New insights into how the Brain regulates Reproduction

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Professor, Department of Physiology
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Neuroendocrinology is the study of how the brain controls hormones circulating in the body and how those hormones act back on the brain to control its function.
Ten research groups from Anatomy and Physiology clustered in a purpose-built research facility

Around 70 scientists and students including
19 Post-docs/Res Fellows  9 Technicians  18 PhD students
The CNE has particular expertise in understanding the processes of reproduction, body weight/metabolism and stress.

- Neural regulation of reproduction
  - Fertility
  - Parturition and lactation
  - Maternal brain

- Neural regulation of body weight & metabolism
  - Blood glucose levels
  - Body weight
  - Developmental origins of obesity

- Neuroendocrinology of stress
  - Neural circuits regulating stress responses
  - Adrenal gland stress response
  - Interactions between stress and reproduction
Fertility
“The brain is my second favourite sex organ”  Woody Allen
Why put the brain in charge?

- environment (e.g. nutrition)
- physiological status
- psychological status

Ovary (or Testis)
Infertility in NZ

1 in 4 New Zealanders experience infertility
Infertility in NZ

2005 fertilityNZ report

- 21% of NZ women self-report being infertile at some point
- 19% of NZ women have sought medical help for infertility
- Infertility problems double over the age of 26

Van Roode et al., Fertil Steril 2015

Dunedin Multidisciplinary Study (to age 38)
- 22% men infertility
- 26% women infertility
- One third did not seek help
- 40% unresolved at age 38

Righarts et al., NZMJ 2015

Survey Otago & Southland women
- 25% women experience infertility
- Age, body weight, Uni degree
Infertility in NZ

What are the causes?

Otago Fertility Service

- 26% due to male disease
- 31% due to tubal/endometrial disease
- 40% ovulation disorder, PCOS, “other”

“Preventable”

Sexually transmitted diseases
Smoking
Obesity
Age at childbearing
Ageing and Fertility

[Graph showing the relationship between age and fertility, with labels for different stages: Birth, Optimal Fertility, Decrease Fertility, End of Fertility, Irregular Cycles, and Menopause.]
Assisted Reproductive Techniques (ART)

2-5 % of babies born by ART in most Western countries.

2.0% in NZ  3.6% in Australia
In 2007, this Spanish woman gave birth to twins following IVF treatment in the US (after convincing the clinic that she was 55).

She died two years later at age 69.
The gonadotropin-releasing hormone (GnRH) neuron in the brain controls fertility.
The race to discover GnRH

The Nobel Prize in Physiology or Medicine 1977

Roger Guillemin
Prize share: 1/4

Andrew V. Schally
Prize share: 1/4

Rosalyn Yalow
Prize share: 1/2

The Nobel Prize in Physiology or Medicine 1977 was divided, one half jointly to Roger Guillemin and Andrew V. Schally "for their discoveries concerning the peptide hormone production of the brain" and the other half to Rosalyn Yalow "for the development of radioimmunoassays of peptide hormones".
Strange but true……

GnRH neurons are born here.

E14.5

brain

nose

vno

vno
The curious case of the GnRH neuron

First trimester in humans
Mouse E12 - E16

Kallman Syndrome
Things that GnRH neurons do...

**Puberty**
- birth
- puberty
- years

**Adult reproduction**
- Female
  - follicular
  - surge
  - luteal
- Male
Key Problem in Reproductive Biology
Where’s the GnRH neuron?

Finding a needle in a haystack....
Insert gene for GFP into the mouse gene making GnRH.
GnRH-GFP mice are completely normal
Hypogonadotropic hypogonadism due to loss of function of the KiSS1-derived peptide
Discovery in one field makes a hit in another


**KiSS-1, a Novel Human Malignant Melanoma Metastasis-Suppressor Gene**

Jeong-Hyung Lee, Mary E. Miele, Deana J. Hicks, Karen K. Phillips, Jeffery M. Trent, Bernard E. Weissman, Danny R. Welch*

Dept. Experimental Pathology, The Pennsylvania State University, Hershey, USA
GPR54 is essential for normal fertility in humans

Gpr54 deletion mutation

Gpr54 activating mutation
Where is kisspeptin acting to control fertility?

- GnRH neurons
- Estradiol
- Median eminence
- Ovary
- LH / FSH
- Anterior pituitary
Kisspeptin is the most potent activator of GnRH neurons discovered to date

Han et al., *J Neurosci* 2005
Kisspeptin is the most potent activator of GnRH neurons discovered so far.

Highly conserved through vertebrate species.
Kisspeptin has a key role in regulating many aspects of GnRH neuron function.
Fertility & chocolate stirs up a media frenzy

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Kisspeptin has a key role in regulating many aspects of GnRH neuron function
Kisspeptin-10 is a potent activator of LH secretion in humans

Kisspeptin-10 Is a Potent Stimulator of LH and Increases Pulse Frequency in Men


J Clin Endocrinol Metab, August 2011,

Increasing LH Pulsatility in Women With Hypothalamic Amenorrhoea Using Intravenous Infusion of Kisspeptin-54

Kisspeptin-54 triggers egg maturation in women undergoing in vitro fertilization


1Department of Investigative Medicine, Imperial College London, Hammersmith Hospital, London, United Kingdom. 2IVF Unit, Hammersmith Hospital, London, United Kingdom. 3Imperial Clinical Trials Unit, Imperial College London, St. Mary’s Hospital, London, United Kingdom.
Opportunities for kisspeptin to treat infertility

PCOS

normal

Hypo. amenorrhea
Uli Boehm - Homburg
Bill Colledge - Cambridge
Guenther Schuetz - Heidleberg