Psych 2220A Lecture 12

Neuroendocrinology
• Hormones and Behaviour
– Endocrine System
– Classes of Hormones
– Control of Hormones
– Sexual Differentiation
– Aromitization and Neural Sex Differences
– Levels of Sexual Determination
– Hormones and Stress

Hormones
• "Secretory blood-borne product"
• Internal chemical messengers
• An organic chemical messenger released from endocrine cells that travels through the blood system to interact with cells at some distance away and causes a biological response
• Molecules that have effects on cells (like NT)
• Can have effects on distant tissues due to blood transportation
• Important parts: Chemical messenger, travels through blood*, endogenous compound, released from endocrine cells*, interact with target cells at some distance away *

Endocrine Glands
• Ductless glands
• Exocrine glands have ducts
– E.g. sweat glands, mammary glands, scent glands

Chemical Communication
• Endocrine
– Secreting cell --> Blood vessel --> Target cell

Target Cells
• Hormones require receptors to have actions

Endocrine vs. Nervous

Hormones	Neurotransmitters
Released from endocrine gland	Released from presynaptic neuron
Travels through blood	Travels across synaptic cleft
Received at distant target organ	Received at postsynaptic neuron

Psych 2220A Lecture 12

Neurohormones
• Released from neurons (neurosecretory cells)
• Travel through blood
• Received at distant target organ
• Not hormones; not produced by an endocrine gland. Produced by neurosecretory cells

Chemical messengers
• Hormones
• Neurohormones
• Neurotransmitters
• The same molecule may act as more than one type, depending on nature of secretory cell
• Adrenaline aka epinephrine; released by the adrenal medulla

Hormone Action
• Hormone action via 2 main processes
• Water soluble hormones (e.g. peptides)
– Cannot cross cell membranes on their own; bind to receptors on the external part of the cells
• Fat soluble hormones (e.g. steroids)
– Liophilic; trouble getting transported in blood plasma. No problem going through cell membrane

Water Soluble Hormones
• Cannot cross cell membranes
• Bind to membrane receptors
• Initiate 2nd messenger system within cell
– Pretty much like a neurotransmitter binding to a metabotropic receptor!

Fat Soluble Hormones
• E.g. steroid hormones
• Freely cross cell membrane
• Bind to intracellular receptors
• Steroid-receptor complex modifies cell
• Act as transcription factors (change gene transcription)
• Need protein to help dissolve so they can go through the blood; at the target tissue they can go through. Float in cytoplasm waiting to bind to receptor. Steroid and receptor bind to form complex (acts as transcription factor). Enter cell and bind to promotor regions to effect the transcription of genes

Hormones and Behaviour
• How can hormones affect behaviour?
• Hormone receptors found on – effector organs (e.g. muscles)
– Sensory organs
– The central nervous system!
• Main target for most hormones are the brain. Hormones MODIFY how the nervous system is

Psych 2220A Lecture 12

working (neuromodulator)
• Hormones modulate behaviour by affecting how the nervous system works *
• Hormones do not directly cause a behaviour
• For a behavior to occur you need a functioning CNS leading to a potential change in behavior
• Hormones change the probability or intensity of a behaviour in the appropriate context
• How can hormones affect behaviour?
1 - Development long term effects (organizational effects)
2 - Short term change in adulthood (activational effects) --> Activate behavior happening now

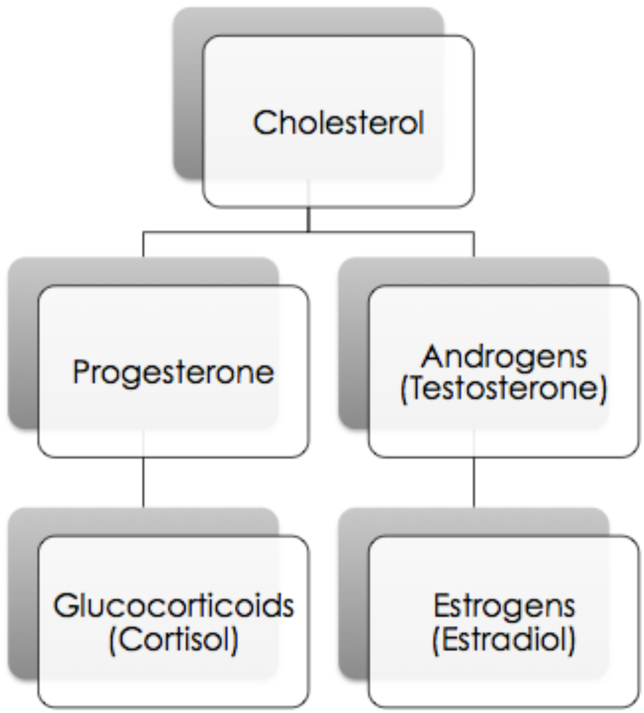
<u>Organizational effects</u>
• Example: urinary posture in dogs
• Sex difference in posture (male lifts leg)
– Adult castration does not make male urinate like female
– Early testosterone treatment induces females to urinate like males
• Hormone effects during early stage of development. Later in the life the hormone doesn't need to be there as the change has already taken place. Eventually don't "need" the hormones around
• Hormones can alter the development of the nervous system, effector organs, and sensory system *

<u>Activational Effects</u>
• Short term changes in behaviour
• Neurons can have hormone receptors
• Hormones induce change in activity of nervous system
– Mammals: suckling leads to oxytocin release which leads to milk letdown (released from the pituitary gland)
– Stress response, stress hormones released in minutes
• Rodents: sexual behavior is hormone dependent. Male won't mount female unless he has circulating testosterone. To exhibit behavior he needs to be exposed to testosterone in early development. Treat female with testosterone? She won't mount. BOTH activational and organizational

<u>Classes of Hormones</u>
• Peptide/ protein hormones
– Direct product of gene transcription. Water soluble (growth hormone, comes through expression of gene)
• Steroid hormones
– Lipid soluble; derivative of cholesterol. Gene for enzyme to take cholesterol to testosterone, no gene for testosterone
• Monoamines
• Lipid-based hormones (but don't affect behaviour directly in vertebrates
• Usually only one class produced by any given gland *

Psych 2220A Lecture 12

Sex steroid hormones
- All steroids are derivatives of cholesterol
- Enzymes convert steroids into different molecules in a series of steps



Sex steroids
- Produced primarily by the gonads, the adrenal cortex, and the brain!!

Steroids
- Androgens ≠ male hormones
- Estrogens ≠ female hormones
- Varies by ratio of hormone present

Hypothalamus
- Subdivided into many nuclei multiple afferents and efferents
- Integration of environmental cues
- Endocrine output via neurosecretory cells

Pituitary
- "Master gland"
- Two glands sitting behind the "stalk"
- Aka hypophysis
- Actually 2 distinct glands

– Anterior = adenohypophysis (Travel through blood supply in the stock. Neurohormones bind to receptors and release hormones from anterior pituitary. Endocrine gland)

Psych 2220A Lecture 12

– Posterior = neurohypophysis (Neurons axons project all the way down the stalk. Terminals of neurons in posterior. Release products into the blood stream. Axon synaptic terminals from the hypothalamus)

Anterior Pituitary
• Hypothalamus secretes neurohormones in portal blood stream
– Releasing hormones, inhibiting hormones
• Stimulate release of tropic hormones from anterior pituitary
– E.g. growth hormone, follicle stimulating hormone

Posterior Pituitary
• Receives projections from hypothalamic neurosecretory cells
• Acts as reservoir for oxytocin and vasopressin

Cyclic vs. Steady Gonadal Hormone Levels
• Female hormones go through a ~28- day cycle, the menstrual cycle
• Male hormone levels are more constant, but still have pulsatile release and circadian cycles
• Cyclic release of anterior pituitary hormones under control of hypothalamus

Control of the Pituitary by the Hypothalamus
• Posterior – neural input from hypothalamus
– Vasopressin – antidiuretic hormone
– Oxytocin – labor and lactation
– Synthesized in hypothalamic paraventricular and supraoptic nuclei
– These nuclei have terminals in the posterior pituitary
• Anterior pituitary – hypothalamopituitary portal system carries hormones from the hypothalamus to the anterior pituitary

Discovery of Hypothalamic Releasing Hormones
• Thyrotropin-releasing hormone first isolated from the hypothalamus of sheep and then pigs
• Triggers the release of thyrotropin from the anterior pituitary
• Thyrotropin then stimulates release of hormones from the thyroid gland

Regulation of Hormone Levels
• Neural
– All endocrine glands (except the anterior pituitary) receive neural signals
– From cerebral or autonomic neurons
• Hormonal
– Tropic hormones, negative feedback • Nonhormonal chemicals
– Glucose, Ca^{2+}, Na^+

Pulsatile Hormone Release
• Hormones tend to be released in pulses
• Leads to often large minute-to- minute fluctuations in levels of hormones

Psych 2220A Lecture 12

See Figure 13.5
- Neural signals project to hypothalamus
- Integration of environmental cues
- Environmental output
- Travels through portal to anterior pituitary
- Gonads release steroid hormones, which are released into body tissues

<u>Sex differences</u>
• Sex differences are ubiquitous
• By definition sexes differ in behaviour
• How are sexes determined through development?
• How does this process give rise to sex differences in behaviour?

<u>Levels of Sex Determination</u>
• Genetic sex
• Chromosomal sex
• Gonadal sex
• Gametic sex
• Hormonal sex
• Morphological sex
• Behavioural sex
• Genetic sex
• Human specific:
– Gender identity
– Gender role
– Legal sex

<u>Sexual Differentiation Mammals</u>
• Genetic sex determination
• XX (female) versus XY (male)
• SRY gene
– Sex determining Region of the Y chromosome

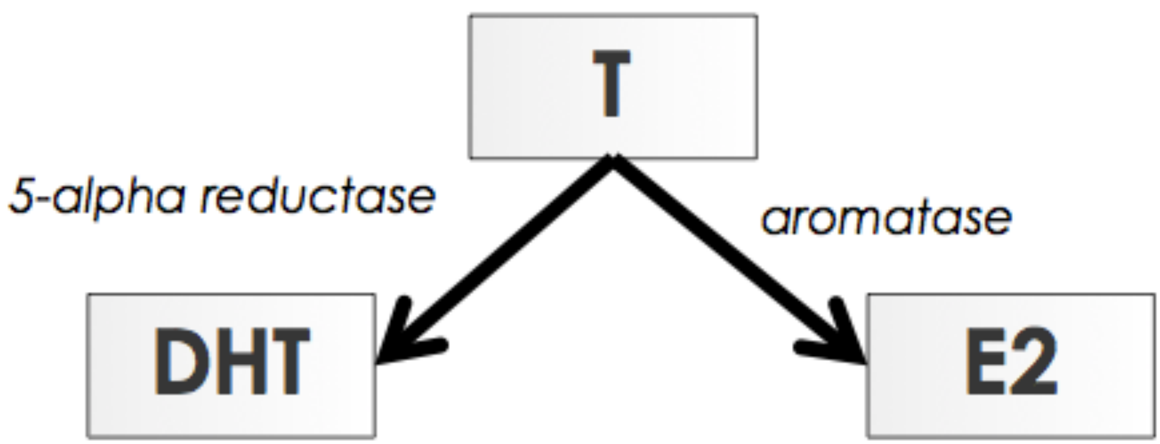
<u>Genetic sex</u>
• Developing embryo has a bipotent gonad
• In XY embryo, expression of SRY in the gonad produces TDF (testis determining factor)
– Default developmental pathway to become an ovary when TDF is absent
• TDF binds to other genes results in development of testis
• In absence of TDF gonad develops into ovaries
• Mice that are XY, but lack SRY gene develop as female
• XX mice transgenically given SRY gene develop as male
• Mammals only
• **Bipotent:** become either testicular tissue or ovarian tissue

Psych 2220A Lecture 12

Morphological sex
• Differentiated gonads produce hormones
• Testis produces androgens
– Organization of morphology and brain to male phenotype
• Ovaries produce more estrogens than androgens
– Development of female phenotype
– Even in absence of gonads
    • Remove ovaries early in development you get typical female development. "Default pathway" --> happens in the absence of testosterone
• Female development “default”, however requires low levels of estrogens for normal development
• Embryonic bipotent gonads
• Embryonic dual sexual ducts

Müllerian ducts
• Develop into female sexual ducts unless told otherwise
– Fallopian tubes, uterus and cervix
• Development proceeds in presence of ovaries, or absence of gonad
• Testes produce MIH (Müllerian Inhibiting Hormone) which induces regression of Müllerian ducts

Wolffian ducts
• Develop into male sexual ducts
– Seminal vessicles, vas deferens
• In presence of ovaries or absence of gonad Wolffian ducts regress
• In presence of androgens (from testes) Wolffian ducts develop



Psych 2220A Lecture 12

Morphological sex
• Genitalia, bipotent genital tissue
• Genital folds
– Form labia or scrotum
• Genital tubercle
– Forms clitoris or penis
• Masculinization through organizational effects of androgens
• In absence of androgens, feminization occurs
• Genital tissue (both sexes) expresses the enzyme 5α-reductase
– Converts T to 5α-DHT in males
• Turns testosterone to dihydro testosterone. Due to no androgens in females, this conversion doesn't happen (leading to typical female development)

Masculinization
• Masculinization of peripheral tissue usually mediated by 5α DHT

Sexual differentiation
• Multiple levels of sexual development

Puberty: Hormones and the Development of Secondary Sex Characteristics?
• Fertility achieved
• Secondary sex characteristics develop
– Features unrelated to reproduction that distinguish sexually mature men and women
• Increase in release of anterior pituitary hormones
– Growth hormone – acts on bone and muscle
– Gonadotropic hormone
– Adrenocorticotropic hormone

Sex Differences in the Brain
• Pfeiffer first discovered a sex difference in mammalian brain function
• Pfeiffer (1936) – gonadectomized and implanted gonads in neonatal rats
– Gonadectomy causes cyclic (female) gonadotropin release pattern
– Transplant of testes to males or females causes steady (male) gonadotropin release pattern
• Hormone treatment early in life changes the brain; endocrine tissue responds in either a male or female typical pattern (hypothalamus changes)
• Perinatal androgens lead to male pattern

Aromatization Hypothesis
• Sex steroids are all derived from cholesterol and are readily converted from one to the other
– Aromatized testosterone becomes estradiol
• Evidence suggests that estradiol masculinizes the brain

Sexual differentiation
• Multiple levels of sexual development

Psych 2220A Lecture 12

Evidence that Estradiol Masculinizes the Neonatal Brain
• Neonatal injections of estradiol masculinize
• Dihydrotestosterone can't be converted to estradiol – doesn't masculinize
• Alpha fetoprotein deactivates circulating estradiol but does not cross the blood-brain- barrier
• Blocking aromatization or estradiol receptors interferes with masculinizing effects of testosterone
– Testosterone delivery system to get estradiol to brain. Females produce in the ovaries yet is blocked going to the brain

Mother's Estradiol Doesn't Masculinize Female Brains
• In female rodents, Alpha fetoprotein in blood during perinatal period …
– Protects the female brain from estradiol
– Binds to circulating estradiol, so none gets to the brain
• In male rodents, testosterone enters the brain and then is converted to estradiol

Organizational Hypothesis
• W.C. Young and colleagues study of guinea pigs
– Phoenix et al. (1959)
• Laid the theoretical framework of much of behavioural endocrinology
• Castrate adult male – decrease mounting (gets rid of testosterone)
• T treatment of male results in mounting
• T treatment of female does not
• Males brain has been organized to respond to T
• Prenatal T exposure in females, plus later T exposure results in mounting

Gender Identity
• Self-view as male or female
• Established early in development
– Traditionally assumed to be product of gender role/ gender specific rearing

David Reimer
• See p. 342 in Pinel
• Boy whose penis was destroyed during circumcision
• Surgically altered, hormone therapy and raised as a girl
• But still had male gender identity
• Biological basis of gender identity still not clear, but it appears to be set very early in life or in utero
• Attempts to socialize of force a gender identity on someone is a failure

Androgen Insensitivity Syndrome
• Aka testicular feminization mutation
• XY individuals with no functional androgen receptors
• Testes produce MIH, but Wolffian ducts not stimulated
• Develop female genitalia, lack internal reproductive ducts

Psych 2220A Lecture 12

• External female morphology
• Complete and partial forms

5α-reductase deficiency
• Turns testosterone into dihydrotest.
• Little impact on female development
• Males produce androgens, but not converted to DHT
• Ambiguous genitals at birth, undescended testes
• At puberty, surge in androgens can result in masculinization

Androgen Exposure
• Exposure to exogenous androgens may lead to masculinization
• Typical exposure during pregnancy to synthetic steroids (DES, MPA)
• Masculinization of reproductive function and behaviour
• Potential psychological effects, enlarge clit

CAH
• Congenital adrenal hyperplasia
• Fetal adrenal glands secrete high levels of androgens
• Partial masculinization of females
– Sometimes partial masculinization of genitals
– Many behavioural and cognitive effects

Sexual Development
• Complexity of sexual differentiation revealed by variety of developmental patterns

Male Reproduction-Related Behavior and Testosterone
• Effects of orchidectomy (Bremer, 1959)
– Reduced sexual interest and behavior
– Rate and degree of loss varies
– Still have adrenal testosterone
• Level of male sexuality is NOT correlated with testosterone levels in healthy men
• Increasing male testosterone levels does NOT increase sex drive

Individual Differences
• Sex drive varies greatly among individuals in many species
• Guinea pigs
– Castration and androgen treatment
– same dose of androgens restore sex drive to pre-castrate levels (high, med, low)
– see Fig. 13.11 in Pinel
• Individual differences likely arise from sensitivity to androgens, not variation in circulating levels (depends on receptor numbers and locations)
• Rats
– Very low T levels can maintain copulation in castrated rats

Psych 2220A Lecture 12

• High T important for spermatogenesis, some secondary characters
• T's action on sexual behaviour may be a threshold phenomenon

<u>Female Reproduction-Related Behavior and Gonadal Hormones</u>
• Rats and guinea pigs – surges of estrogen and progesterone initiate estrus, a period of fertility and receptivity
• Women – sexual motivation and behavior not tied to cycle
• Sex drive may be under androgenic control

<u>Human Female Sexuality and Androgens</u>
• Testosterone increases the proceptivity of ovariectomized and adrenalectomized female rhesus monkeys
• Correlations seen between sexual motivation and testosterone
• Testosterone found to rekindle sexual motivation in ovariectomized and adrenalectomized women

<u>Stress</u>
• What is it?
– Final exams
– Public speaking
– Danger of bodily harm
– Sexual activity? Sports? Overeating?

<u>What is Stress?</u>
• Common response to diverse physical or psychological factors
• Some argue to no longer use the term
• Definitions often confound stressor, stress response and intervening physiological events

<u>Stress and Health</u>
• Stress Response – reaction to harm or threat
• Stressors – stimuli that cause stress
• Chronic psychological stress – most clearly linked to ill health
• In the short-term, stress is adaptive; in the long-term, it is maladaptive

<u>Selye: General Adaptation Syndrome</u>
• Common reaction to diverse events (stressors), or general stress response
– Alarm reaction
– Stage of resistance
– Stage of exhaustion

<u>1) Alarm reaction</u>
• Response to immediate acute stress (neural reaction)
• Arousal of sympathetic ANS
• Release of catecholamines from adrenal medulla

Psych 2220A Lecture 12

– Epinephrine, norepinephrine
• Reversed by parasympathetic stimulation

2) Stage of resistance
• Chronic stress
• Hypathalamic- pituitary stimulation of adrenal cortex leads to glucocorticoid release
– Cortisol or corticosterone

3) Stage of exhaustion
• Long term chronic stress
• Maladaptive responses
– Immune suppression, reproductive suppression etc.

Animal Models of Stress
• Some early models used levels of stress that might not have a human equivalent
• Some more recent models use social stresses
– For example, subordination stress

Psychosomatic Disorders: The Case of Gastric Ulcers
• Gastric ulcers – lesions of stomach lining and duodenum (produced by bacterial infections)
• More common in those who are stressed; readily created in the animal lab
• Ulcers are caused by a bacteria – stress appears to makes the body vulnerable to this bacteria
• 75% of healthy subjects have the bacteria

Psychoneuroimmunology
• Study of the interaction of psychological factors, the nervous system, and the immune system

Immune System
• Divisions of the mammalian immune system
– Innate immune system
  • First line of defense
  • Attacks generic classes of pathogens
– Adaptive immune system
  • Targets specific pathogens identified by their antigens
  • Has memory (the basis of effectiveness of vaccination)
  • Cytokines activate lymphocytes (white blood cells)
    – Cell-mediated (T lymphocytes)
    – Antibody-mediated (B lymphocytes)

What Effect Does Stress Have on Immune Function: Disruptive or Beneficial?
• Effects of stress on immune function depends on the kind of stress
– Acute stressors improve immune function
– Chronic stressors impair immune function

Psych 2220A Lecture 12

• Many ways that stress can impact immune function
– Effects of stress can be good (adaptive and healthful), bad, or mixed

Stress and Immune Function
• Immediate stress response
– Increase neutrophils and lymphocytes
  • Cell mediated response
– Activation of immune response, but suppression of cell proliferation
• Long term stress
– Suppressed cell proliferation eventually decreases cell-mediated response

Early Experience of Stress
• Stress or mistreatment early in life may cause brain and endocrine abnormalities later in life
– Rat pups handled by researchers had more adaptive stress response in adulthood (less circulating glucocorticoids following stress), probably due to less negative feedback from hippocampal glucocorticoid receptors
– A good example of *epigenetic* ("not of the genes") transmission: fearful, poor- grooming mothers raise daughters who become fearful, poor-grooming mothers

Perinatal Stress
• Glucocorticoids can have organizational as well as activational effects
• Prenatal effects of stress can have long-lasting impact

Prenatal Stress
• Restraint stress of pregnant rats leads to activation of HPA axis
• Offspring have permanent effects in brain, physiology and behaviour
• Long-term effects on negative feedback of HPA axis
– Decreased hippocampal glucocorticoid receptors in pups
– Elevated baseline CORT as adults

Stress and the Hippocampus
• Hippocampus has many glucocorticoid receptors
• Following stress
– Dendrites of pyramidal cells are shorter and less branched
– Adult neurogenesis of granule cells reduced
• Effects blocked with adrenalectomy; produced with corticosteroids

Prenatal Stress
• Effects on pups mediated by mother's HPA response
• Adrenalectomy of pregnant mother eliminates effects of stress on pups