Sexual Differentiation in Mammals (Chap 7)

How do we become the sexual individuals we are?

What defines male or female?
(not all countries or organizations use the same criteria)

The doctor in the delivery room most often just looks at the baby’s genitals. But there is more to it than that!

What defines male or female?
(not all countries or organizations use the same criteria)

• Early in sexual differentiation, body and brain development is characterized by BIPOTENTIALITY — we all start out looking the same and have the potential to go in either the M or F direction.

Genetic Sex

Role of Sex Chromosomes

• Genetic sex (XX or XY) is determined by the sperm (X-bearing or Y-bearing) that fertilizes the egg.

• Early gonads have potential to be either ovaries or testes for ~6 weeks. We also all have the beginnings of both male (Wolffian) and female (Mullerian) internal ducts.

• Sex-determining region of the Y chromosome (SRY) is a gene producing a *protein causing the middle of baby gonads to become testes.

• This sets off a cascade of later genetic & hormonal steps.

• If testes develop, they begin to produce androgens like testosterone and also Mullerian inhibiting hormone (MIH)

• If SRY gene is not present, the outside of the early gonads turns into ovaries.

*sometimes called testis-determining factor
Experimental Evidence

• Removal of SRY gene from Y→XY mouse develops as a female
• Add SRY gene to X→XX mouse develops as a male
• Injection of SRY’s protein in genetic female develops testes
• Inject genetic male with drug that blocks the SRY’s protein develops ovaries

Organizational Effects

• After gonad development, the remainder of sexual development depends largely on the hormone environment during critical or “sensitive” period of sexual differentiation.
• Normal sources of sex hormones:
  • Testes & ovaries
  • Adrenal cortex

Organizational vs Activational Effects Of Sex Hormones

• Organizational
  • permanent effects
  • occur mostly during early critical period
  • produce structural changes in body and brain

• Activational
  • transitory effects; can disappear in absence of hormone
  • Seen in puberty→adulthood
  • produce motivational and functional changes (like the menstrual cycle)

• We all begin with ducts, genitals & brains which can go either way (male or female)
• The “default” setting for early development of the reproductive system is “female”. This will occur in the absence of hormones. (Female differentiation of brain however IS affected by early estrogens)
• Prenatal differentiation of male ducts, genitals, & brain depends on action of androgens (testosterone (T) & dihydrotestosterone (DHT)).
• In fact, in males, development of female ducts must be actively inhibited by release of another hormone from testes: Mullerian inhibiting hormone (MIH), usually in 2nd & 3rd month of gestation for humans.
Masculinization of genitalia occurs primarily in response to dihydrotestosterone (DHT).

Hormonal transformation:
- Testosterone is converted to estrogen by aromatase enzyme.
- Estrogen is then converted to dihydrotestosterone by 5-alpha reductase.

Differentiation of the Brain
- Androgens have defeminizing & masculinizing effects on developing brain.
- Example: Exposure to androgens “program” the hypothalamus for the fairly constant sex hormone secretions seen in males vs the cyclic hormone secretion of females. Exposure to androgens leads to growth of certain brain areas; their absence develops other regions.
- Masculinization of brain appears to occur later in gestation than masculinization of body.
- Early estrogens have some feminizing effects on the brain.
- Early hormone environment also leads to corresponding behavioral changes.

Sexually Dimorphic Nucleus (SDN) of Preoptic Region of Hypothalamus
- Do male and female animals show different sex-typical behaviors because of genetic makeup or because of hormone exposure?
Sex-Typical Behaviors

Early exposure to androgen → mounting & thrusting later in life

No early androgens → lordosis (female sexual posture) later in life

Another of Mother Nature’s Jokes:
The Aromatization Theory
• Masculinizing of the rat brain is not just due to testosterone
• Testosterone entering rat brain is turned into estradiol!
• Estradiol, in turn, triggers “masculinization” of the brain.
• Brain areas like the hypothalamus which show sex differences have high levels of aromatase enzyme that converts T → E during the sensitive period.
• If this enzyme is blocked then T does not masculinize brain!
• Maternal estrogens bind to alpha-fetoprotein & can’t leave the bloodstream so don’t masculinize brain.
• However, if excess synthetic estrogens are present, some do get into brain and can bias brain/behavior in a male direction in a variety of species including humans.
• * Now know this is not the only mechanism causing sex diffs in brain & that this does not seem to be the primary influence in humans, but unusual exposure to estrogens may have some impact.

Congenital Adrenal Hyperplasia or Adrenogenital Syndrome
One cause of androgen exposure in females

• The effects of androgen exposure of a female fetus
• Degree of masculinization depends on amount of androgen and timing
• Also about 1 in 13,000 births

The Female Spotted Hyena.
• Females produce large quantities of androgens from the ovaries.
• In pregnant females this compound is converted into testosterone by the placenta.
• Female offspring are extremely masculinized - they are larger and heavier than males, are dominant, and highly aggressive.
• They also display male-typical external genitalia including a scrotum and testicles penis (Ockelmann et al., 1987).
CAH is associated with
• Greater preference for boy toys and later for sports magazines, masculine sports, even male dominated professions like auto mechanic, truck driver
• Increased physical activity; increased aggression
• Low romantic interest in males at adolescence; less interest in infants
• Moderate increase in bisexuality or homosexuality, or continued low interest in sexual relationships
• Usually score intermediate between females and males and degree is correlated with androgen level

Androgen Insensitivity Syndrome
• X-linked recessive defective variant of the androgen receptor gene
• Androgen ineffective → small testes, no male ducts, female genitalia but no female ducts. Have female identity
• (supports a role for androgen receptors in some aspects of masculinization of human brain)
• At puberty don’t see pubic hair or darkening of nipples (normal androgen effects in females)
• If AIS is known to exist in a family, genetic testing can reveal whether a woman carries the recessive gene
• 1 in ~13,000 births have complete androgen insensitivity; in addition some are born with partial insensitivity (probably another mutation)

Sexual Orientation
• ↓ mid-pregnancy testosterone in males OR testosterone treatment of females induces same sex preferences and changes in other sex-typical patterns of behavior in a wide range in species (rats, hamsters, ferrets, pigs, finches, dogs, sheep etc.).
• Data from both men and women shows a correlation between early hormone environment and later sexual orientation.
• Maternal stress & some drug used during pregnancy can decrease testosterone exposure; other drugs may act like androgens (e.g. diethylstilbestrol (DES))

Other Evidence for a Biological Basis of Sex Orientation – Bailey & Pillard
• Brothers both homosexual?
  • Identical twins - 52%
  • Fraternal twins - 22%
  • Non-identical brothers - 9.2%
  • Adopted brothers - 11%
• Sisters both lesbian?
  • Identical twins - 48%
  • Fraternal twins - 16%
  • Non-identical sister - 14%
  • Adopted sisters - 6%
• Pattern of results replicated in small representative sample from national twin study
60 Minutes segments

- http://www.youtube.com/watch?v=d5vrNWA_nik
- http://www.youtube.com/watch?v=S5QYVe0miY&feature=channel
- National Geographic
- http://www.youtube.com/watch?v=saO_RFVWfWA&feature=related

- The more older brothers a male has, the greater the probability that he will be homosexual.
- Hypothesis – mother’s earlier pregnancies carrying a male fetus triggered future immune responses against testosterone or some related protein.

- So is the androgen environment not just "masculinizing" body and brain, but actually influencing factors like motor programs for how one moves, vocal tone and inflection, and interests/preferences?
- There is also a growing body of research looking at early hormone environment, brain differences and genetic contributions related to transgender cases.

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- 62% Heritability of gender dissatisfaction
- Gene associated with $F \rightarrow M$ transgender increases T exposure in females
- Gene associated with $M \rightarrow F$ transgender results in reduced sensitivity to androgens
- Brain anatomy of transgenders resembles that of the sex they identify with

Sexual Orientation Brain Differences

- Simon LeVay- 3rd interstitial nucleus of the anterior hypothalamus (INAH3) in humans is larger in heterosexual males and smaller in females and gay males. Recent research shows it is also small in $M \rightarrow F$ transgenders. (Another area showing this same pattern is the BSTc).
- Other areas of brain that differ with sexual orientation:
  - Anterior commissure
  - Supraciasmatic nucleus
  - Both are larger in heterosexual women and gay men
  - These are not areas known to be related to sexual behavior, but the pattern does suggest the brains of gay men are more similar to female brains than heterosexual male brains.

Other examples of brain differences

- Females
  - More neurons in Wernicke’s area
  - Larger corpus callosum
  - More programmed cell death (apoptosis) during development

- Males
  - Larger cortex
  - Thicker right hemisphere cortex
  - Different cellular organization in several regions of cortex

The fact that there are brain differences should make us expect to see some behavior or ability differences.
Gender Differences in Behavior

- Females better at:
  - Verbal fluency
  - Verbal memory
  - Perceptual matching
  - Fine motor skills
  - Preference for dolls & related "female" toys

- Males better at:
  - Mathematical reasoning
  - Spatial tasks
  - Large muscle skills
  - Higher in sensation seeking
  - Preference for "boy toys"
  - Higher in rough & tumble play, physical activity
  - Higher aggressiveness
  - Not all due to environment or upbringing

Parallels in animals
- Correlated with anatomical changes
- Anatomy changes with experimental hormone manipulation in animals

Data That Gender Diffs in Play Not All Due to Socialization

- Infants too young to yet display a behavioral preference show a gender difference in what toys they look at the most.
- Baby monkeys show the same gender diffs in toy preferences.

- Young female monkeys or female humans who had greater exposure to early T show increased male-typical play & toy preferences.
- Sons of women who tested high in phthalates (which decrease T) during pregnancy show less interest in boy toys and more interest in girl toys.

Data That Gender Diffs in Play Not All Due to Socialization

- Early hormone variations in the normal range predict later behavioral tendencies.
- We all produce both T and E – but in different amounts.

How About the Relationship of Early Hormones to Play Preferences of Females With Normal Prenatal Sexual Development?

- First: Sampled blood of pregnant women to determine level of testosterone present
- Then: When their daughters were 3 years old, observed play preferences
- Higher maternal testosterone was associated with higher preference for 'boy toys'

- T levels at different ages

Fetal T Levels & Male-Typical Play

- Graphs showing correlation between fetal testosterone levels and male-typical activities
Fetal T negatively correlated with empathy

Another M/F size difference:
Digit ratio
• Finger length distribution is sexually dimorphic – especially the 2nd (2D) and 4th (4D) fingers of the right hand
• Dimorphism results as male hormones, particularly testosterone, affect finger growth in utero

Digit ratio

Masculine
4D>2D
Especially on right side

Ablatio Penis (or the case of John/Joan)
Are gender identities learned?
• Baby John (real name David Reimer):
  • Normal male baby boy
  • Penis accidentally burnt off during circumcision
  • Parents advised that male genital could not be reconstructed, but could be fashioned into female vulva/lower vagina.
  • Parents advised by psychologist John Money to totally & consistently raise baby as a female so child will learn a female sexual identity

Feminine
2D= or >4D
Lesbians have more masculine finger lengths, and gay males, more feminine as well as shorter arms and leg bones.
Role of Environment?

- The Case of John/Joan – unsuccessful rearing as female after penis was burned off
- [http://www.youtube.com/watch?v=QeSvkESZIhk](http://www.youtube.com/watch?v=QeSvkESZIhk)
- DHT deficiency – despite years as a female, easy switch to male identity at puberty.
- In these cases brain would be masculinized by early testosterone.
- Those who pursue sex changes after years of upbringing as a particular gender may also be responding to the particular differentiation of their brain.

Damage to or malfunction of this system could cause loss of activational hormones.