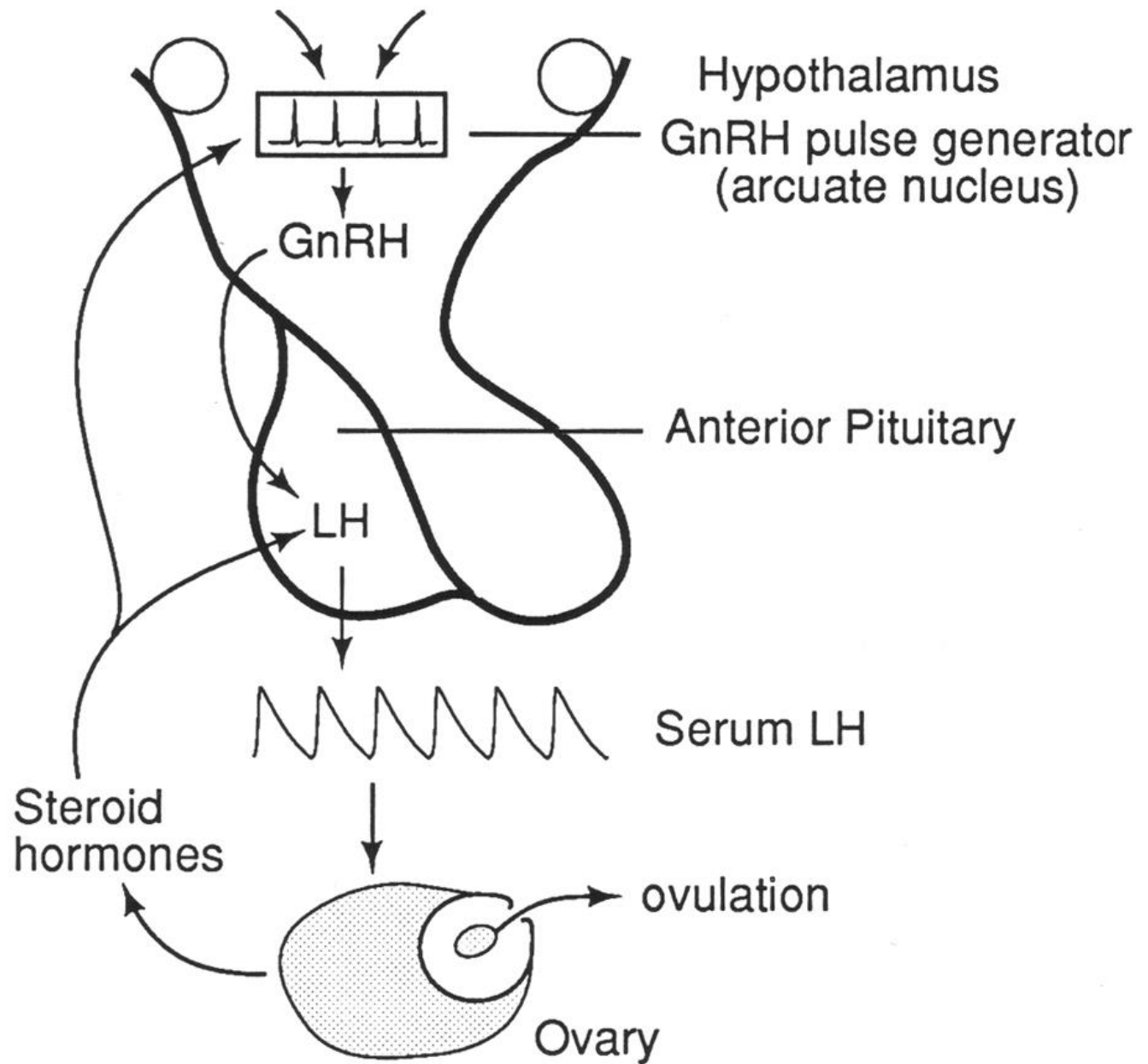


Stress, the GnRH Pulse Generator and Infertility

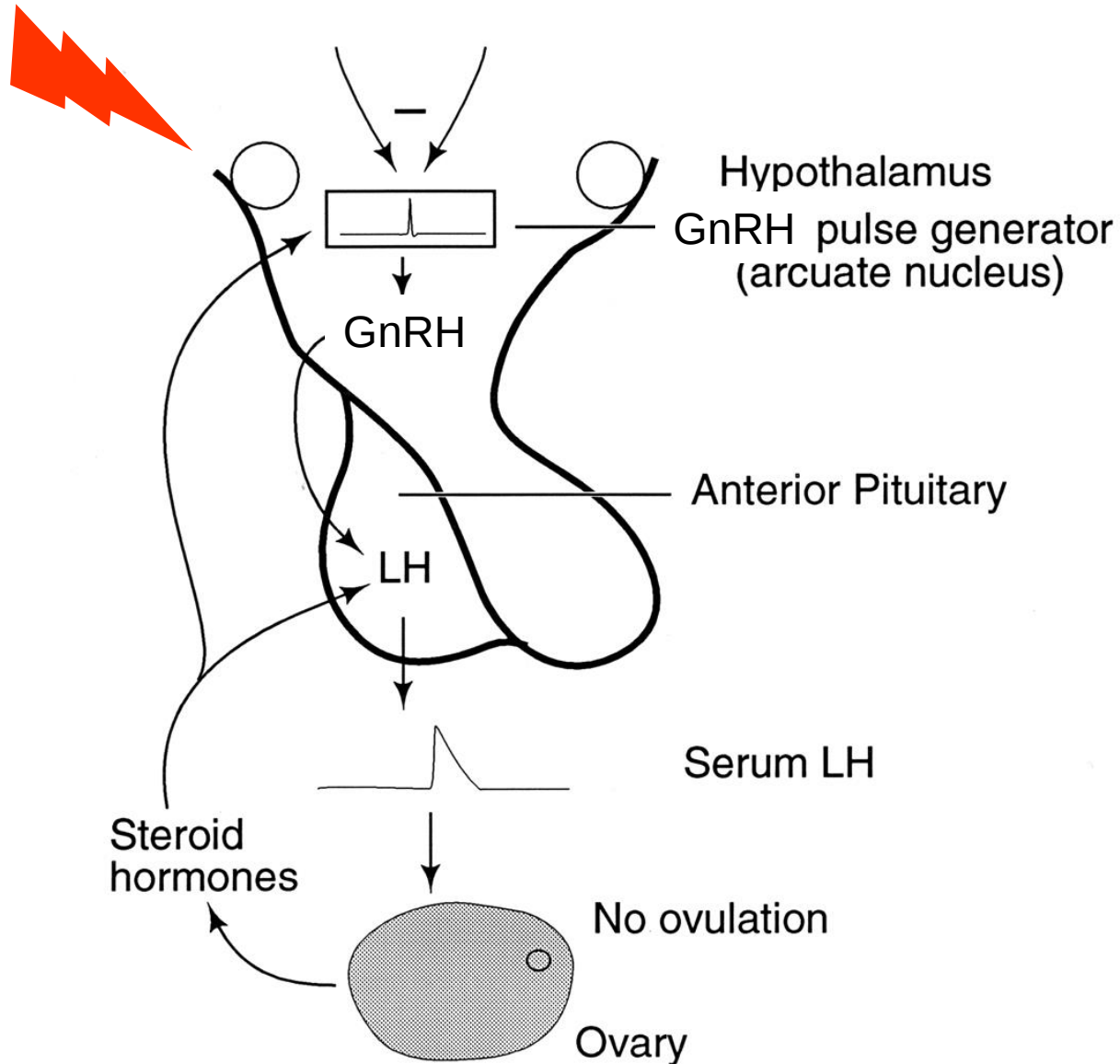
Kevin O'Byrne

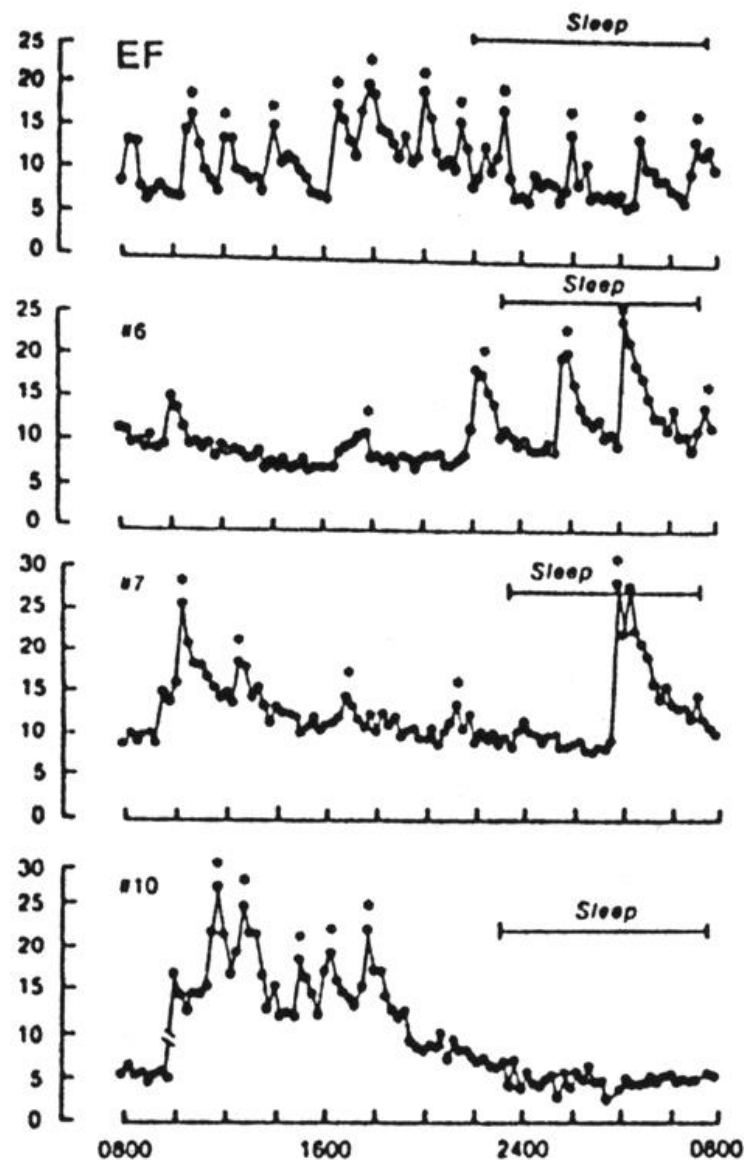
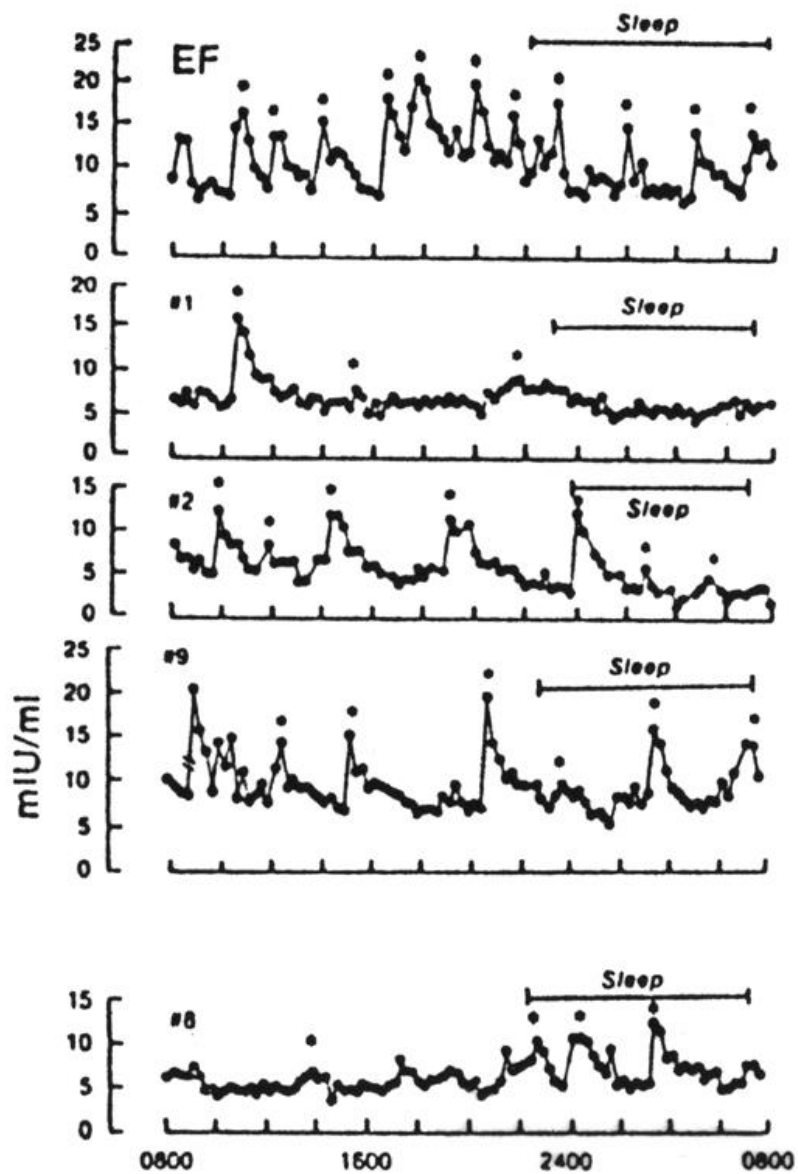
Division of Endocrinology & Reproduction
School of Biomedical & Health Sciences



Functional hypothalamic amenorrhoea

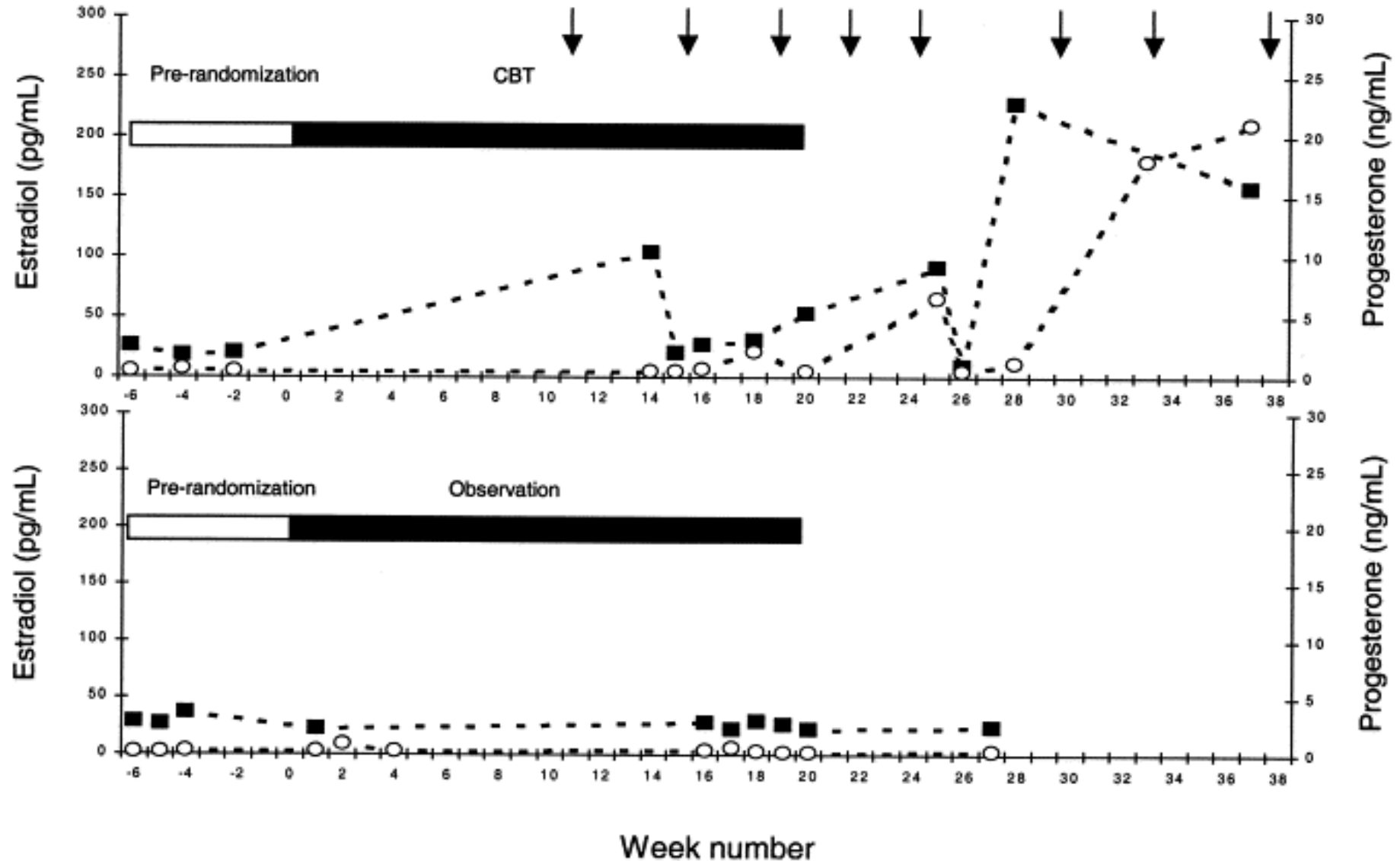
stress

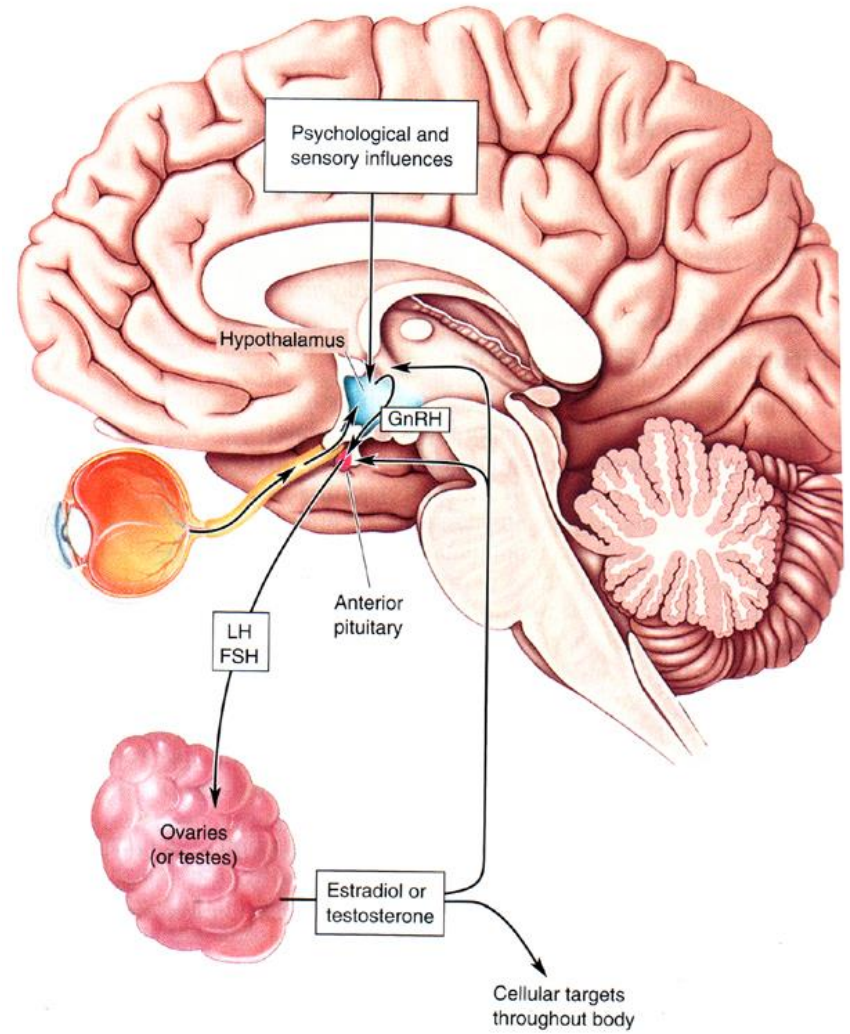
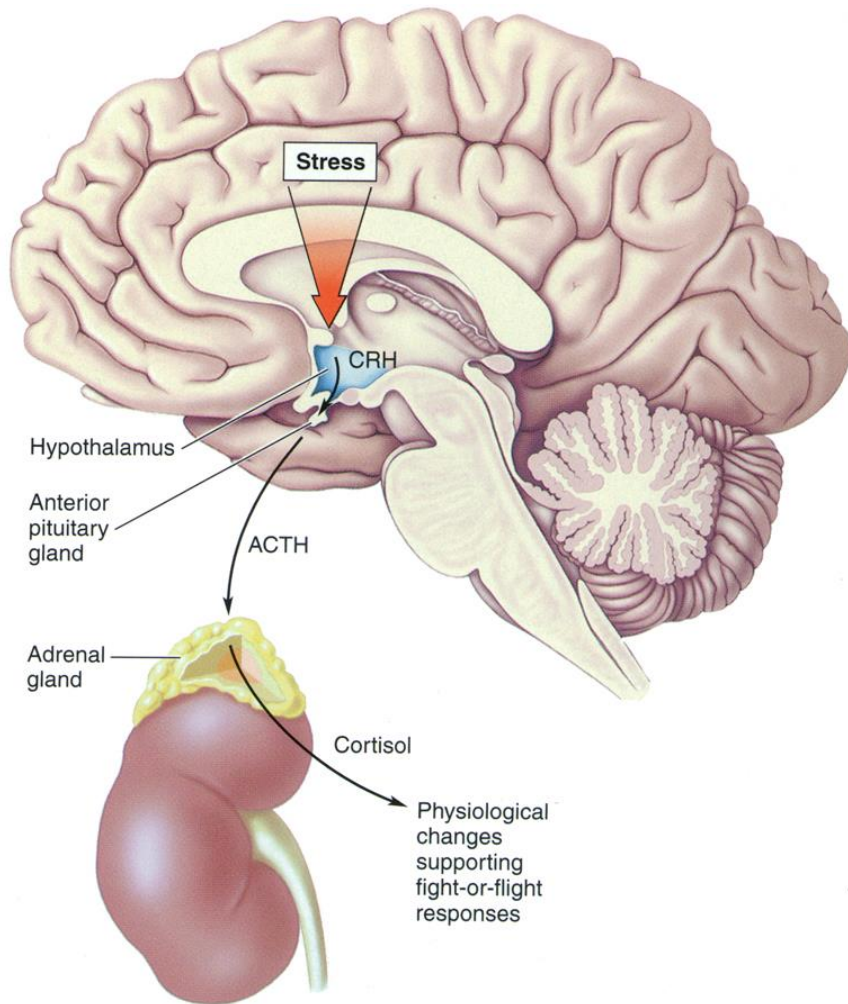




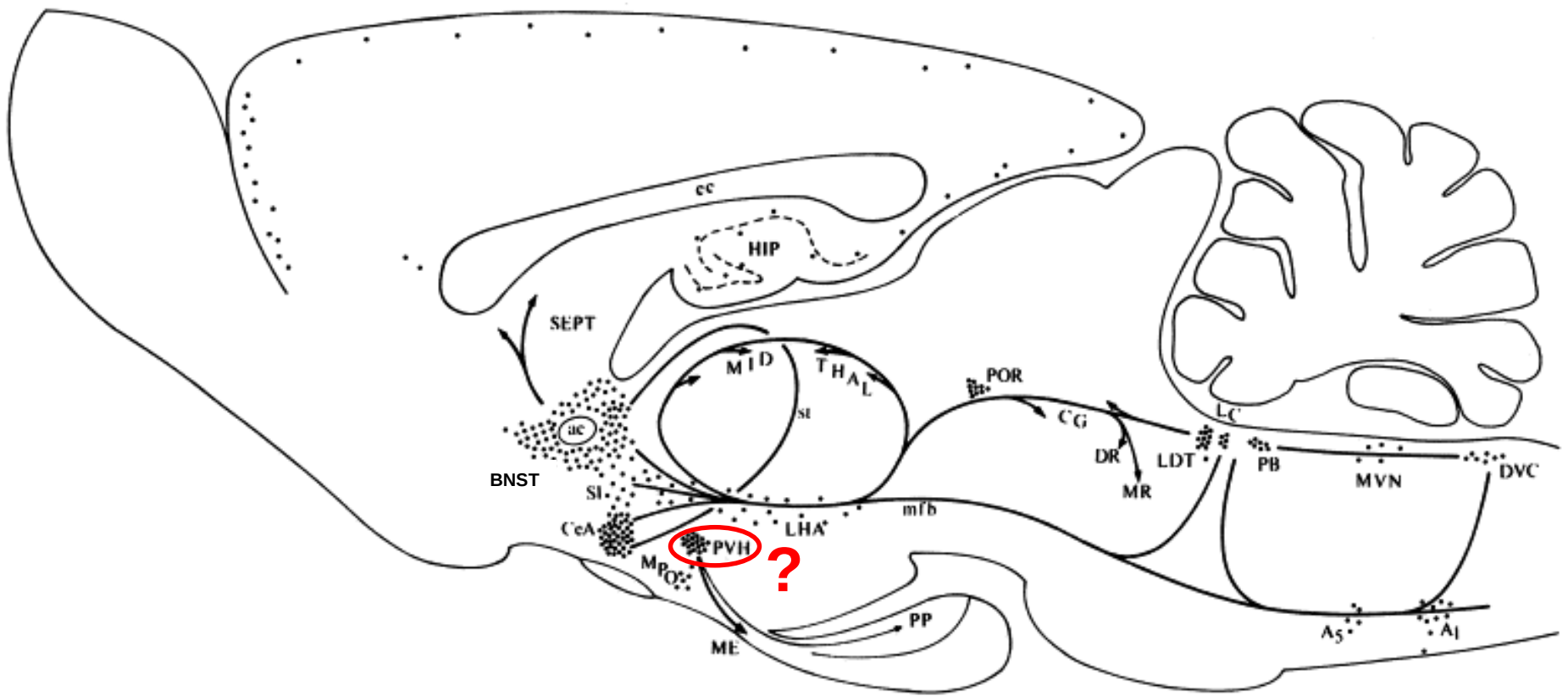
Clock Hours

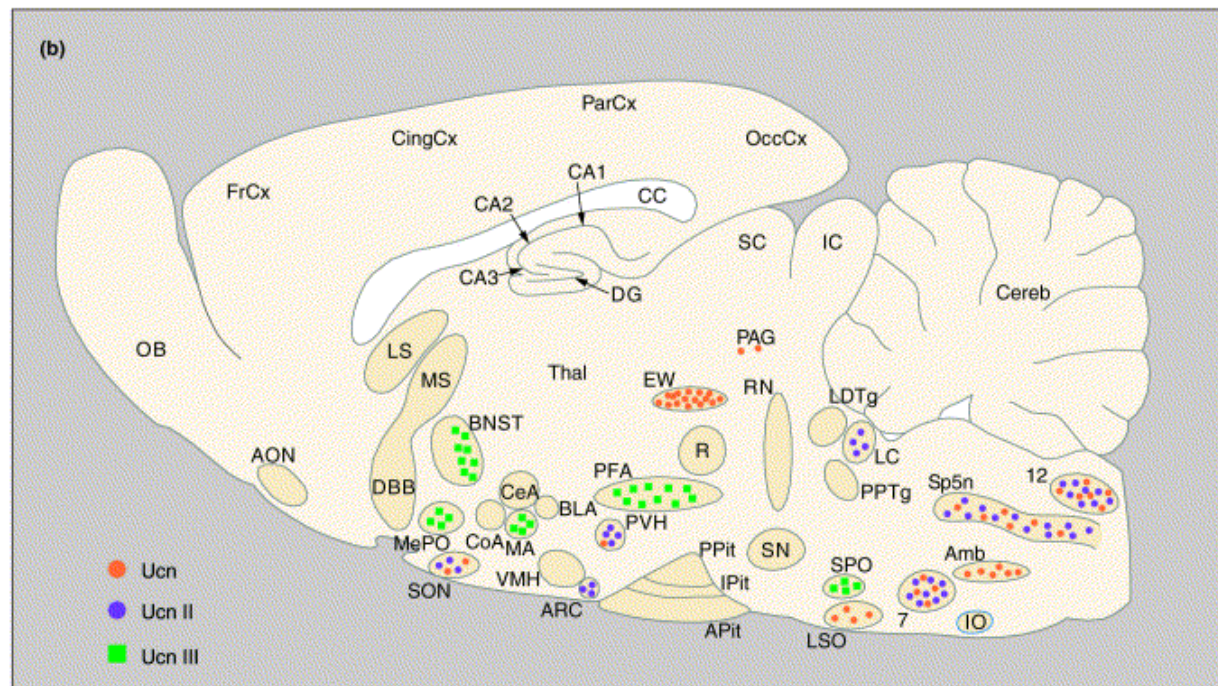
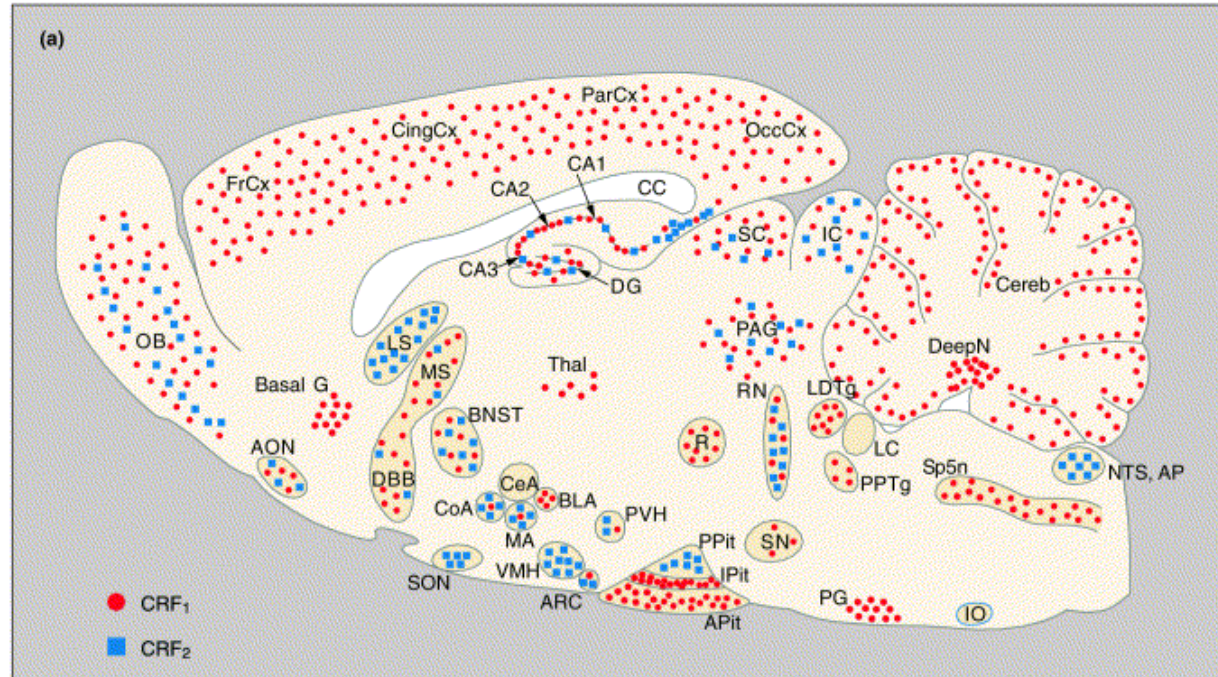
Effects of cognitive behavioural therapy on functional hypothalamic amenorrhoea

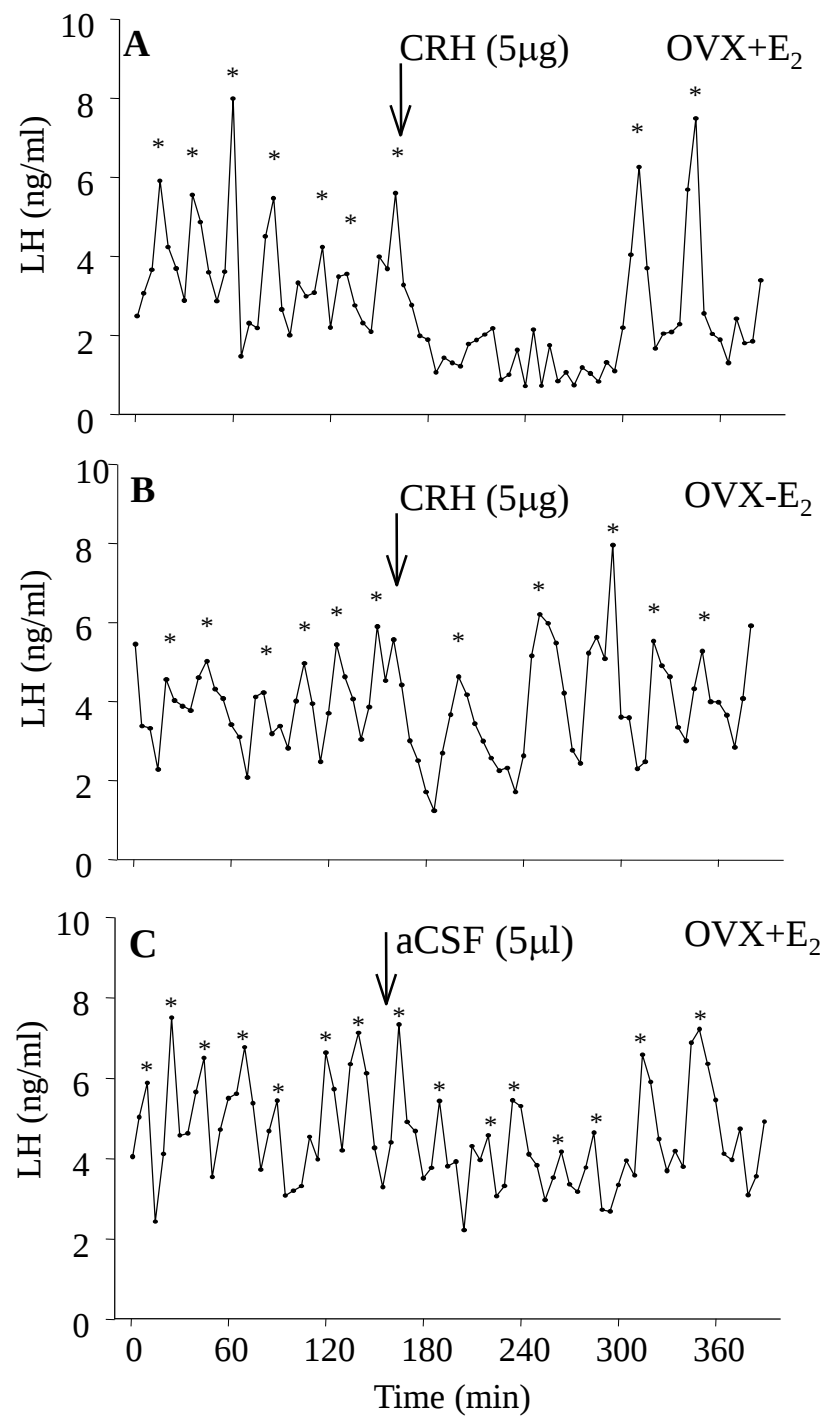


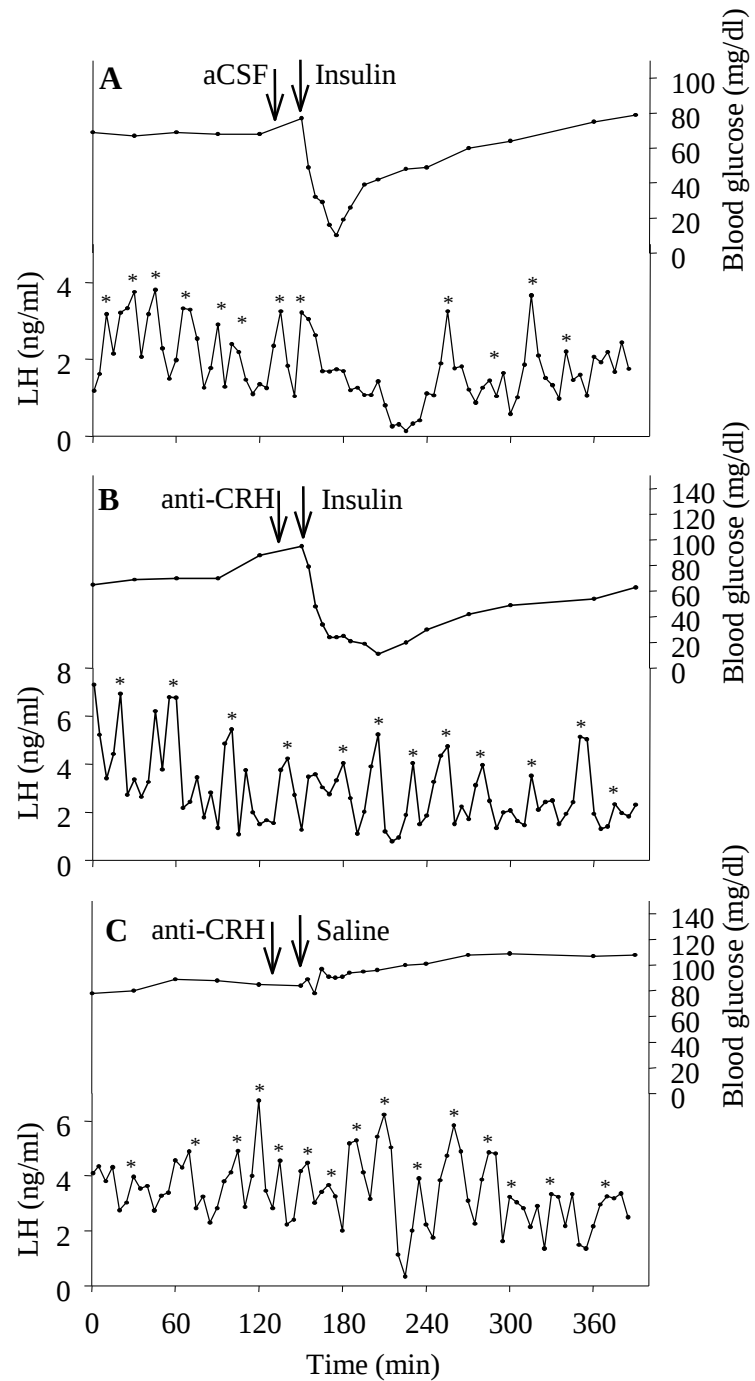


CRH neurones and fibres



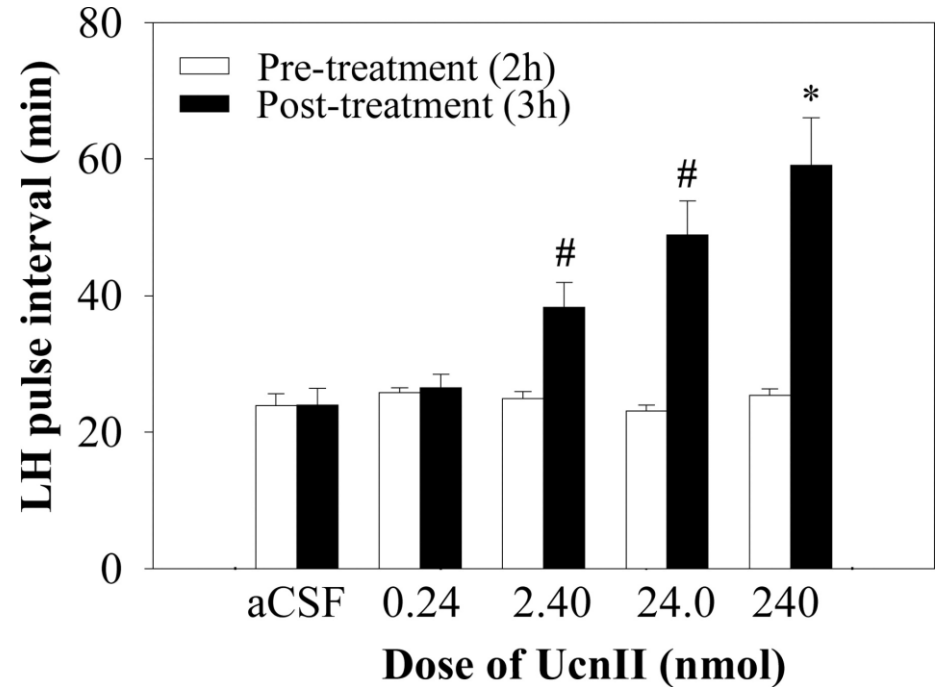
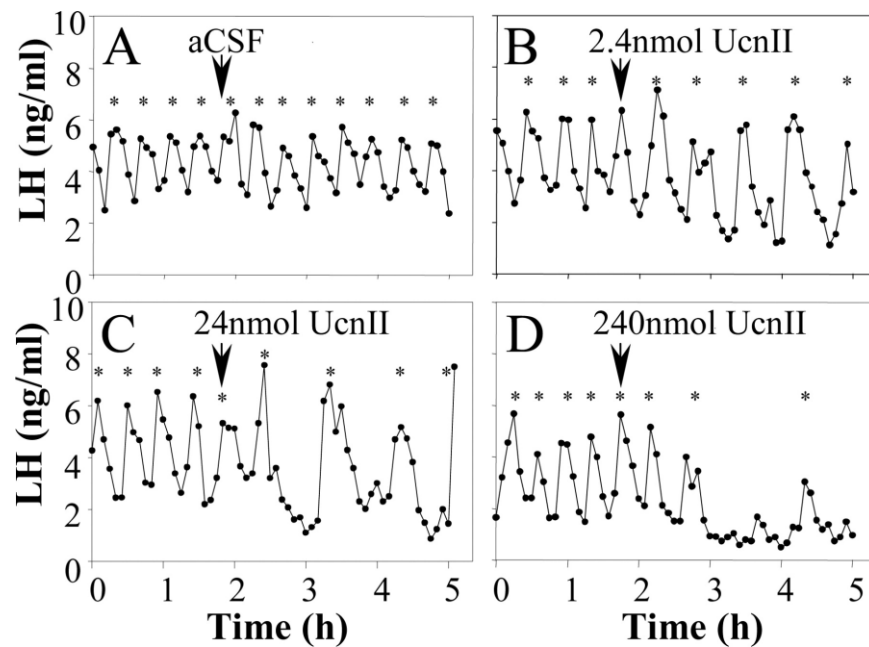




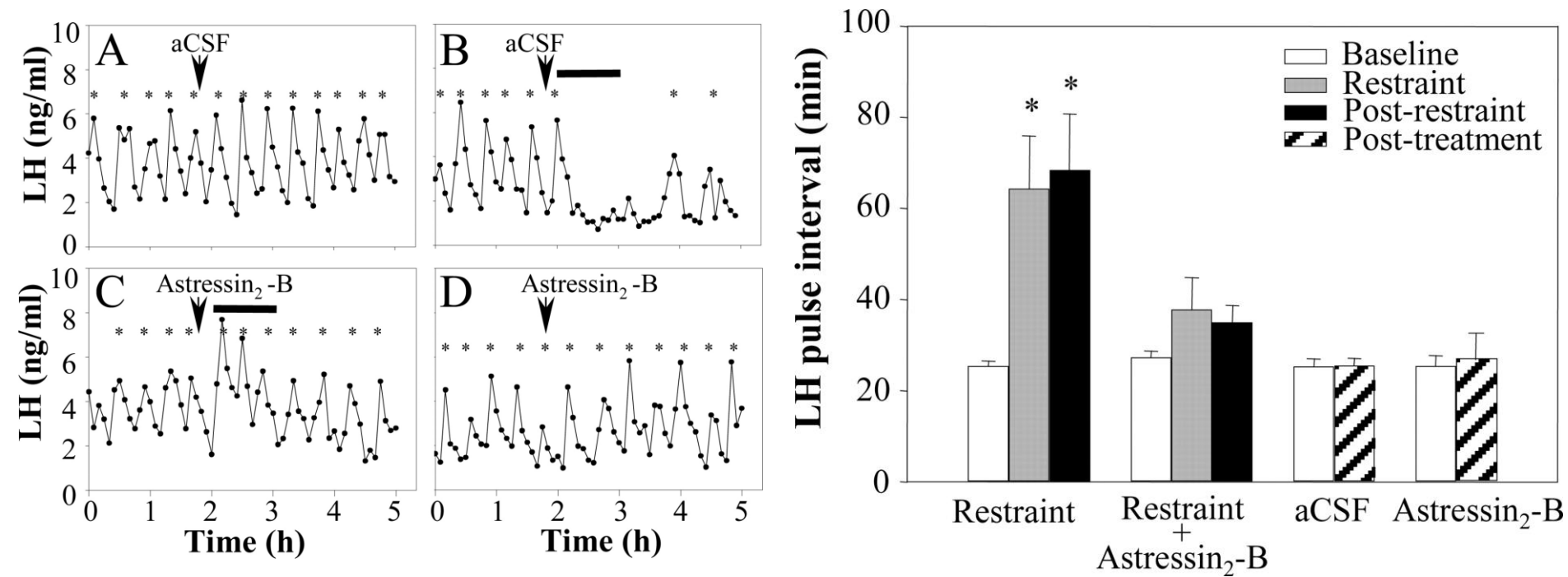


CRF-R1 or R2?

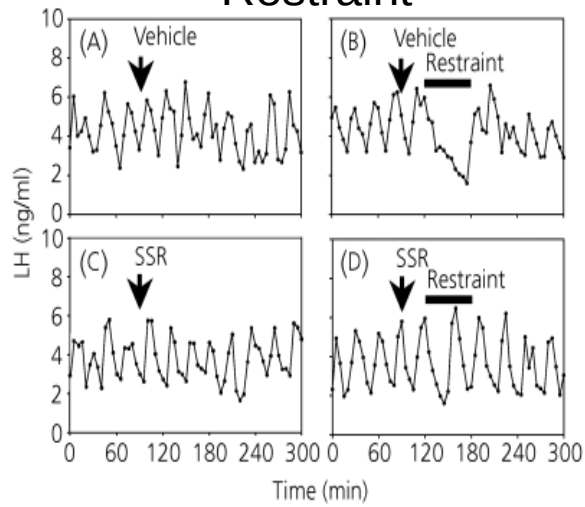
Effect of icv urocortin-II on pulsatile LH secretion in the rat



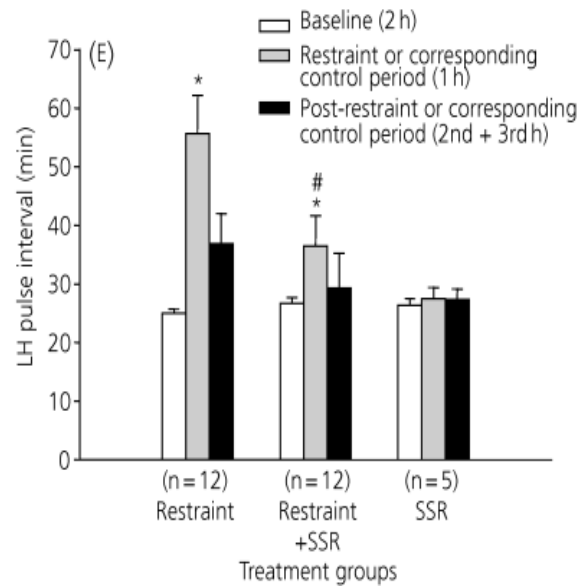
Effects of the selective type 2 CRF receptor antagonist, astressin₂-B, on restraint stress-induced suppression of LH pulsatile secretion in the rat



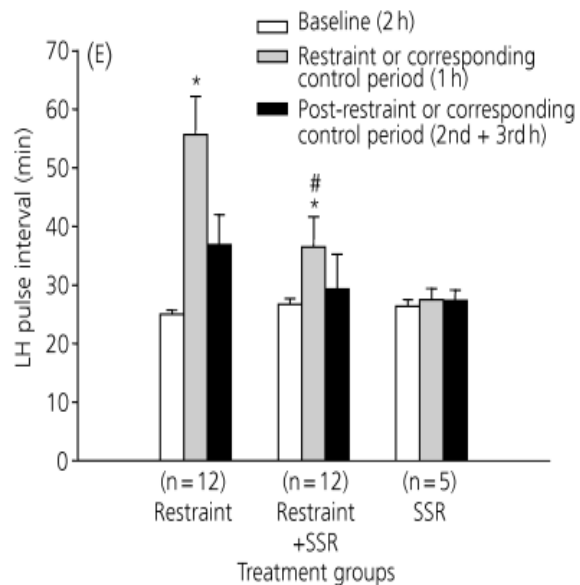
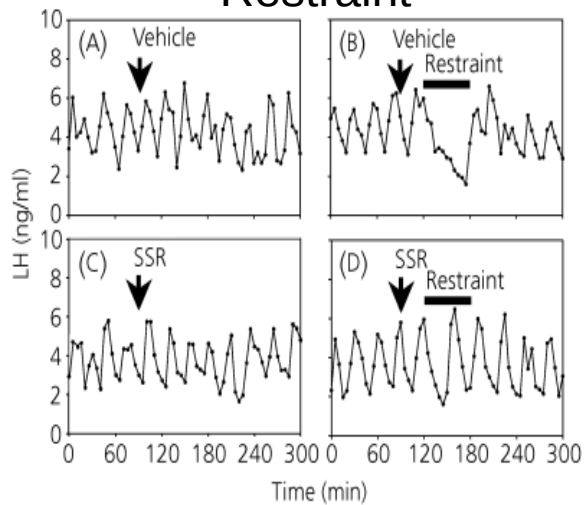
Restraint



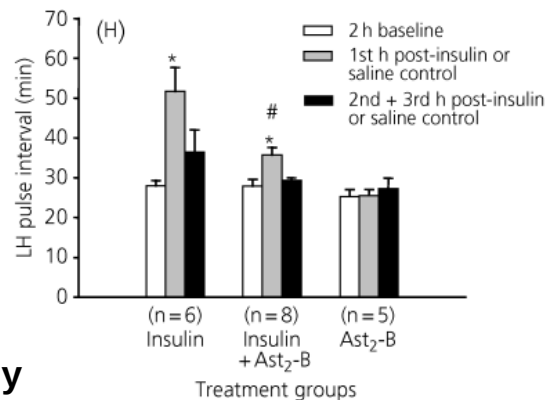
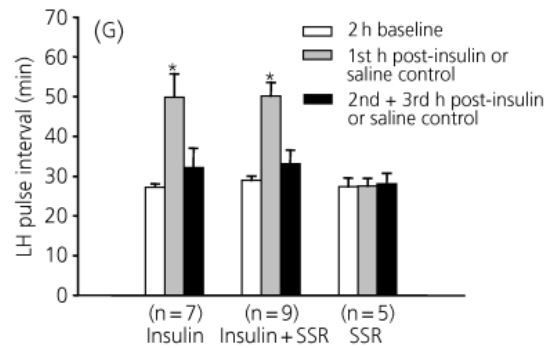
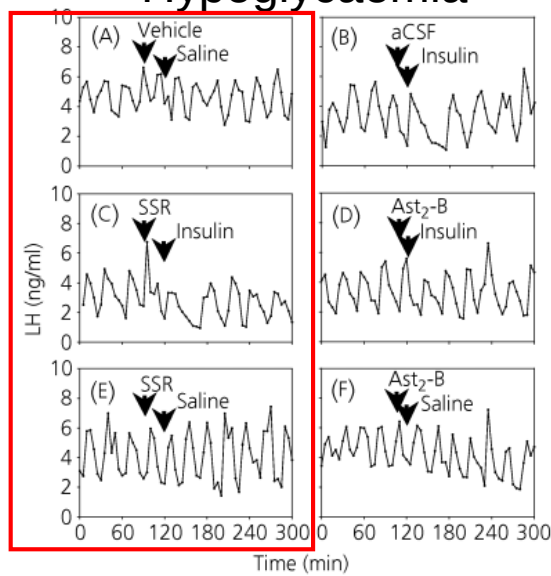
SSR = Selective CRH-R1 antagonist



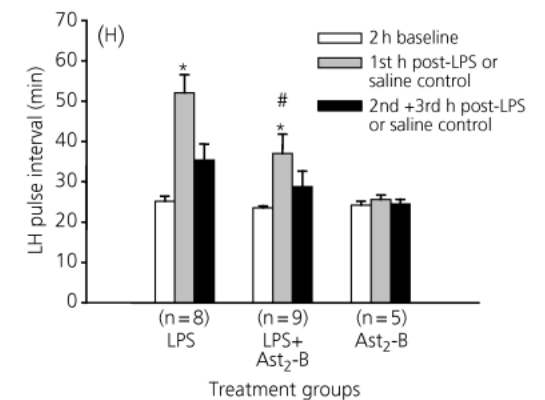
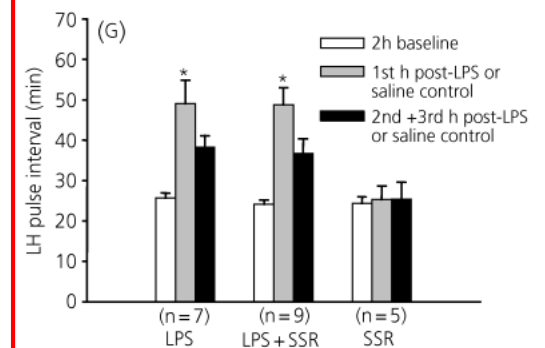
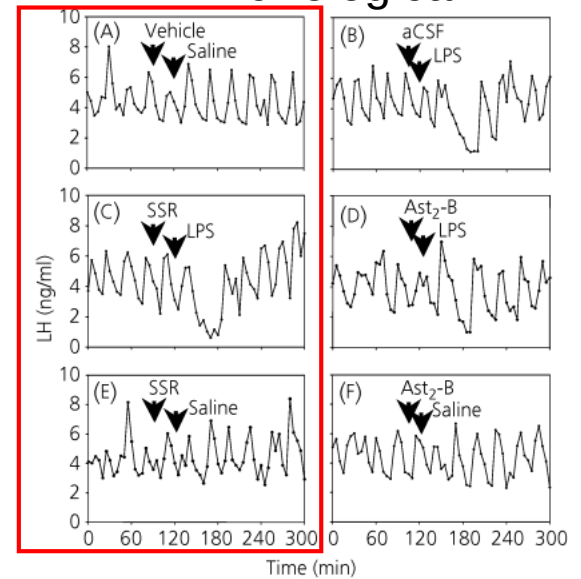
Restraint



Hypoglycaemia

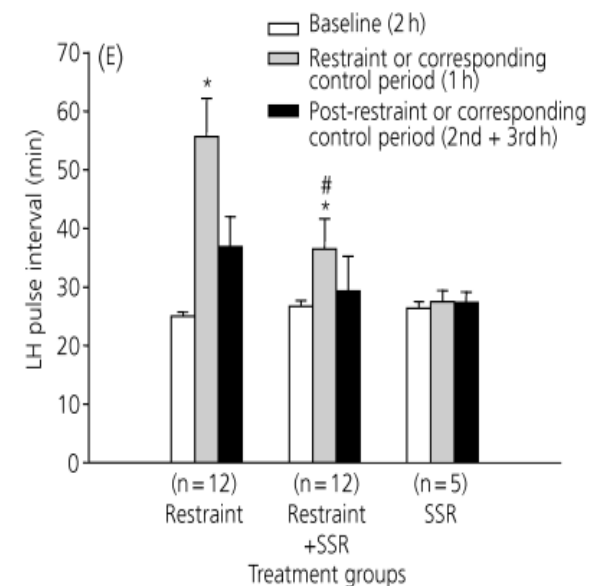
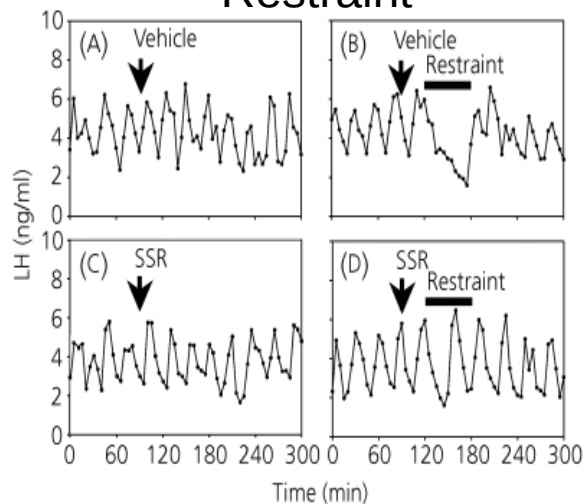


Immunological

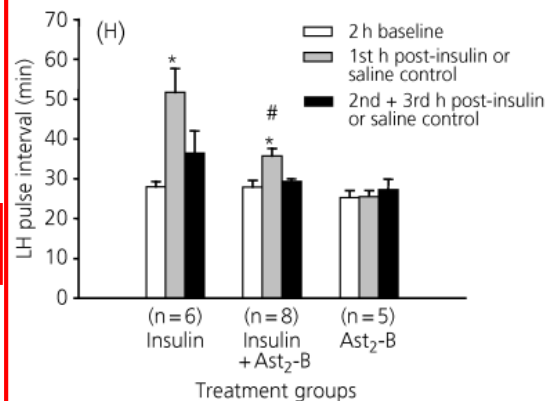
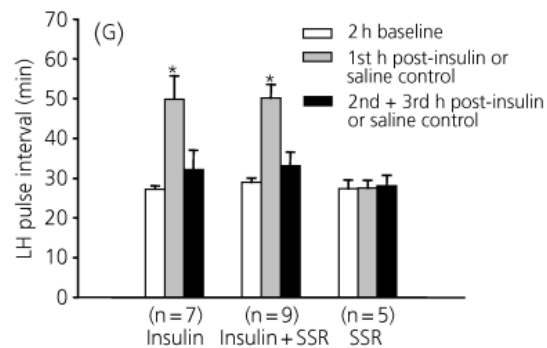
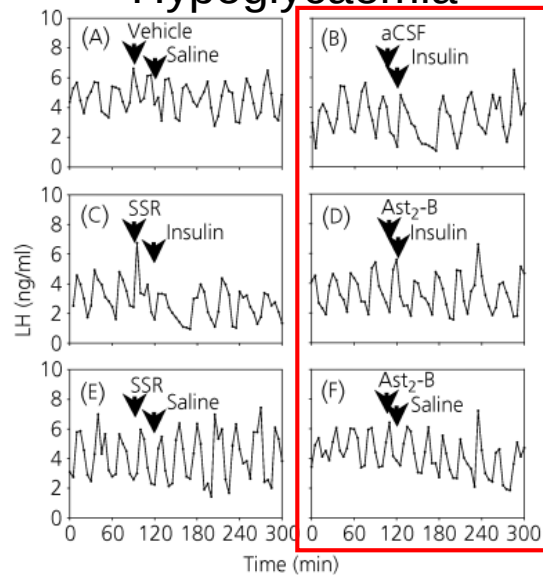


SSR = Selective CRH-R1 antagonist

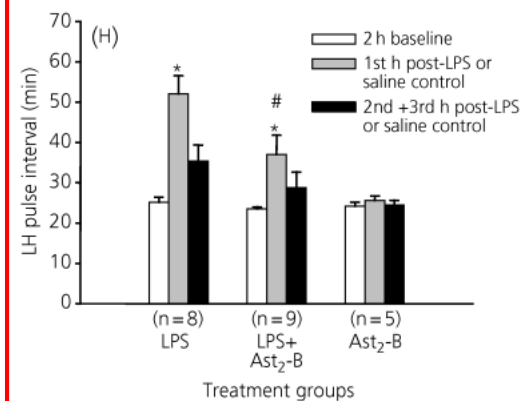
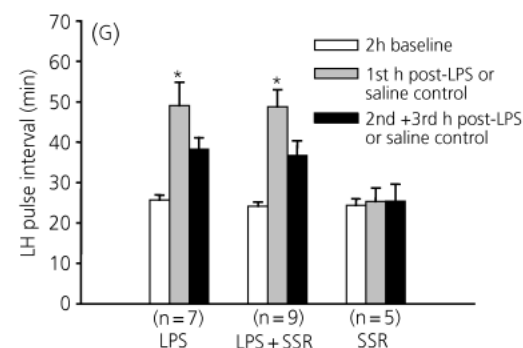
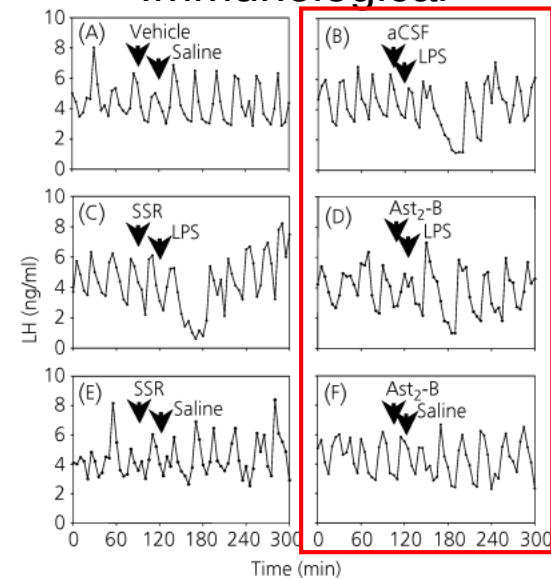
Restraint



Hypoglycaemia

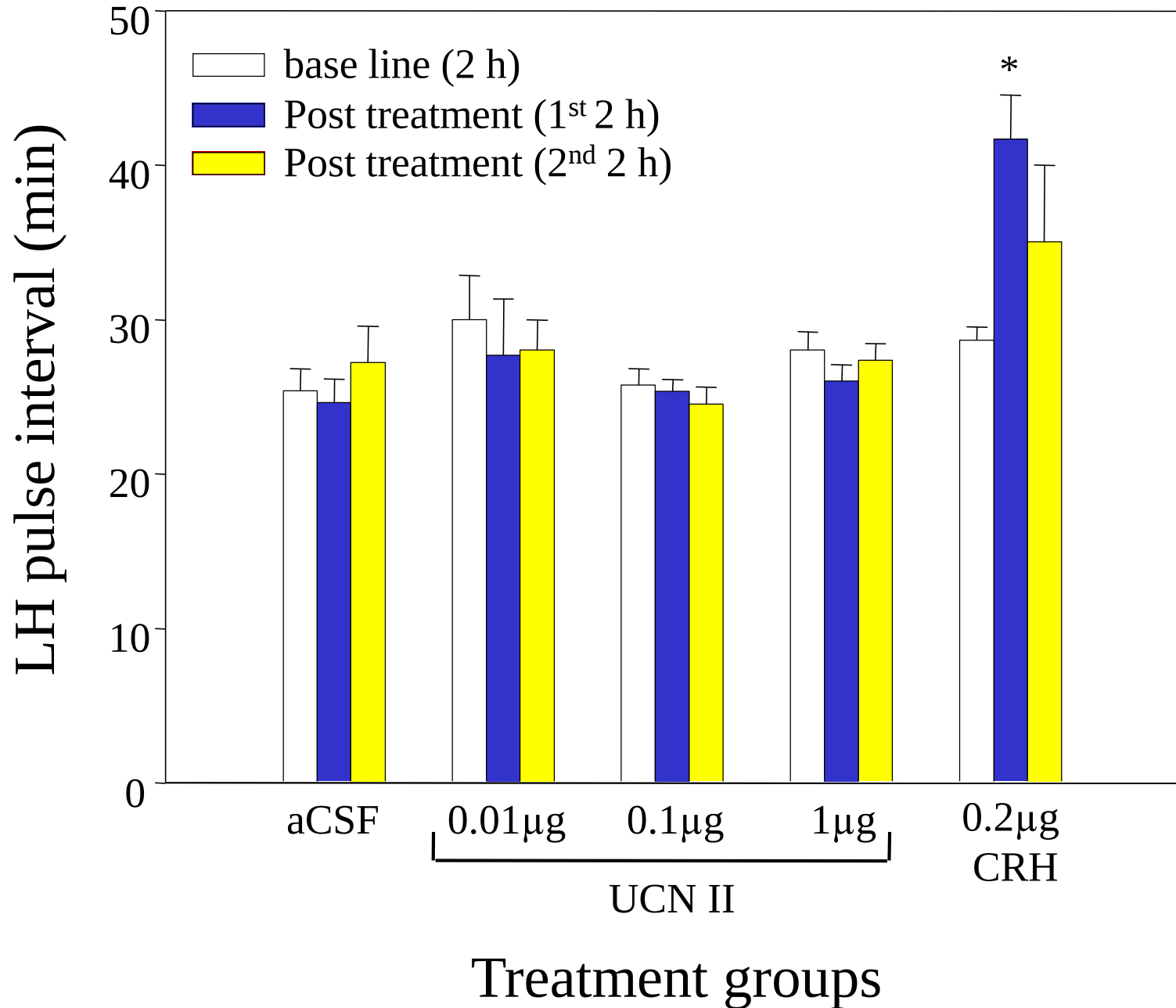


Immunological

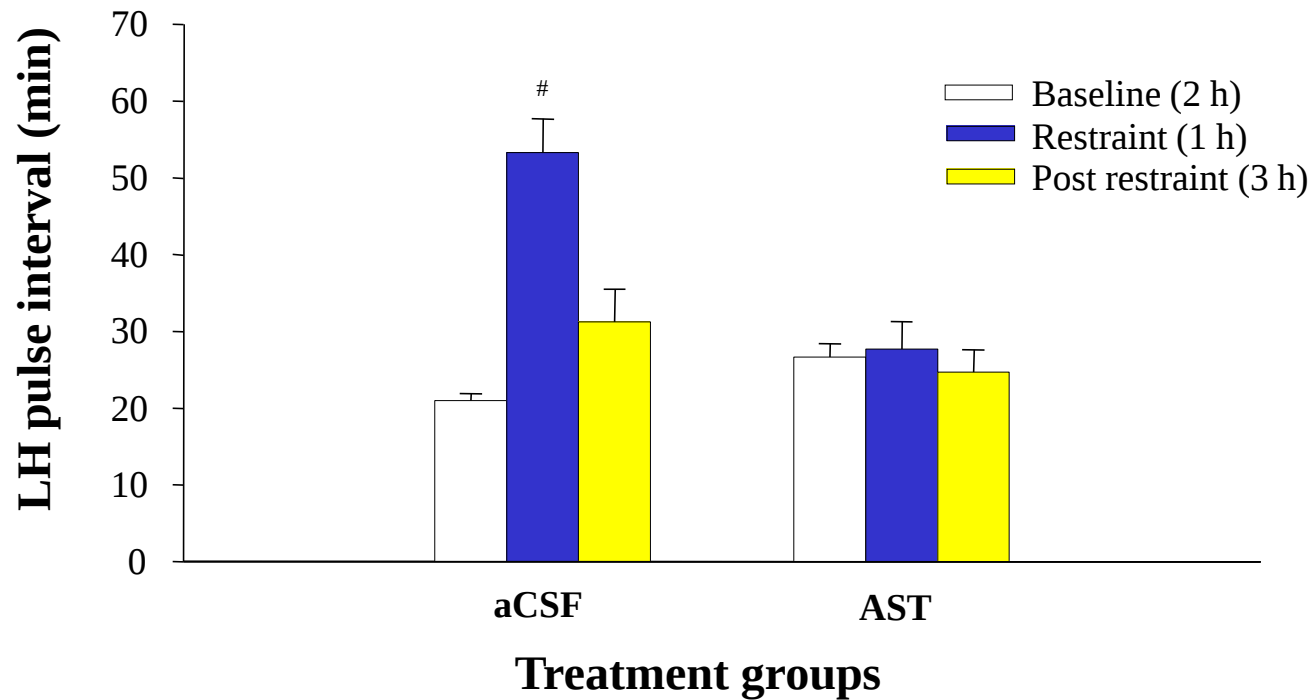
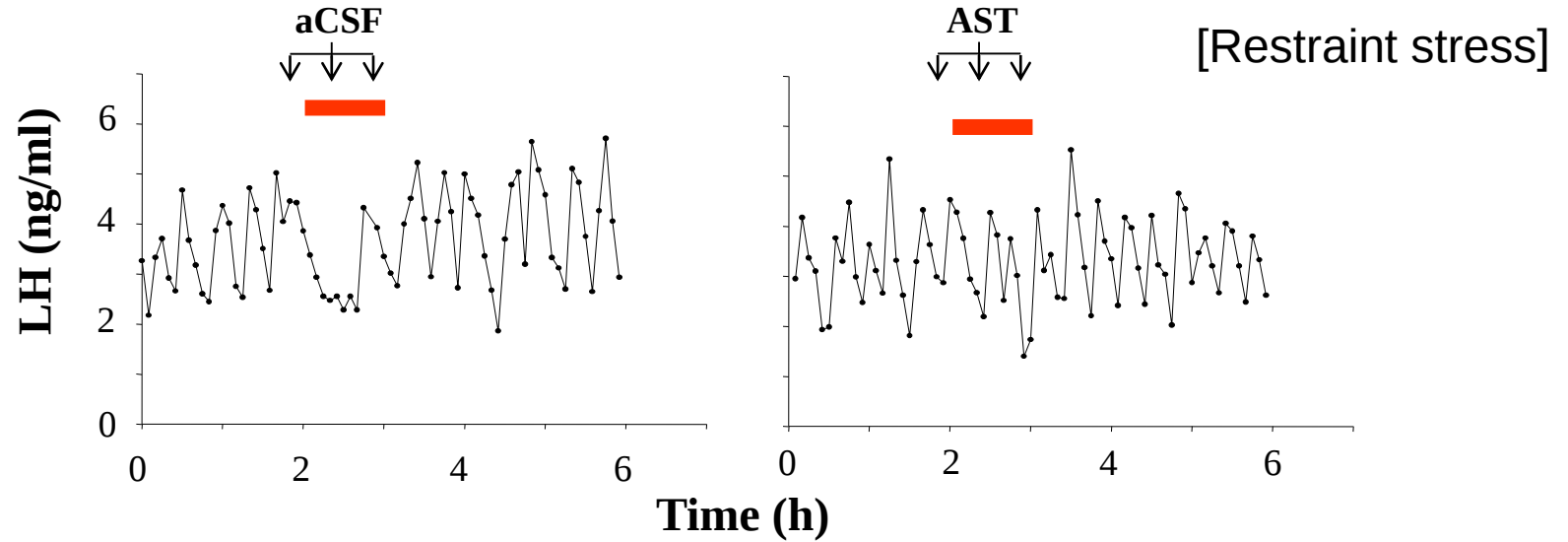


AST₂-B = Selective CRH-R2 antagonist

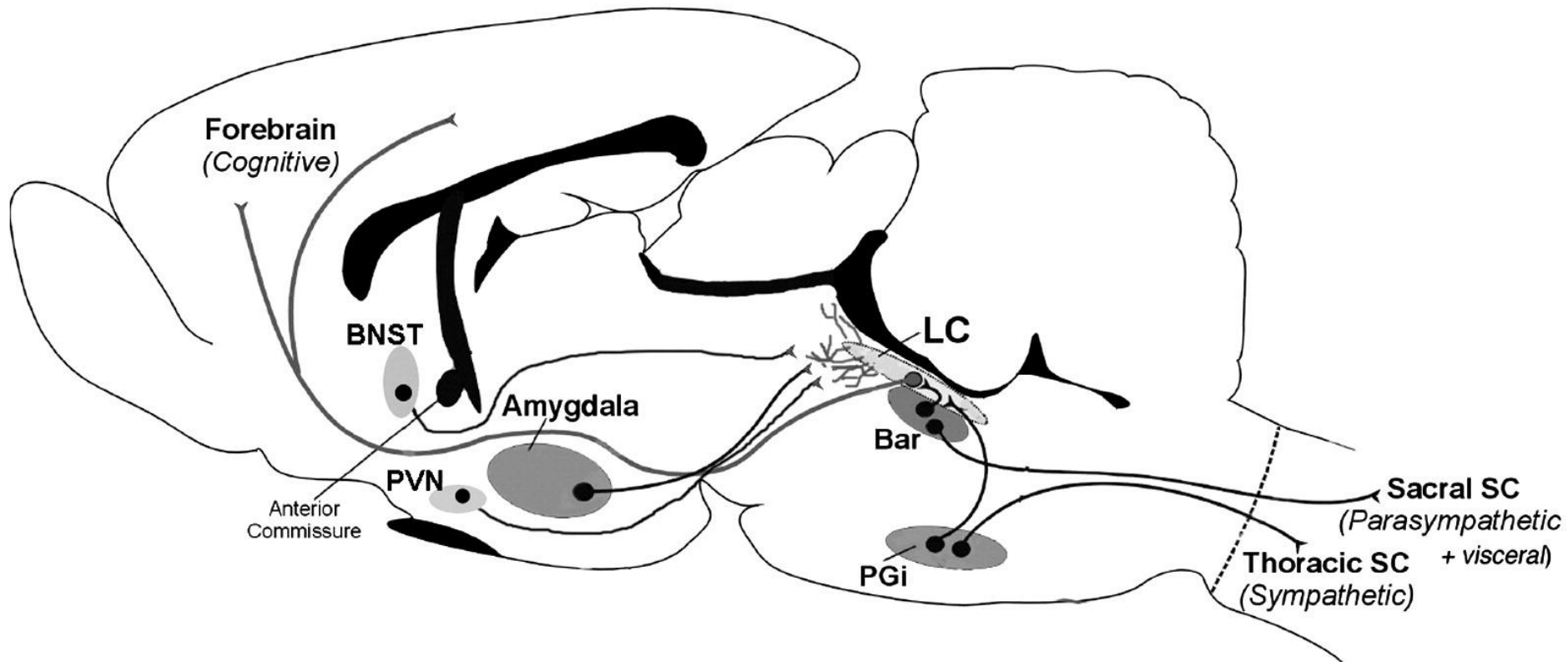
Intra-mPOA Urocortin II or CRH

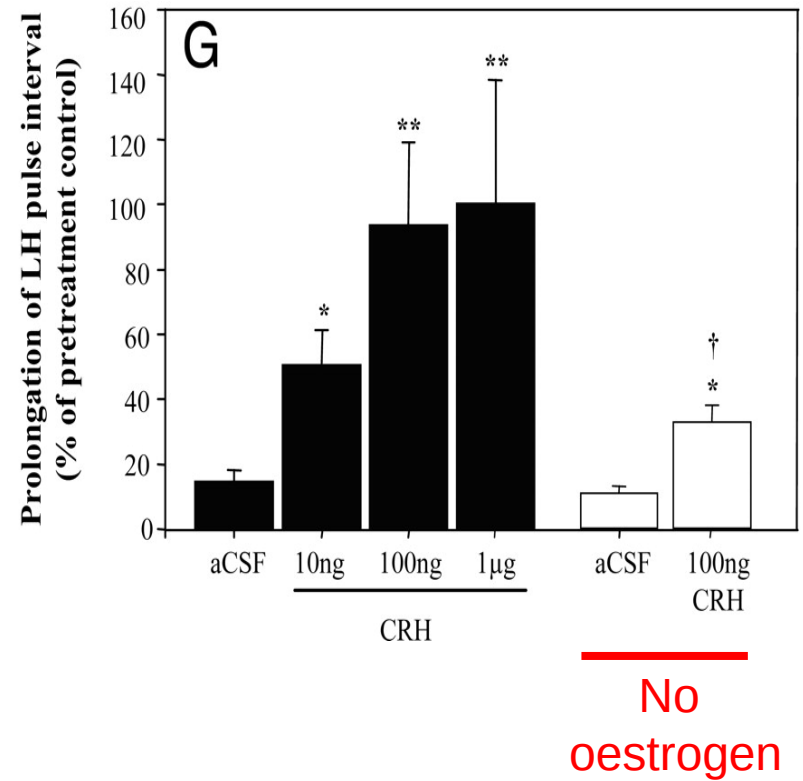
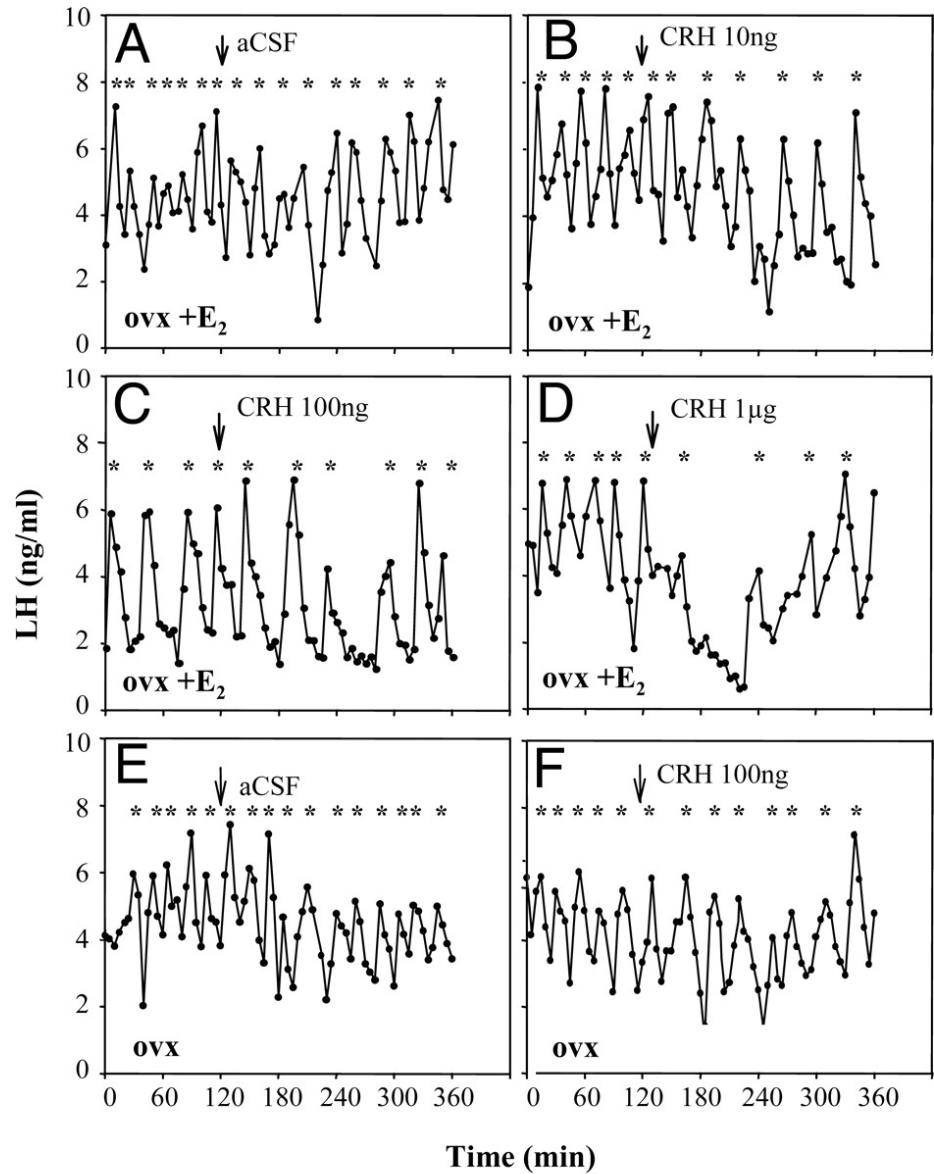


Medial Preoptic Area

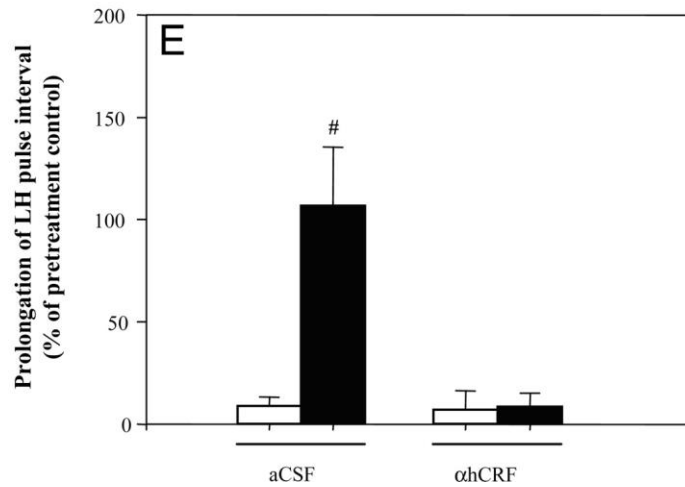
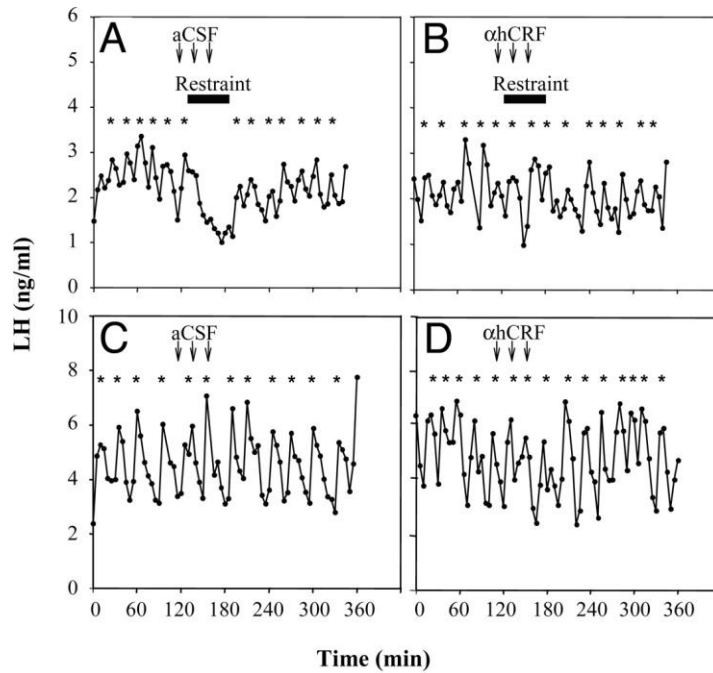


Locus Coeruleus

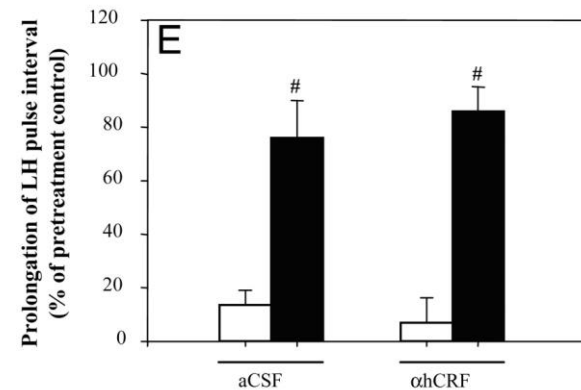
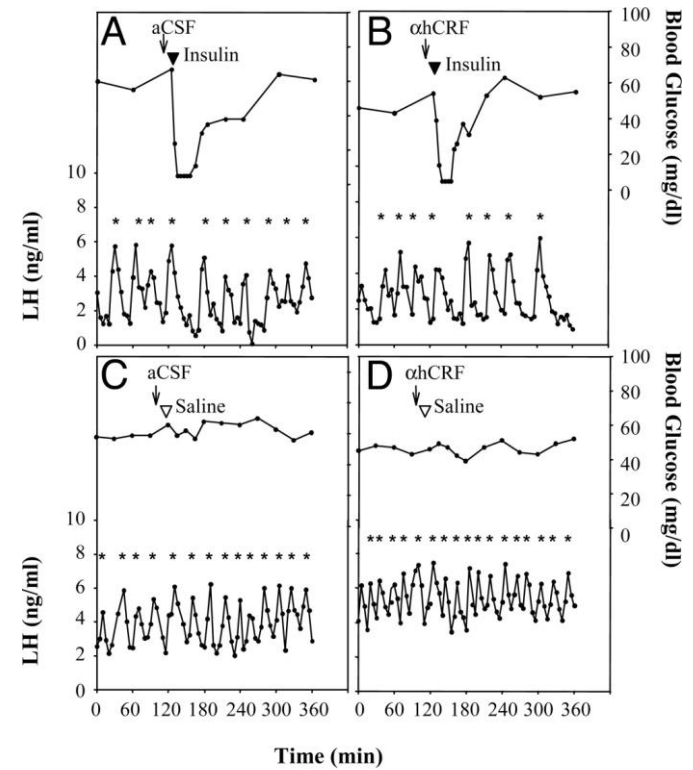




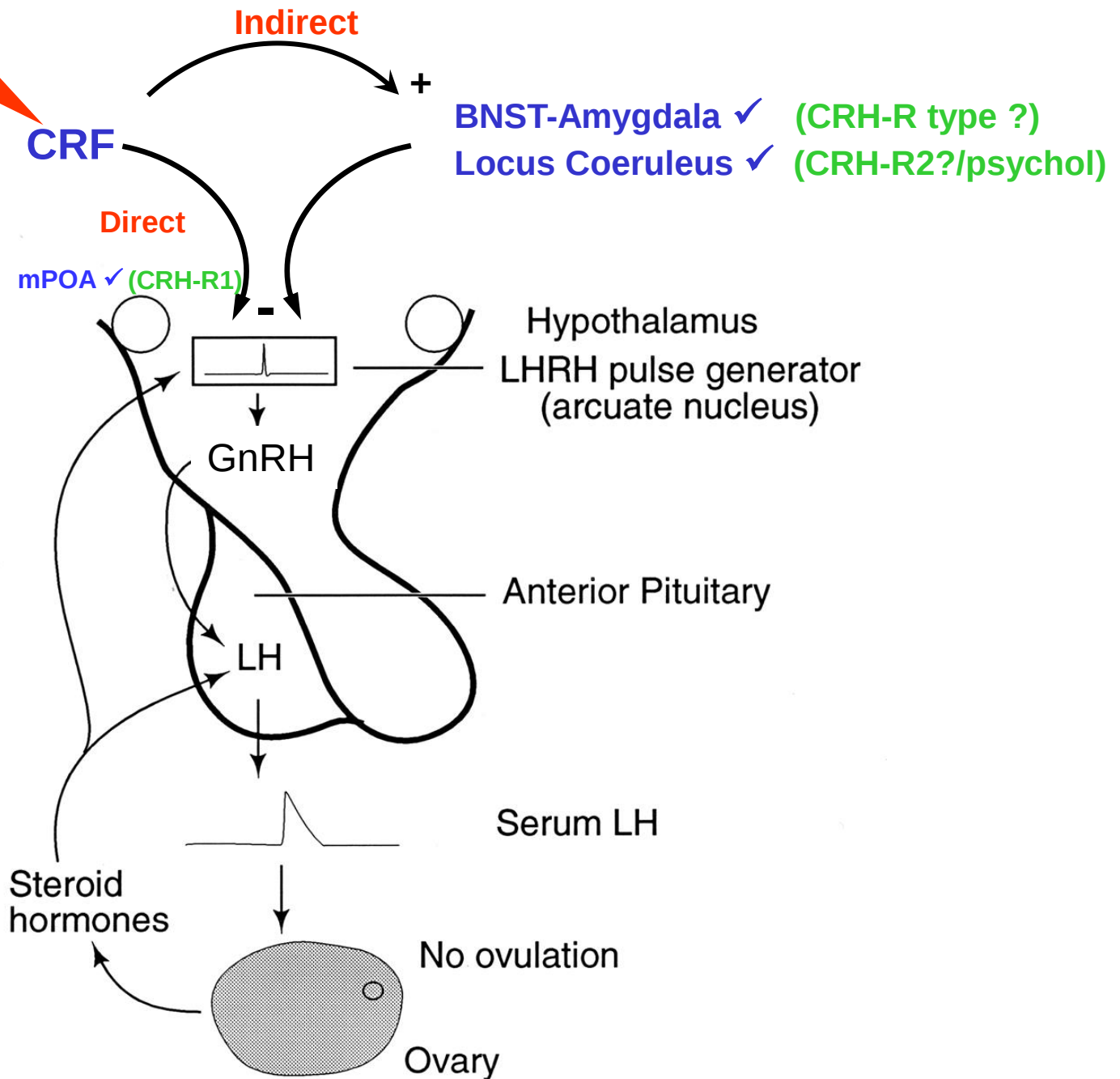
Restraint



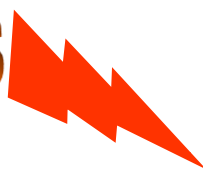
Hypoglycaemia



stress



stress



CRF

Indirect

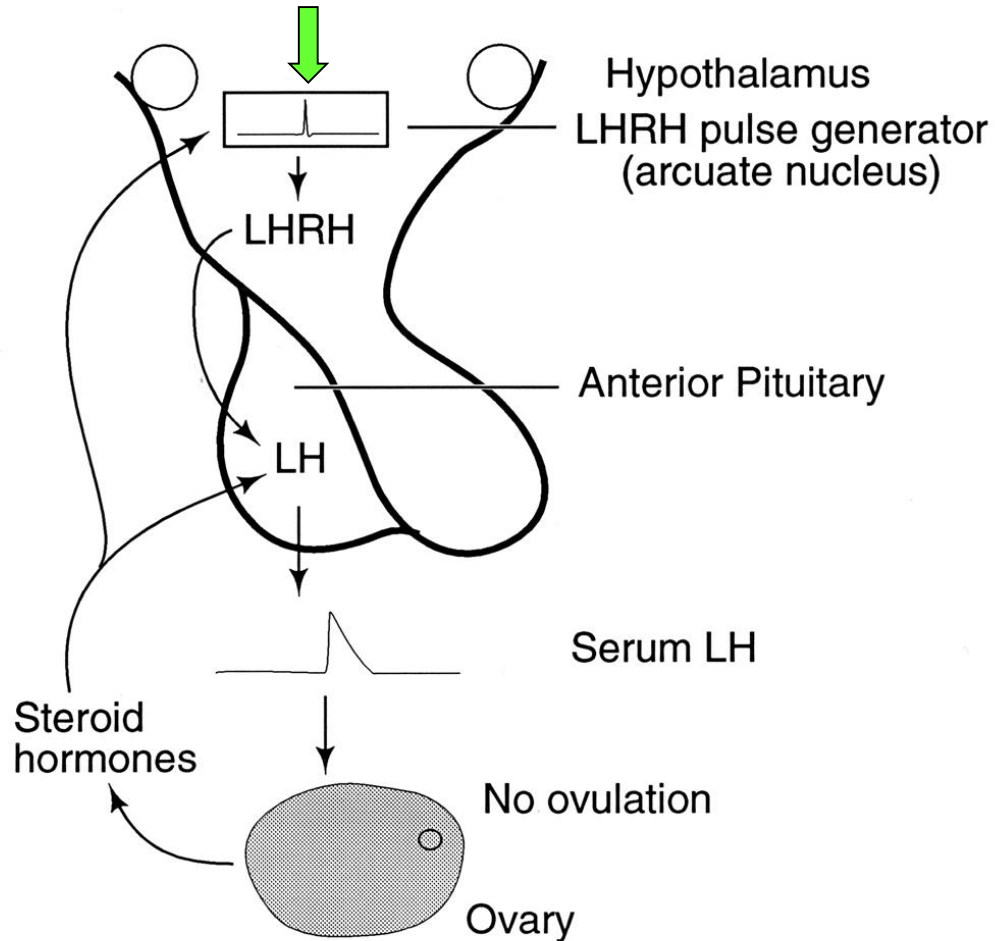
+

BNST-Amygdala ✓
Locus Coeruleus ✓

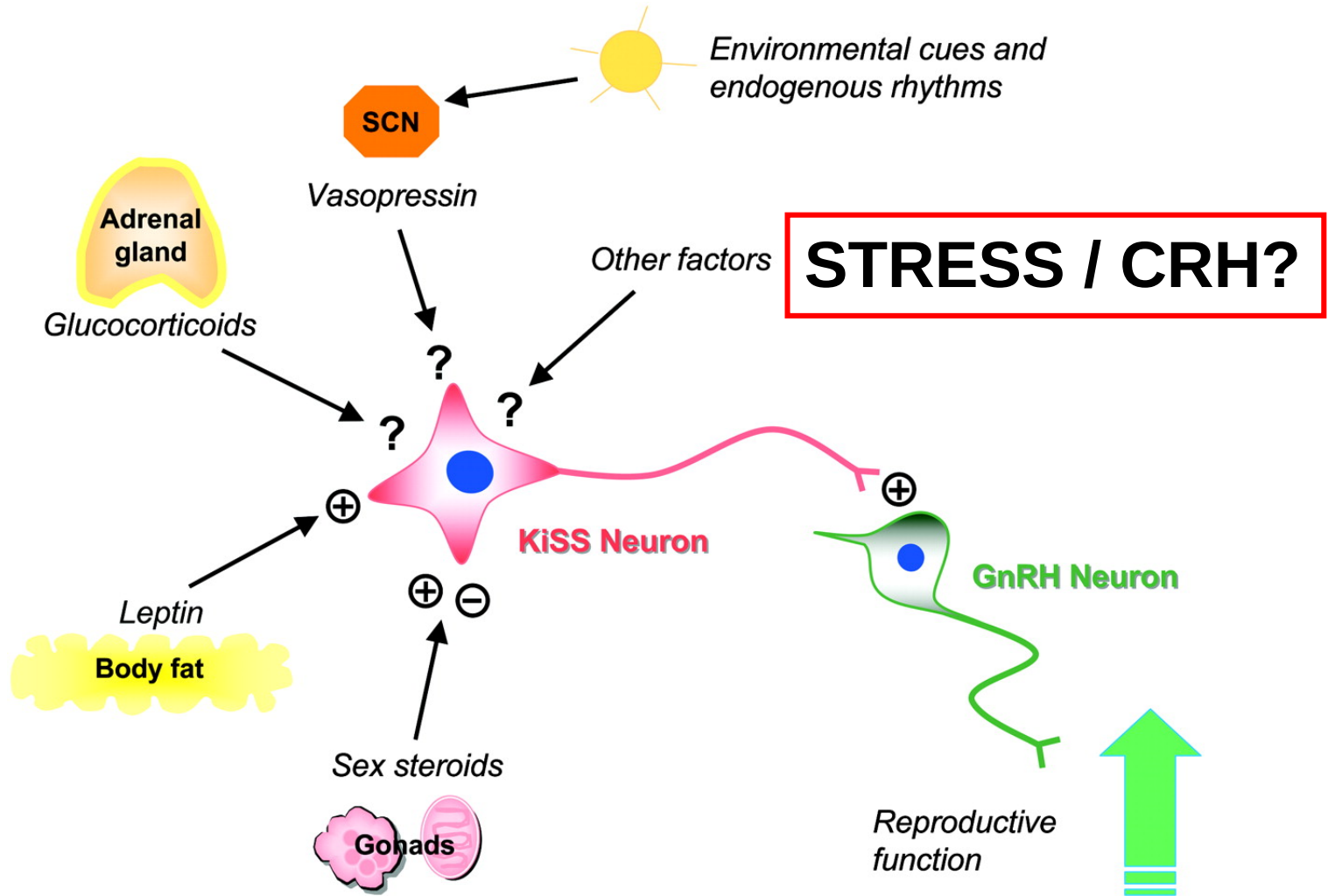
Direct

mPOA ✓

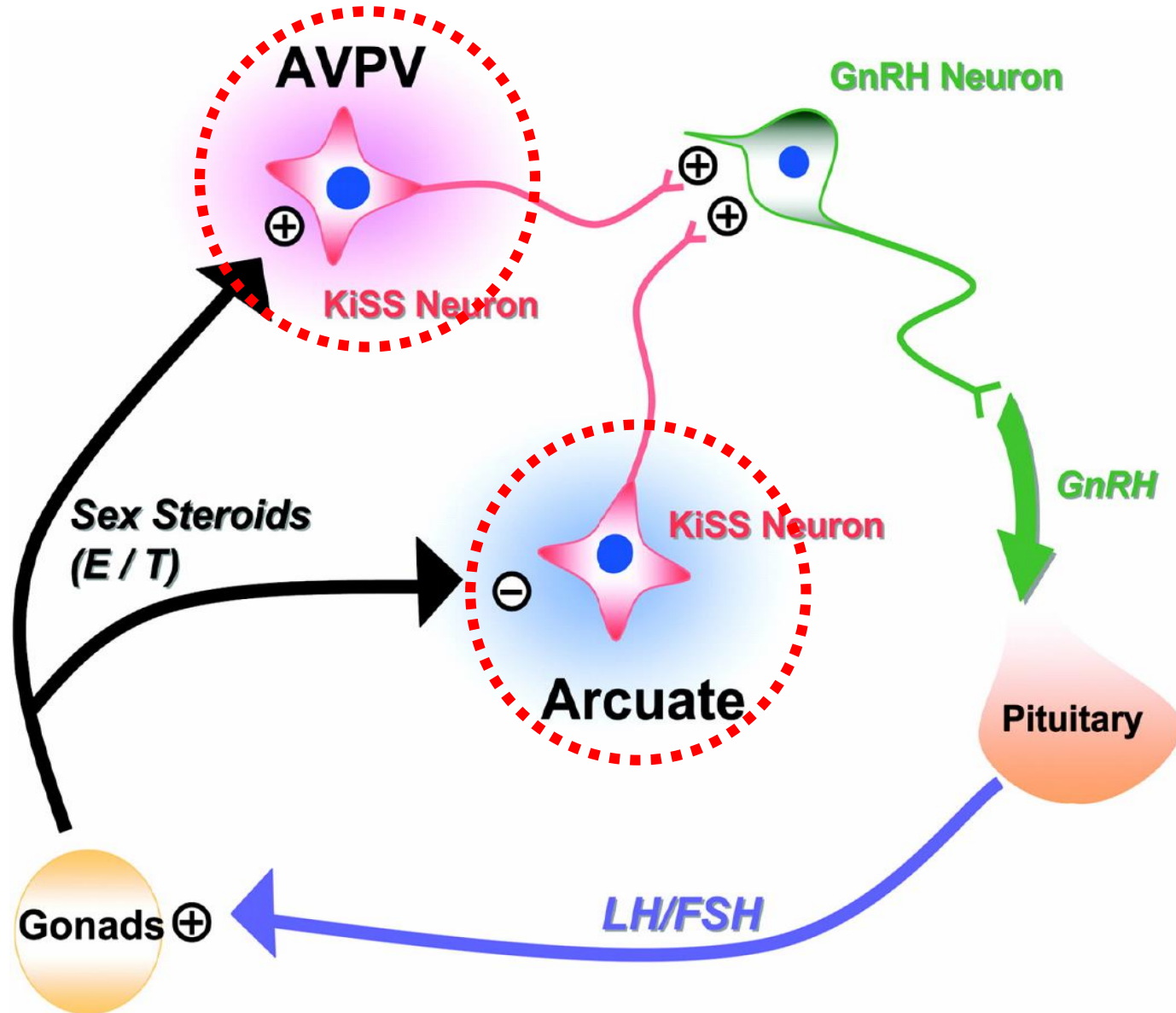
Kisspeptin



Kisspeptin neurones may act as central processors for relaying signals to GnRH neurones

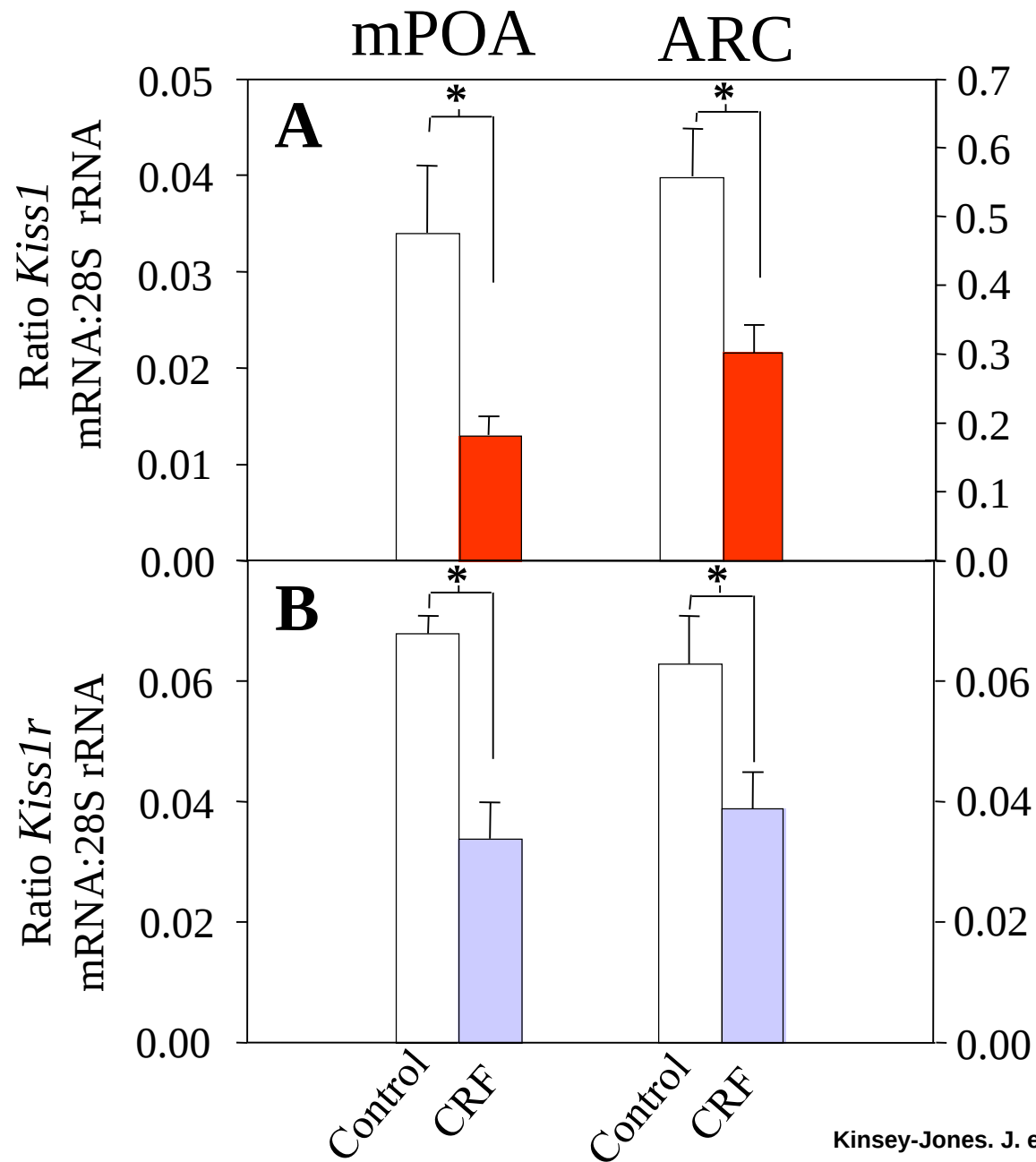


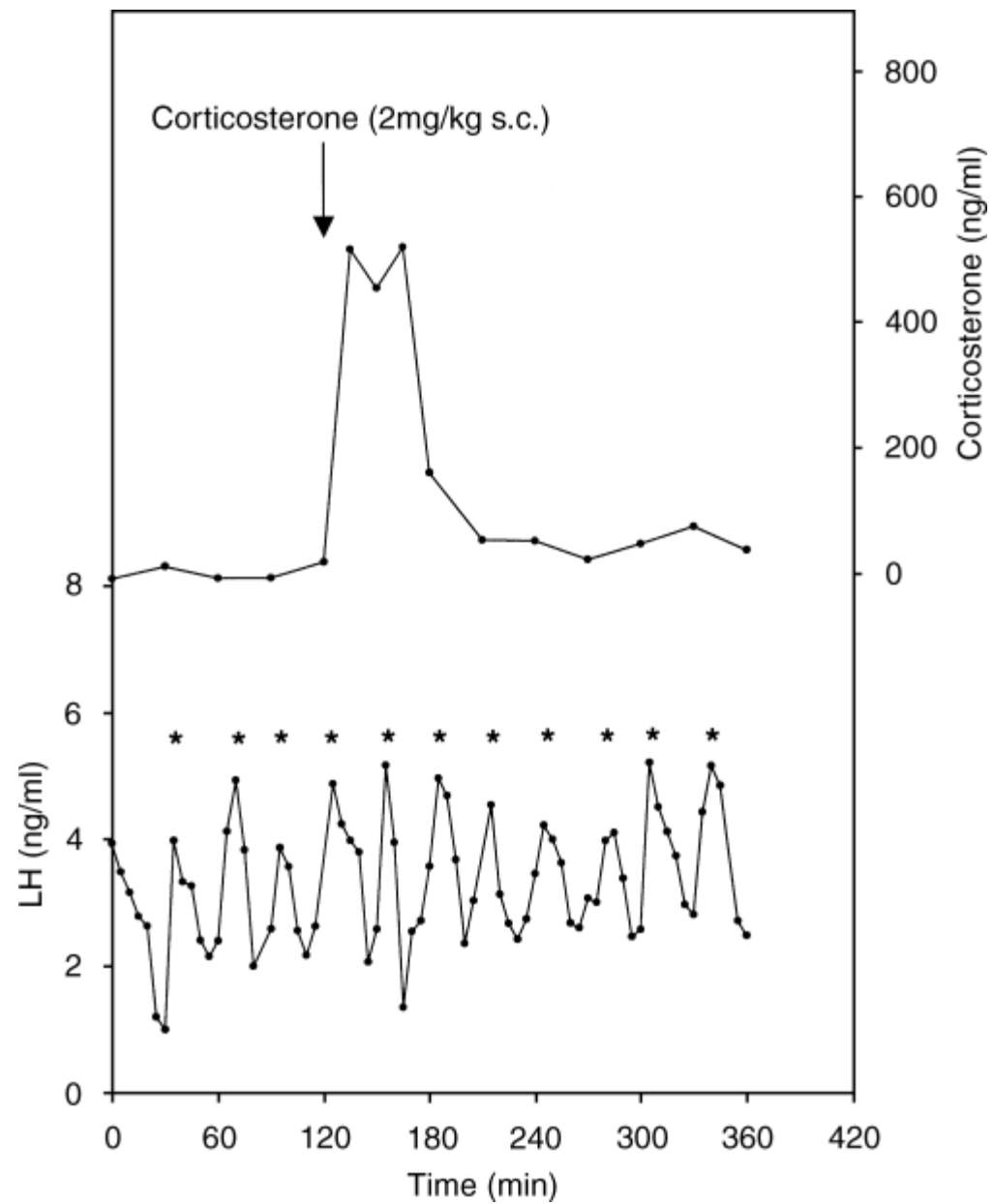
Kisspeptin stimulates the neuroendocrine reproductive axis

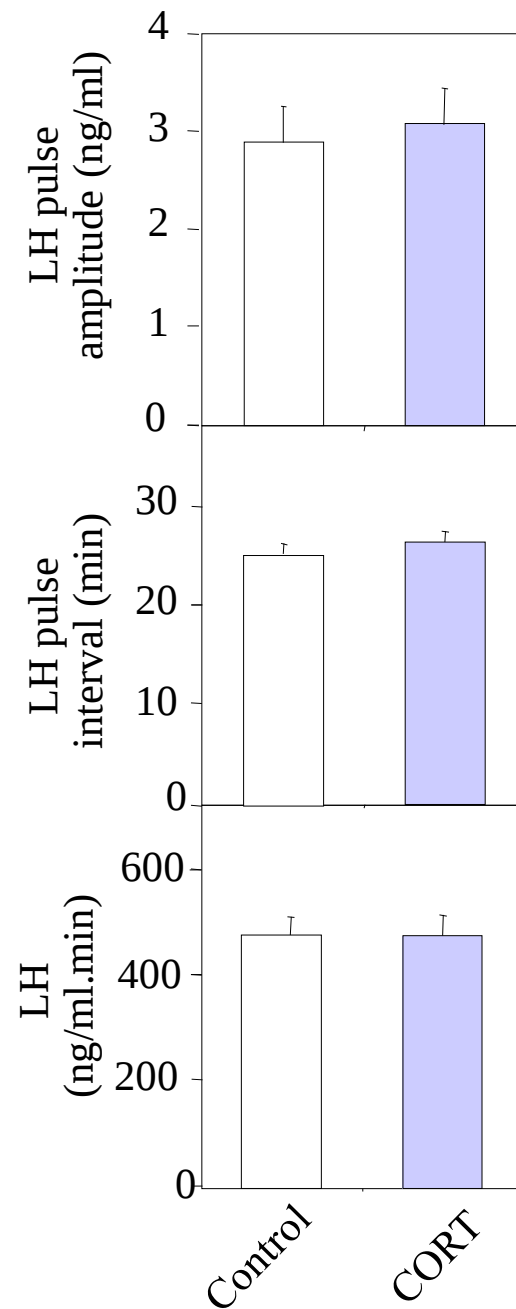
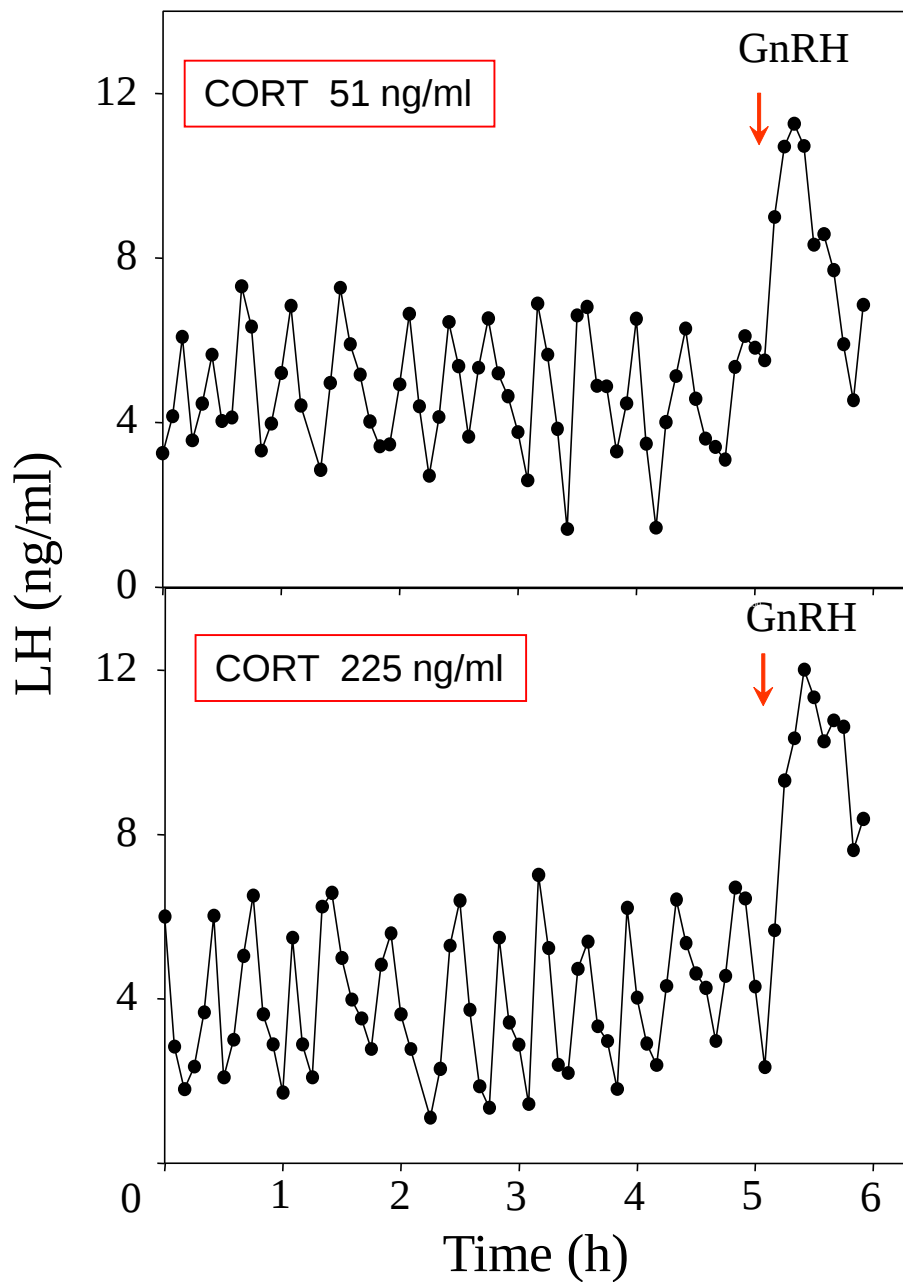


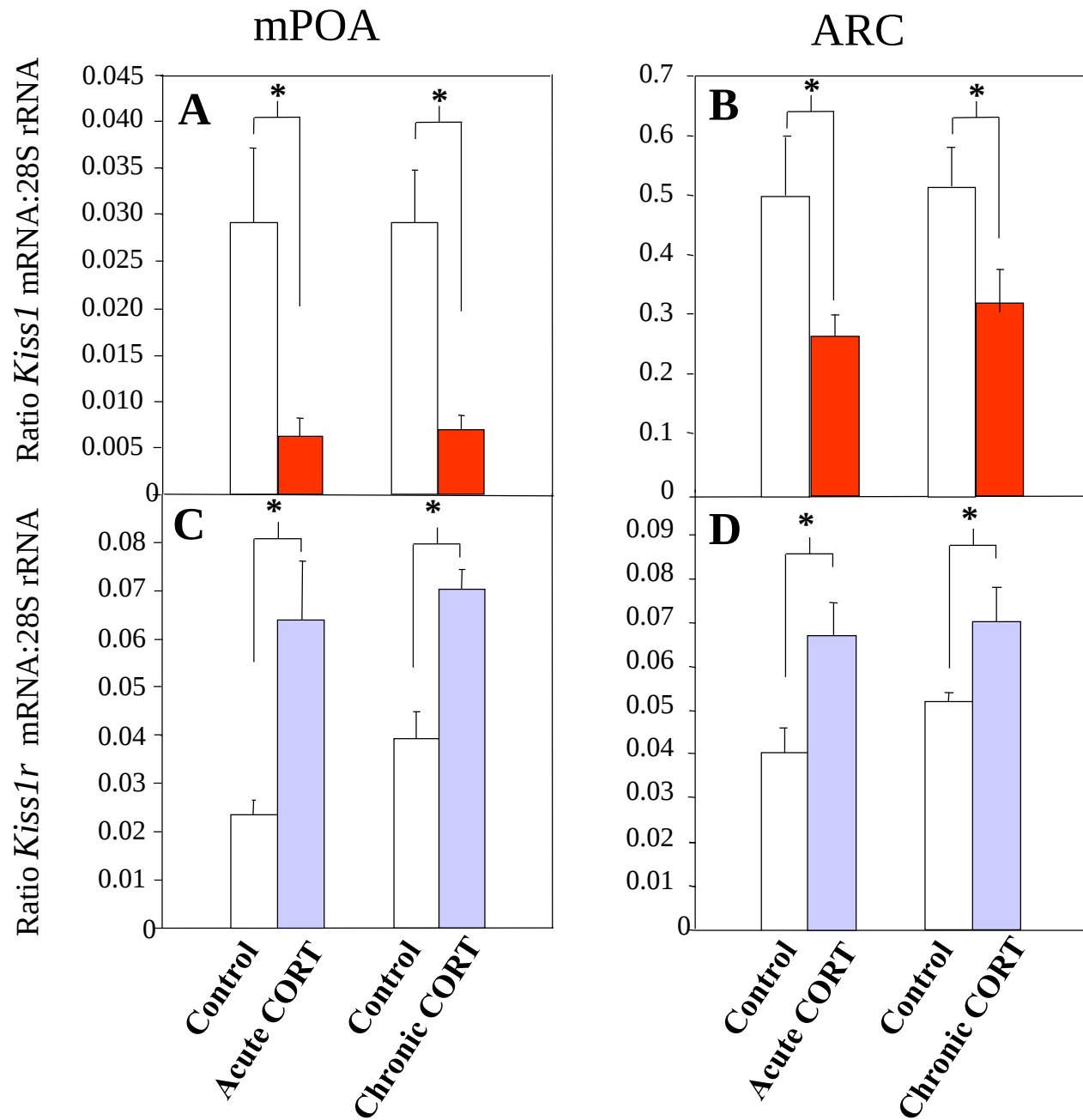
ARC



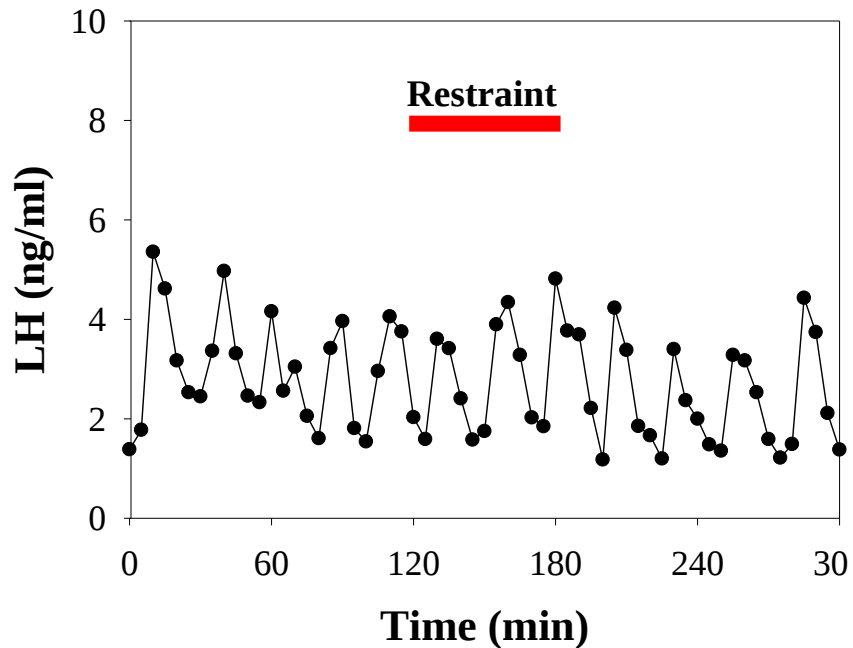




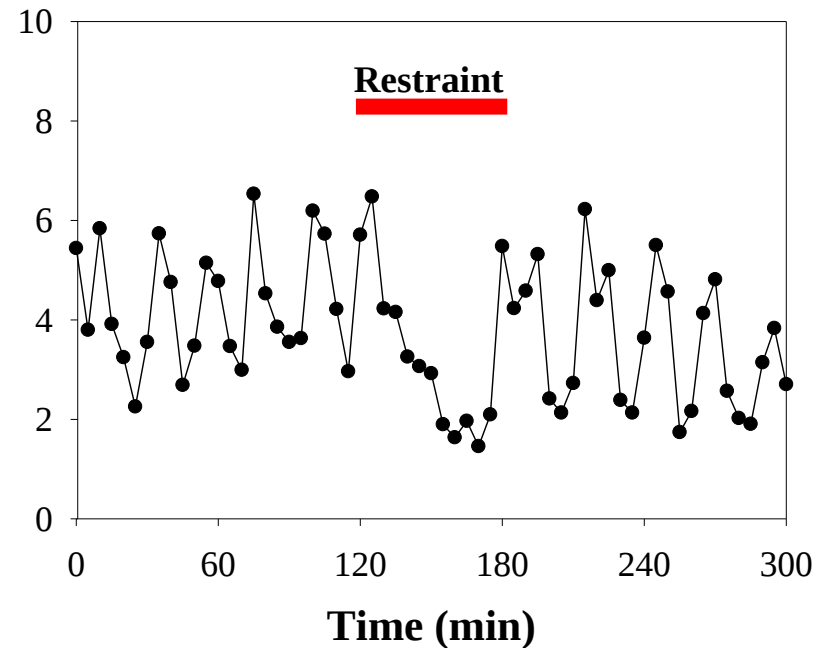




Non-responder (~20%)



Responder



High basal CORT
Low stress CORT

Low basal CORT
High stress CORT

Antisocial behaviour hormone link

Low levels of the stress hormone cortisol have been linked to antisocial behaviour in adolescent boys.

Basal cortisol levels high and cortisol hyporeactivity in response to psychosocial stress in boys with a history of severe antisocial behaviour.



Could antisocial behaviour be a mental illness?

Developmental Origins of Adult Disease

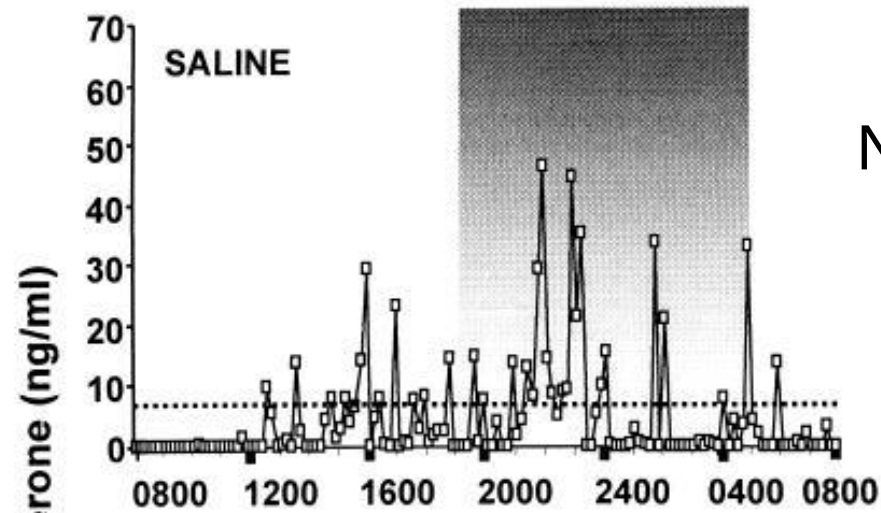
Early experience

Abuse
Family strife
Emotional neglect
Harsh discipline

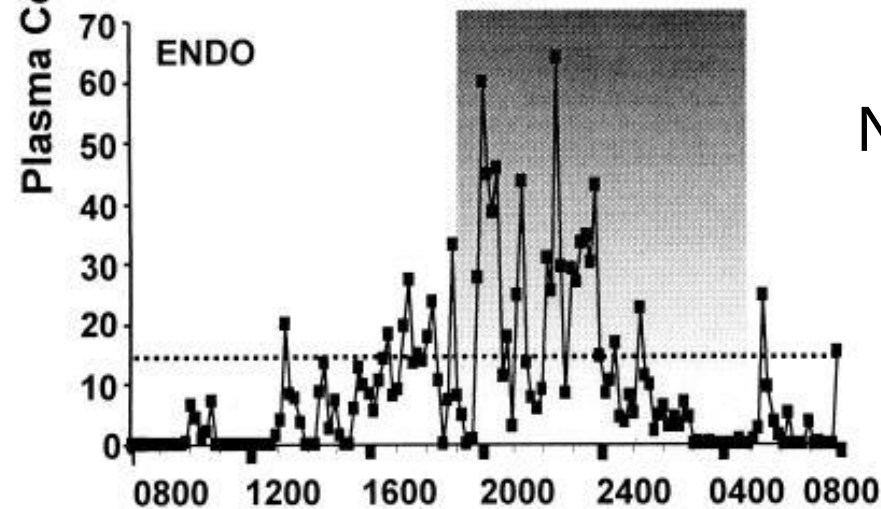


Health Risks

Depression
Drug abuse
Anxiety
Diabetes
Heart Disease
Obesity
Fertility

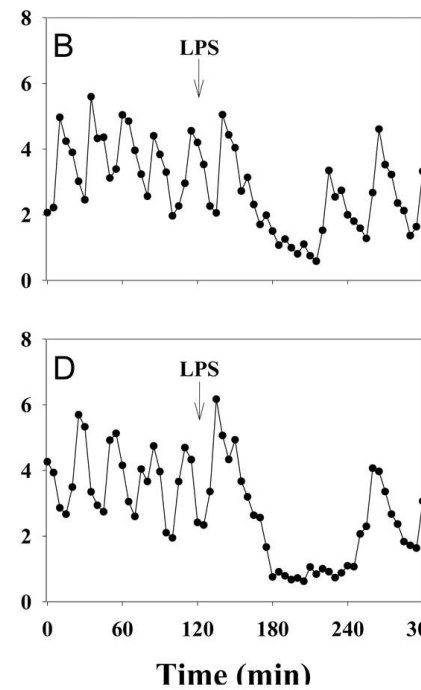
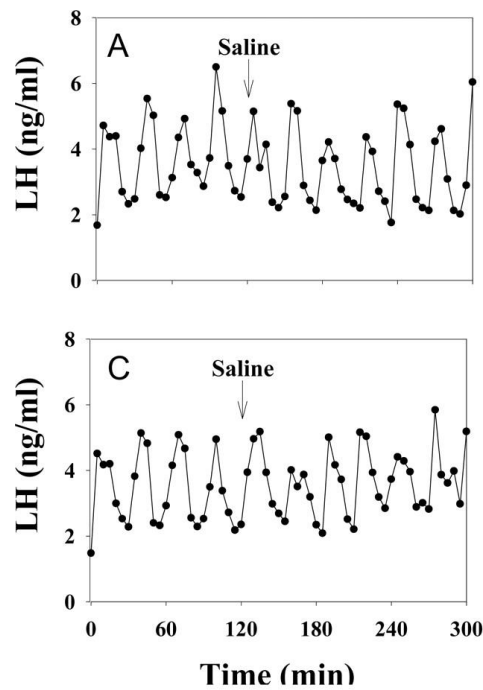


Neonatal-saline

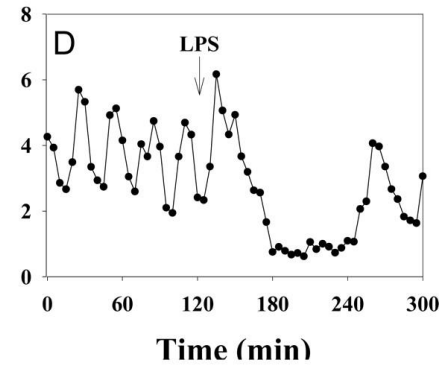
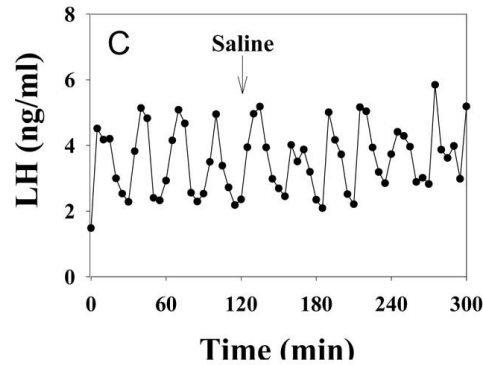


Neonatal-LPS
(pnd 3+5)

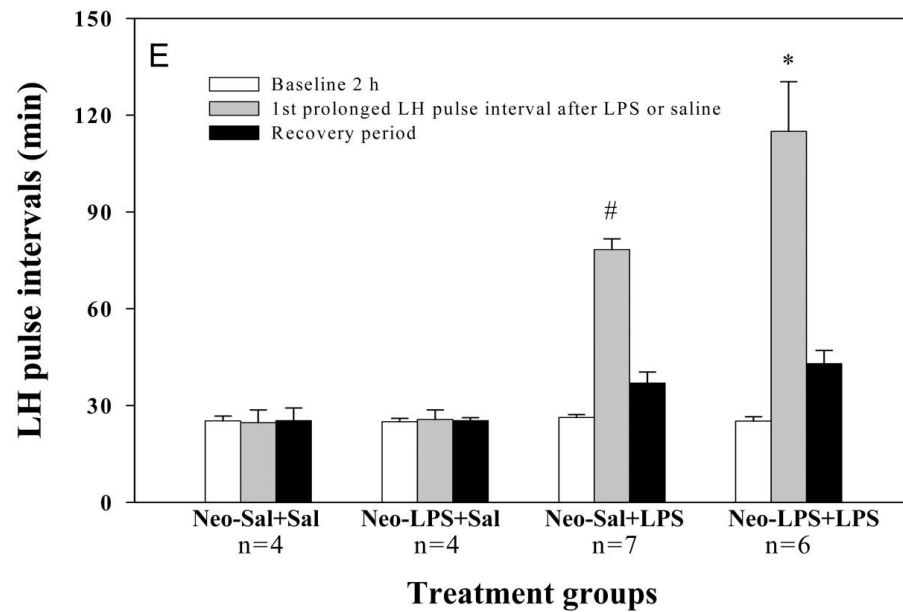
Time of Day

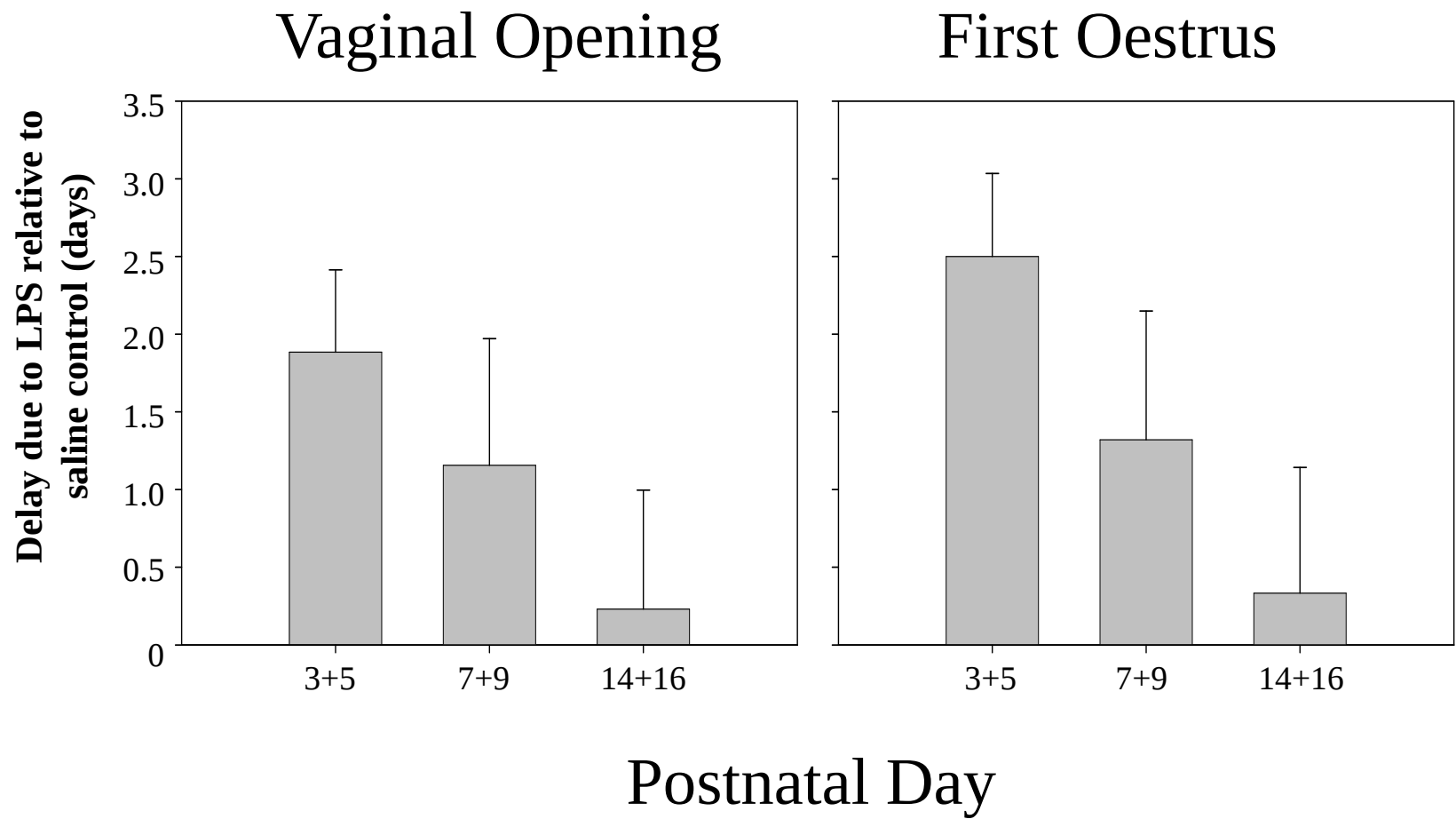


Neonatal-saline



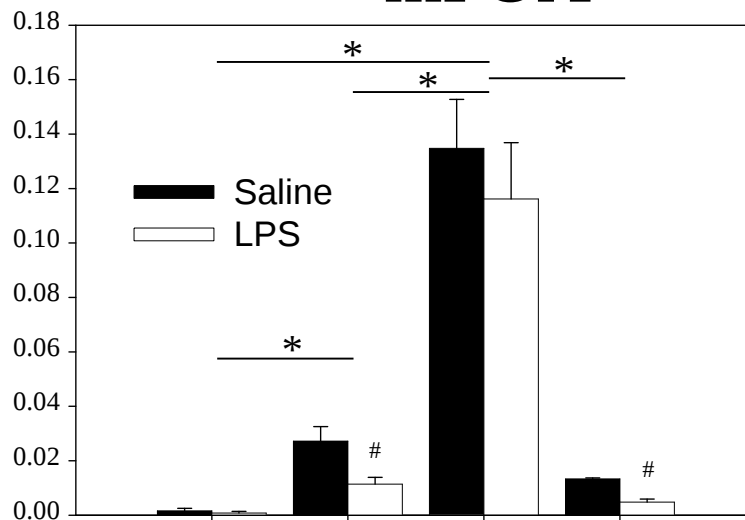
Neonatal-LPS



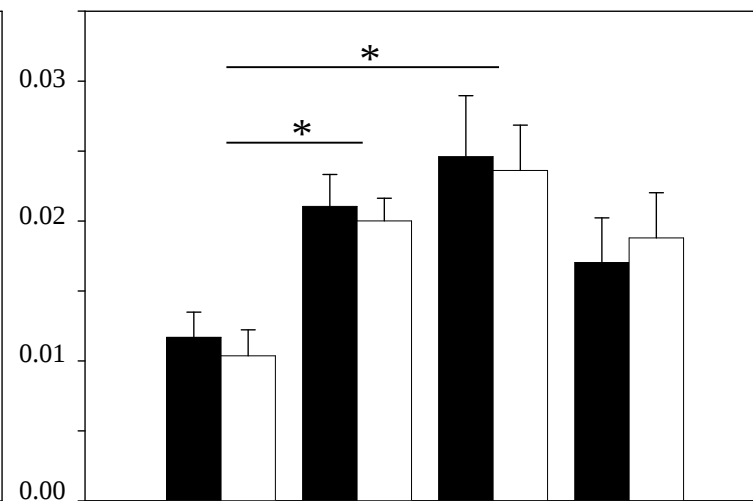


Ratio Kiss1
mRNA : 28S rRNA

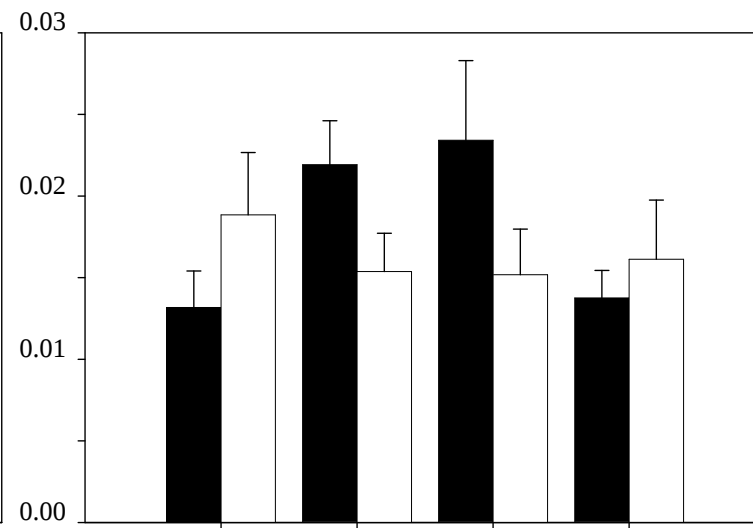
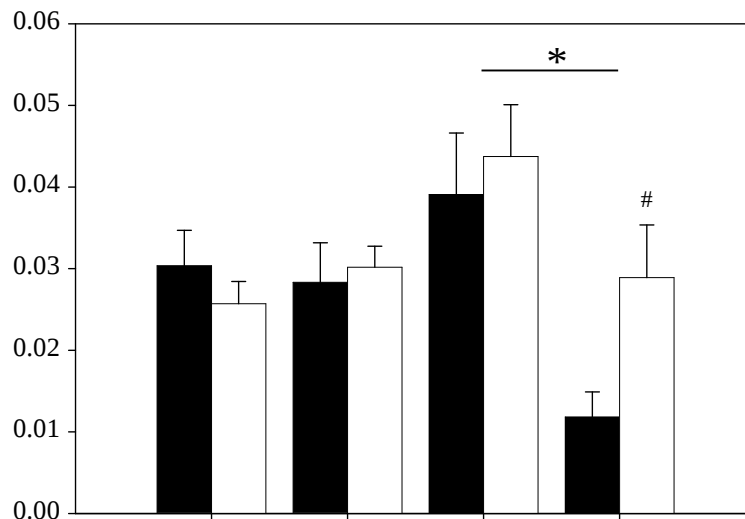
mPOA



ARC



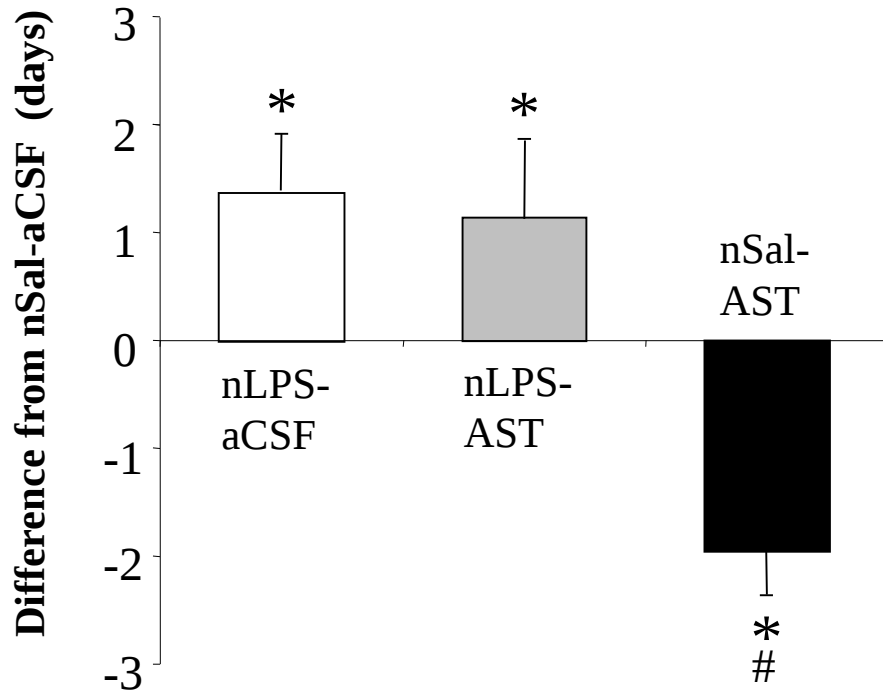
Ratio Kiss1r
mRNA : 28S rRNA



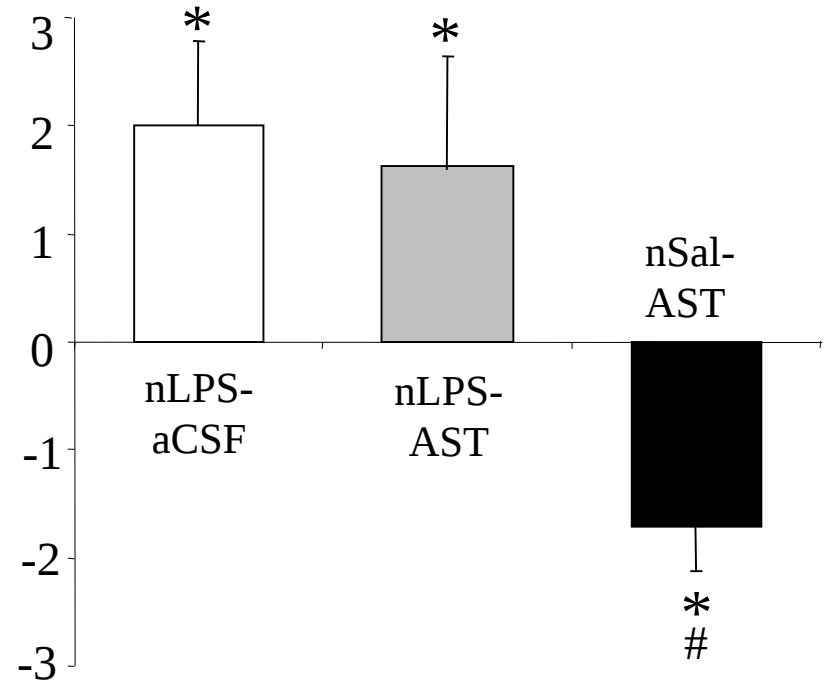
d14 d32 dVO Adult

d14 d32 dVO Adult

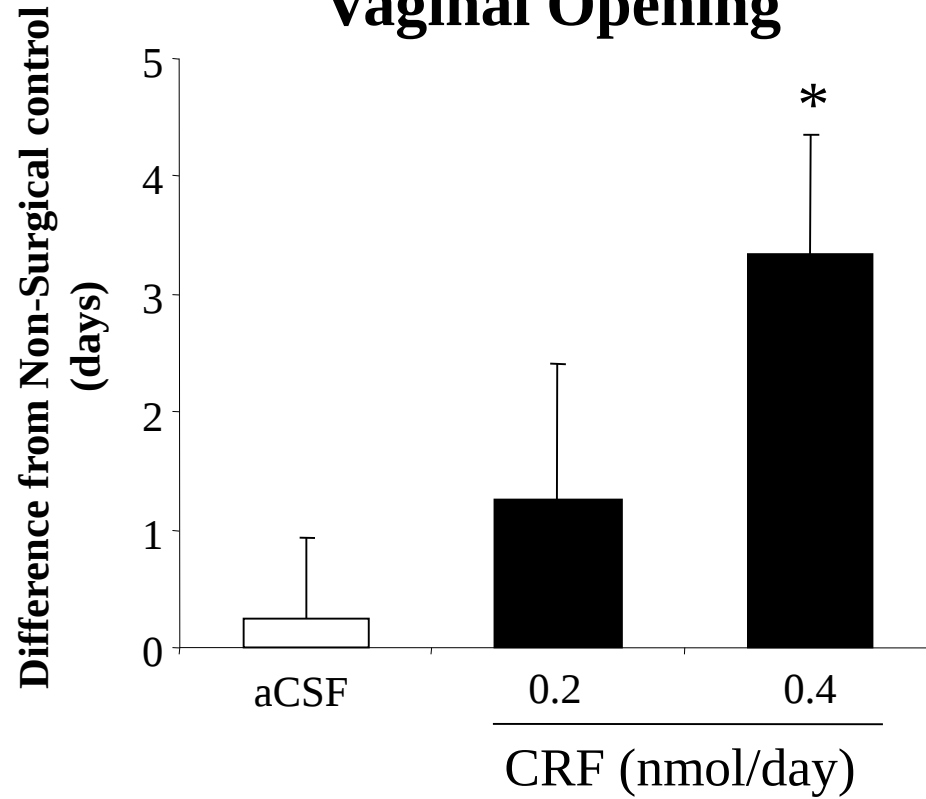
Vaginal Opening



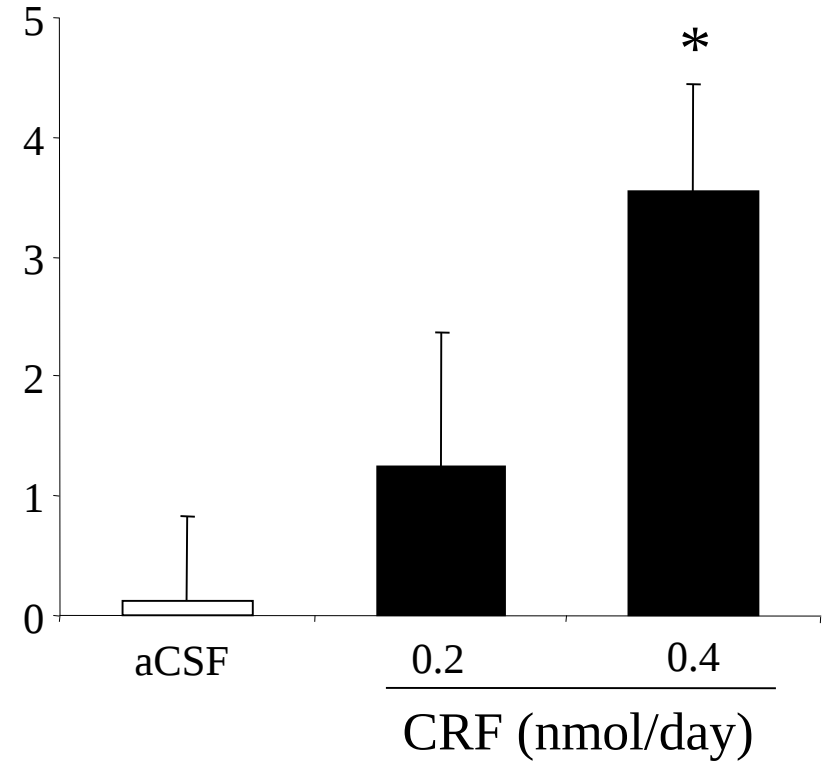
First Oestrus



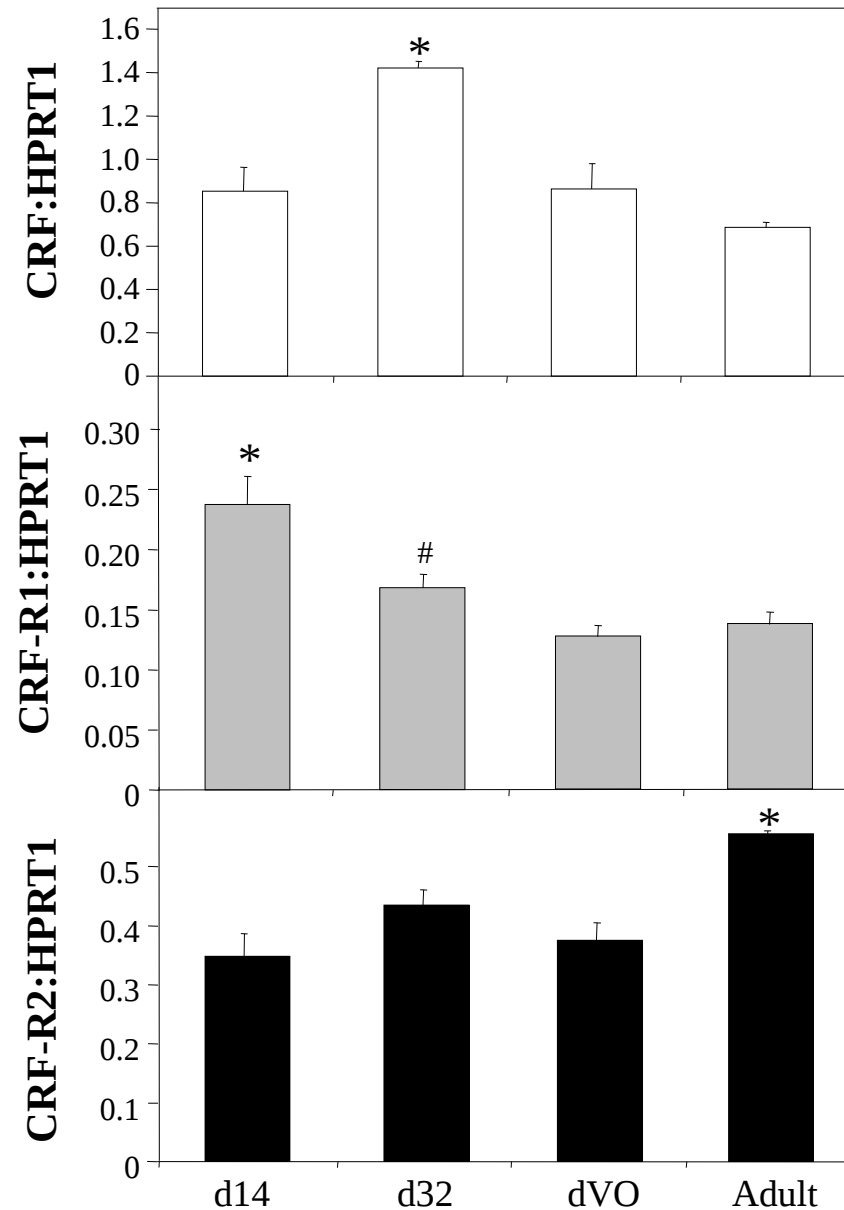
Vaginal Opening

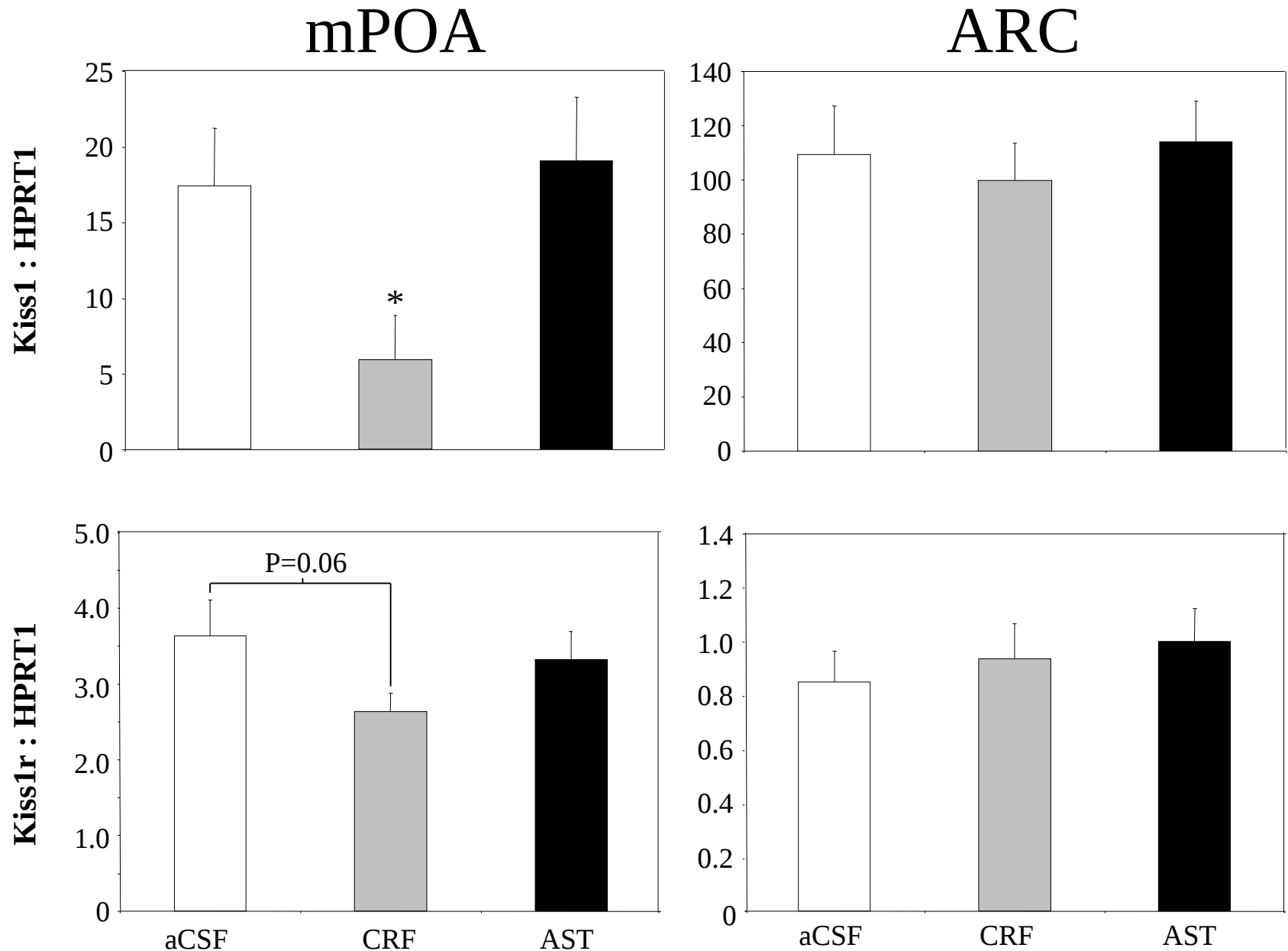


First Oestrus



Developmental changes in mPOA CRF system





Brains collected pnd 35. [Puberty: aCSF ~ pnd 37, AST ~ pnd 35]

Summary

- Stress-induced suppression of the GnRH pulse generator
 - Differential role for CRF-R1 and CRF-R2
 - Neuroanatomical location specific
- Stress and CRF - down-regulates Kiss1 and Kiss1r
- Corticosterone - down-regulates Kiss1, but up-regulates Kiss1r
- Neonatal exposure to LPS
 - Sensitises GnRH pulse generator to inhibitory effects of stress
 - Delays puberty and down-regulates Kiss1 in preoptic area
- CRF tone involved in timing of puberty

Acknowledgement

- Xiao Feng Li
- James Kinsey-Jones
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University of Bristol

- Strafford Lightman

King's College London

- Stuart Milligan

Wellcome Trust
BBSRC