Stress, the GnRH Pulse Generator and Infertility

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Functional hypothalamic amenorrhoea

Stress

Hypothalamus

GnRH pulse generator
(arcuate nucleus)

Anterior Pituitary

LH

Serum LH

Steroid hormones

No ovulation

Ovary
Effects of cognitive behavioural therapy on functional hypothalamic amenorrhoea
CRH neurones and fibres

Swanson LW et al 1983
Cates P et al. Stress 2004
CRF-R1 or R2?

Cates P et al. Stress 2004
Effect of icv urocortin-II on pulsatile LH secretion in the rat

Li, X. F. et al. Endocrinology 2005
Effects of the selective type 2 CRF receptor antagonist, astressin$_2$-B, on restraint stress-induced suppression of LH pulsatile secretion in the rat
SSR = Selective CRH-R1 antagonist
Restraint

Hypoglycaemia

Immunological

SSR = Selective CRH-R1 antagonist

Li et al. 2006. J Neuroendocrinology
Restraint

Hypoglycaemia

Immunological

AST₂-B = Selective CRH-R2 antagonist

Li et al. 2006. J Neuroendocrinology
Intra-mPOA Urocortin II or CRH

![Graph showing LH pulse interval (min) for different treatment groups: aCSF, 0.01µg, 0.1µg, 1µg, and 0.2µg CRH. The graph compares baseline (2 h) and post-treatment (1st 2 h and 2nd 2 h) LH pulse intervals. Asterisk (*) indicates a significant difference.](image-url)
Medial Preoptic Area

![Graph showing LH levels and LH pulse interval over time for aCSF and AST treatment groups.}

**Treatment groups**
- aCSF
- AST

**LH levels**
- Baseline (2 h)
- Restraint (1 h)
- Post restraint (3 h)

**LH pulse interval (min)**
- aCSF
- AST

**Graphs**
- LH (ng/ml) vs. Time (h)
- LH pulse interval vs. Treatment groups
Locus Coeruleus
No oestrogen
Restraint

Hypoglycaemia

CRF

Indirect

+ BNST-Amygdala ✓ (CRH-R type ?)
  Locus Coeruleus ✓ (CRH-R2?/psychol)

Direct

mPOA ✓ (CRH-R1)

Hypothalamus
LHRH pulse generator (arcuate nucleus)

Anterior Pituitary

LH

GnRH

Serum LH

Steroid hormones

No ovulation

Ovary
CRF

Indirect

BNST-Amygdala ✓
Locus Coeruleus ✓

Direct

mPOA ✓

Kisspeptin

Hypothalamus
LHRH pulse generator (arcuate nucleus)

LHRH

Anterior Pituitary

LH

Serum LH

Steroid hormones

No ovulation

Ovary
Kisspeptin neurones may act as central processors for relaying signals to GnRH neurones.
Kisspeptin stimulates the neuroendocrine reproductive axis


**mPOA**

<table>
<thead>
<tr>
<th>Group</th>
<th>Ratio Kiss1 mRNA:28S rRNA</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>*</td>
<td>Control</td>
<td>*</td>
</tr>
<tr>
<td>Restraint</td>
<td></td>
<td>IHH</td>
<td>#</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>LPS</td>
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**ARC**

<table>
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<tr>
<th>Group</th>
<th>Ratio Kiss1r mRNA:28S rRNA</th>
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P = 0.055
mPOA  ARC

A

Ratio KissL
mRNA:28S rRNA

B

Ratio Kiss1r
mRNA:28S rRNA

Control  CRF  Control  CRF

Ratio Kiss1 mRNA:28S rRNA

Non-responder (~20%)  

- Restraint
- Non-responder (~20%)
- Responder
- High basal CORT
- Low stress CORT

Responder

- Restraint
- High basal CORT
- High stress CORT

High basal CORT
Low stress CORT

Low basal CORT
High stress CORT
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?

Graeme Fairchild et al. Biol Psy. 2008
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)
Vaginal Opening

First Oestrus

Delay due to LPS relative to saline control (days)

Postnatal Day

Figure showing the ratio of Kiss1 and Kiss1r mRNA to 28S rRNA in the mPOA and ARC regions of the brain. The graphs display the expression levels of Kiss1 and Kiss1r mRNAs following saline or LPS treatment in different stages of development (d14, d32, dVO, Adult). Statistical significance is indicated by asterisks (*, #) above the bars. The study was conducted by Knox et al. in 2009.
Vaginal Opening

First Oestrus

Difference from nSal-aCSF (days)

nLPS-aCSF  nLPS-AST  nSal-AST

nLPS-aCSF  nLPS-AST  nSal-AST

*  *  *

#  #

*  *
**Vaginal Opening**

<table>
<thead>
<tr>
<th>CRF (nmol/day)</th>
<th>Difference from Non-Surgical control (days)</th>
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<tr>
<td>aCSF</td>
<td>0</td>
</tr>
<tr>
<td>0.2</td>
<td>1</td>
</tr>
<tr>
<td>0.4</td>
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**First Oestrus**

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Developmental changes in mPOA CRF system

![Graph showing changes in CRF:HPRT1, CRF-R1:HPRT1, and CRF-R2:HPRT1 across different developmental stages (d14, d32, dVO, Adult)].
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
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BBSRC