

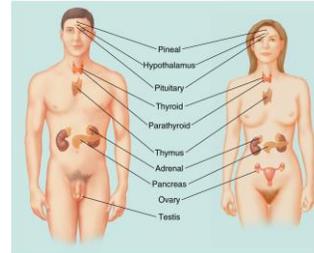
Neurotransmitters convey a message from the sending neuron to the receiving neuron(s).

Hormones, on the other hand, "broadcast" a message throughout the body via the bloodstream, so are able to influence & coordinate changes in cells in many distant organs/tissues.

Both transmitters & hormones act by binding to receptors.

(We'll hold off on hormones for the moment, because before there could be hormones, there had to be the **glands.**)

The Endocrine System



Endocrine glands secrete "hormones" directly into bloodstream. Hormones then can affect multiple target tissues.

In Chap 7 the Hypothalamus, Pituitary, Gonads, and Adrenals are the glands that will play a role in sexuality.

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!)

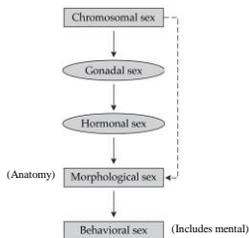


The doctor in the delivery room most often just looks at the baby's genitals.

But there is more to it than that!

What defines male or female ?

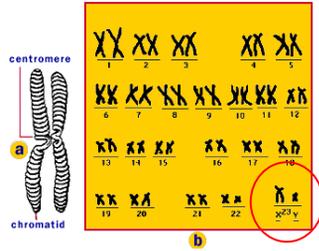
(not all countries or organizations use the same criteria!)



- 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.

Differentiation

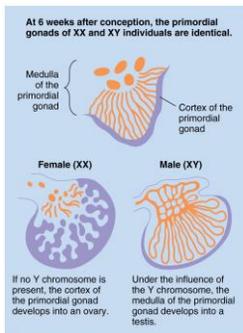
Human chromosomes!



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



Note: "medulla" here means "middle" and "cortex" means "outer layer". They are NOT referring to parts of the brain.

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 and ovaries
 - Adrenal cortex

Organizational vs Activational Effects Of Sex Hormones

- | | |
|---|--|
| <ul style="list-style-type: none"> • Organizational • permanent effects • occur mostly during early critical period • produce structural changes in body and brain | <ul style="list-style-type: none"> • Activational • transitory effects; can disappear in absence of hormone • puberty → adulthood • produce motivational and functional changes |
|---|--|

- We all begin with ducts, genitals & brains which can go either way (male or female)
- The “default” setting for 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 & 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.

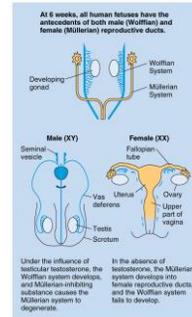
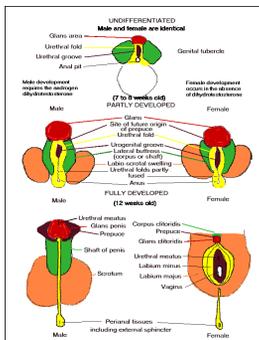
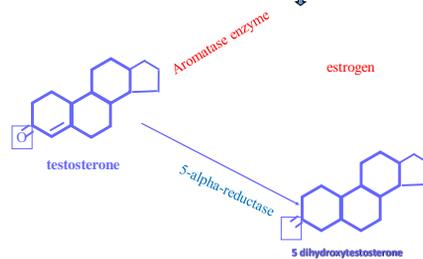


Figure 13.7



• Masculinization of genitalia occurs primarily in response to dihydrotestosterone (DHT)

Hormonal transformation



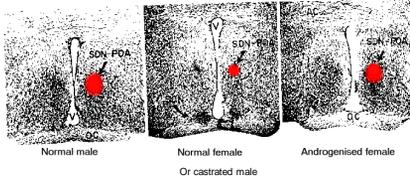
Differentiation of the Brain

- Androgens also have defeminizing and 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.

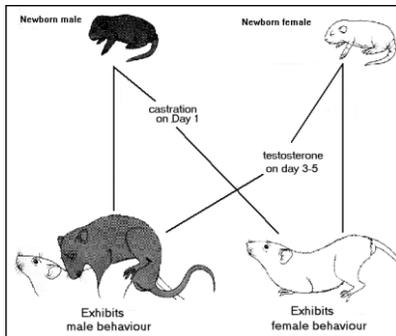
Sex Differences in Brain



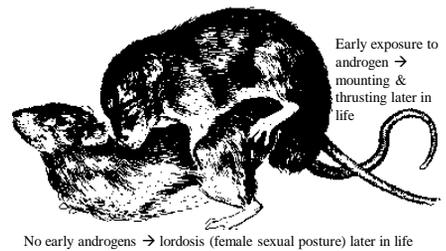
Sexually Dimorphic Nucleus (SDN) of Preoptic Region of Hypothalamus



- Do male and female animals show different sex-typical behaviors because of genetic makeup or because of hormone exposure?



Sex-Typical Behaviors



The Female Spotted Hyena.

- Females produce large quantities of androstenedione 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 genitals including a scrotum and erectile penis (Glickman et al., 1987).



- 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

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
- Parallels in animals
- Correlated with anatomical changes
- Anatomy changes with experimental hormone manipulation in animals
- NOT all due to environment or upbringing

Data That Gender Differs 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 diff in toy preferences.
- Young female monkeys or female humans who had greater exposure to early T show increased male-typical play & toy pref
- 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



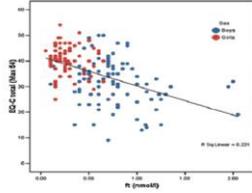
Reprinted from Alexander & Hines, *Evolution and Human Behavior* (2002) 23: 467-479

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

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

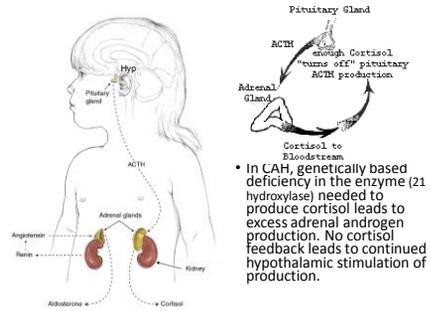
Figure 4 Graph showing relationship EQ-C score and T for both sexes. Fetal testosterone and empathy: Evidence from the Empathy Quotient (EQ) and the "Reading the Mind in the Eyes" Test. Chapman, E. et al. Social Neuroscience, 2006. Taylor & Francis Ltd, reprinted by permission of the publisher (Taylor & Francis Ltd. <http://www.tandf.co.uk/journals>).



Cases of Unusual Sexual Differentiation

Congenital Adrenal Hyperplasia or Adrenogenital Syndrome

One cause of androgen exposure in females



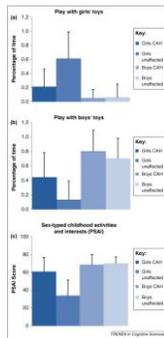
- In CAH, genetically based deficiency in the enzyme (21 hydroxylase) needed to produce cortisol leads to excess adrenal androgen production. No cortisol feedback leads to continued hypothalamic stimulation of production.

- 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



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



5-alpha-reductase deficiency →
“Guevedoces” (“eggs@12”)



Testosterone can't be converted to dihydrotestosterone which is most important androgen for masculinizing genitals before birth.

Testosterone surge at puberty does stimulate growth of penis and scrotum.

Most easily transition to male gender identity despite early upbringing



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)

Role of Environment?

- The Case of John/Joan – unsuccessful rearing as female after penis was burned off
- <http://www.youtube.com/watch?v=QeSvkE9ZtHk>
- 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.

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

- Brothers both homosexual?
 - identical twins - 52%
 - fraternal twins - 22%
 - Non-twin brothers – 9.2%
 - adopted brothers - 11%
- Sisters both lesbian?
 - identical twins - 48%
 - fraternal twins - 16%
 - non-twin 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=d5vrNYA_nik
- <http://www.youtube.com/watch?v=-S5QYVe0mJY&feature=channel>
- National Geographic
- http://www.youtube.com/watch?v=saO_RFWVVA&feature=related

- 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.

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

- 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.

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→F transsexuals.
- Other areas of brain that differ with sexual orientation:
 - Anterior commissure
 - Suprachiasmatic 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.

Digit ratio

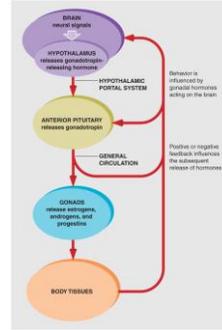


Masculine
4D>2D
Especially on right side

Digit ratio



Feminine
 $2D = \text{or} > 4D$
 Lesbians have more masculine finger lengths, and gay males, more feminine as well as shorter arms and leg bones.



Damage to or malfunction of this system could cause loss of the adult activational effects of hormones and decrease sexual motivation, sexual functioning and secondary sex characteristics.