PART VI

BEHAVIOR

29.

NEURAL CONTROL OF STRESS

It is likely every reader of this chapter has experienced some form of stress, perhaps due to a big exam, a looming deadline, or an unplanned interaction with a spider. The physical reactions to stress, like increased heart rate and breathing, are a result of brain activation.

Resources

- Key Takeaways
- Test Yourself
- Video Version

Types of stress

Stress is often split into two categories: physical and psychological. Physical stress can be caused by trauma, illness, or injury. Blood loss, dehydration or allergic reactions are examples of physical stressors. Psychological stress has an emotional and mental component. Fear, anxiety, and grief are examples of psychological stress. The neural circuits involved in responding to the different stressors are overlapping but separate.

Stress response systems

The body has two main systems for responding to stress: the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. The autonomic nervous system response occurs very quickly because it is synaptic in nature and is responsible for the “fight or flight” response, which stimulates heart rate and breathing and inhibits digestion. The HPA axis is a hormonal response, so it is a slower response relative to the autonomic system. Its downstream effects also promote energy use.

Neural Control

Hypothalamus

The hypothalamus plays a critical role in stress, activating both the autonomic and hormonal responses. The hypothalamus is a region right above the brainstem on either side of the 3rd ventricle. The hypothalamus manages hormone release in the body and maintains homeostasis; this small structure is critical for numerous functions including hunger and thirst, temperature control, regulation of blood composition, sleep, reproduction, and stress.

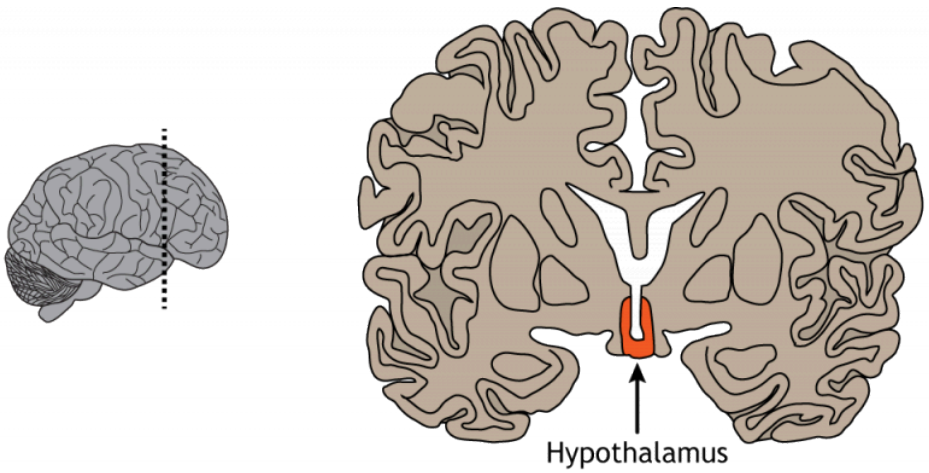

Figure 29.1. The hypothalamus, shown in orange in this coronal view, is located adjacent to the third ventricle. 'Hypothalamus Coronal View' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the hypothalamus using the BrainFacts.org 3D Brain

Although the hypothalamus directly controls the body's response to stress, it is influenced by activity in other regions of the brain. When information from the environment is processed, activity is seen in the prefrontal cortex, hippocampus, and amygdala. These regions have direct and indirect connections to the hypothalamus. The prefrontal cortex plays an executive decision-making role, the hippocampus places events in context with previous memories, and the amygdala assesses a wide range of stimuli for their potential ability to cause harm and places an emotional value on them.

Amygdala

The amygdala is located medially in the temporal lobe. The amygdala, which means "almond" in Latin, is responsible for the processing of emotions and consolidating emotional memories. It is especially active during fear learning and evaluates the salience, or importance, of a situation. For instance, when we look at frightened faces, our amygdala is more activated than when we see neutral faces. Conditions such as anxiety, depression, and post-traumatic stress disorder are all linked to amygdala dysfunction.

Figure 29.2. The amygdala, shown in yellow in a coronal view, is located in the deep in the anterior portion of the temporal lobe. 'Amygdala' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the amygdala using the BrainFacts.org 3D Brain

Hippocampus

Just posterior to the amygdala lies the hippocampus. The hippocampus, which means "seahorse" due to the similarity between its shape and the animal, is important in the long-term consolidation of memories, spatial navigation, and associating contextual cues with events and memories.

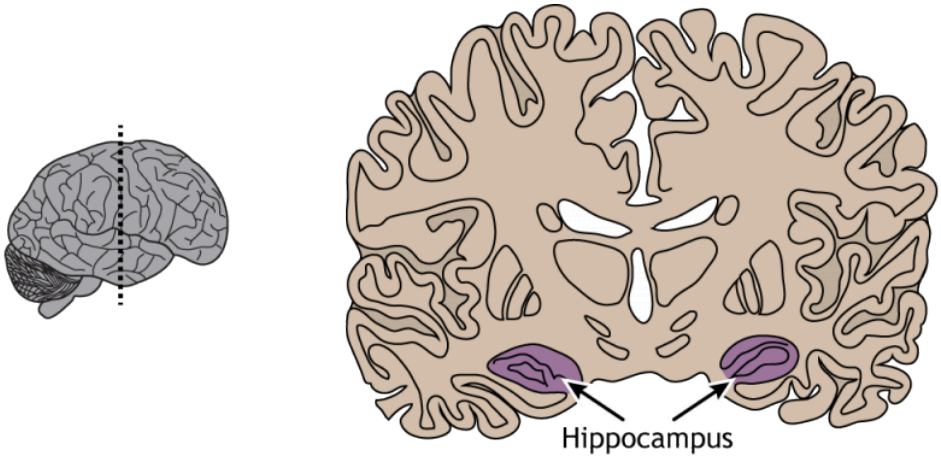

Figure 29.3. The hippocampus, shown in purple in a coronal view, is located in the deep in the temporal lobe. Hippocampus by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the hippocampus using the BrainFacts.org 3D Brain

Prefrontal Cortex

Finally, the prefrontal cortex, which is located in the front of the brain in the frontal lobe, contributes to higher level cognitive functions like planning, critical thinking, understanding the consequences of our behaviors, and is also associated with the inhibition of impulsive behaviors. The prefrontal cortex is one of the last brain regions to fully develop and may not be fully developed until an individual reaches their mid-twenties. Experts think this might explain why teens are more likely than adults to participate in risky behaviors.

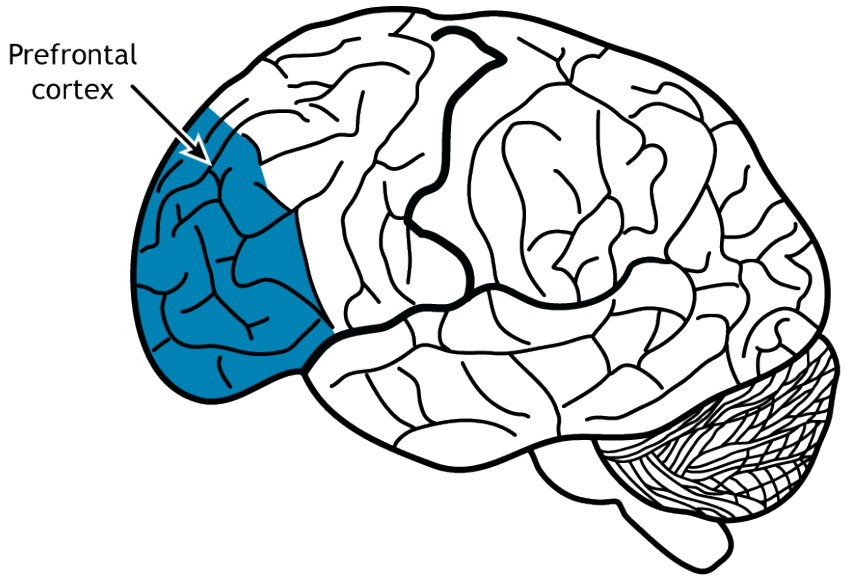

Figure 29.4. The prefrontal cortex, shown in blue in an external view of the brain, is located in the anterior portion of the frontal lobe. 'Prefrontal Cortex' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the prefrontal cortex using the BrainFacts.org 3D Brain

Key Takeaways

- There are two systems that manage physical responses to stress: the autonomic nervous system and the HPA axis
- The hypothalamus is located on either side of the 3rd ventricle, inferior to the thalamus and directly controls both the autonomic nervous system and the HPA axis
- The amygdala, hippocampus, and prefrontal cortex all influence the activity of the hypothalamus

Test Yourself!

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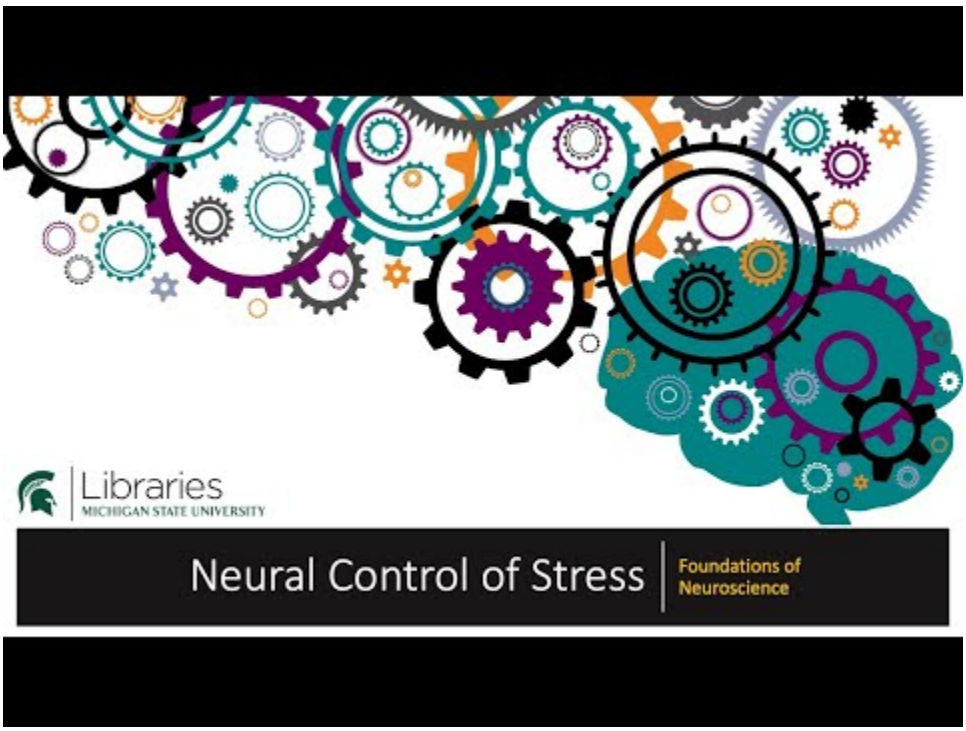
https://openbooks.lib.msu.edu/neuroscience/?p=689#h5p-26

Video Version of Lesson



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https://openbooks.lib.msu.edu/neuroscience/?p=689

30.

HPA AXIS

When presented with a stressor, our brain activates the hypothalamic-pituitary-adrenal (HPA) axis, which initiates a hormonal response.

Resources

- Key Takeaways
- Video Version

Hypothalamus

The hypothalamus, which sits below the thalamus, integrates information from many regions of the central nervous system and plays a critical role in maintaining homeostasis in the body. The hypothalamus regulates temperature, hunger, thirst, blood volume and pressure, sleep and wakefulness, reproductive functions, and stress and fear responses.

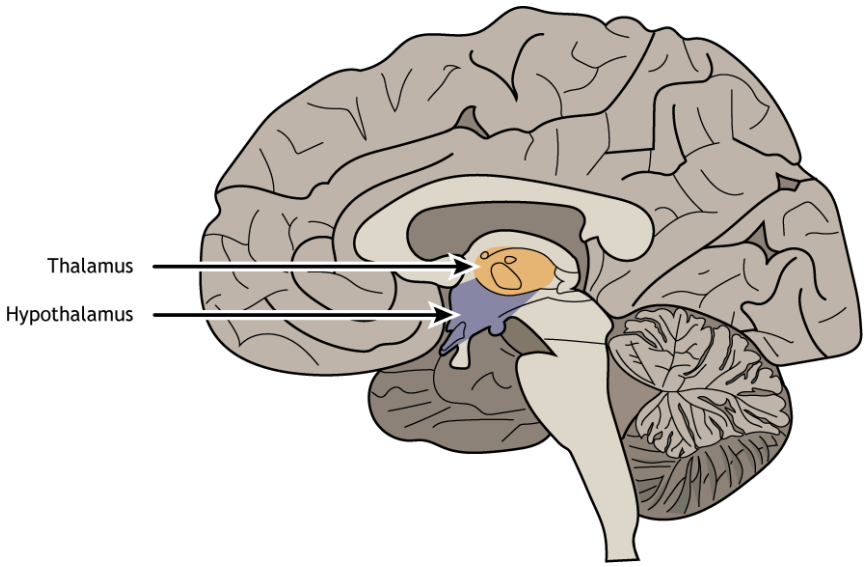


Figure 30.1. The hypothalamus, shown in blue in a mid-sagittal section, sits below the thalamus, shown in orange. 'Hypothalamus Sagittal' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the hypothalamus using the BrainFacts.org 3D Brain

Pituitary

The hypothalamic regulation of the body's response to stress is managed via hormone release by the pituitary gland. The pituitary gland is located inferior to the hypothalamus. The pituitary is divided into two lobes, the anterior and the posterior pituitary. These regions are responsible for the release of different hormones and are controlled by the hypothalamus in different ways.

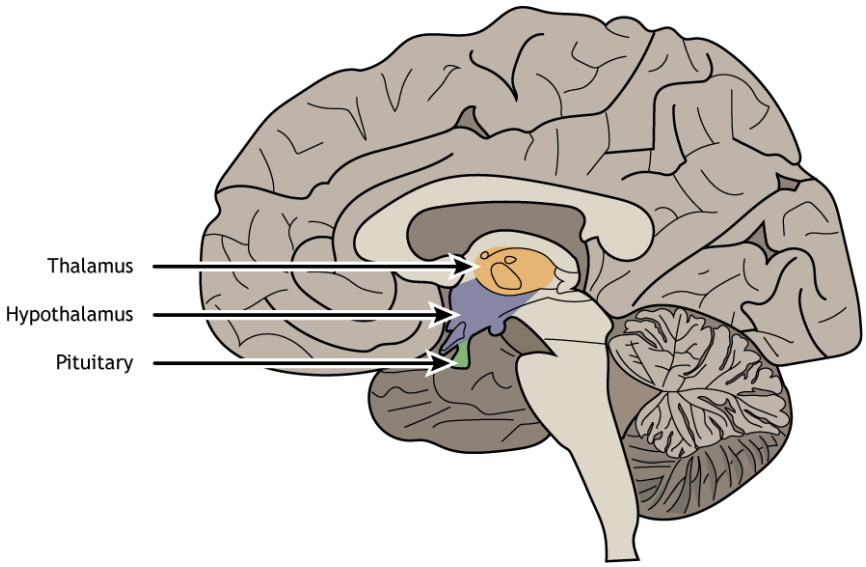


Figure 30.2. The pituitary, shown in green in a mid-sagittal section, lies just below the hypothalamus, shown in blue. 'Hypothalamus and Pituitary' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the pituitary using the BrainFacts.org 3D Brain

Hormone Release

The stress response relies on anterior pituitary function. The hypothalamus contains two types of neurons that secrete hormones into the pituitary: parvocellular neurosecretory cells and magnocellular neurosecretory cells. Parvocellular cells are smaller than the magnocellular neurons (parvus means "small" in Latin). In the HPA axis, the parvocellular neurosecretory cells release a hormone called corticotropin-releasing hormone (CRH) into a specialized capillary system that lies between the hypothalamus and the pituitary called the hypophyseal portal circulation. When CRH reaches the anterior pituitary, it causes the endocrine cells of the pituitary to release adrenocorticotropic hormone (ACTH) into the general circulation.

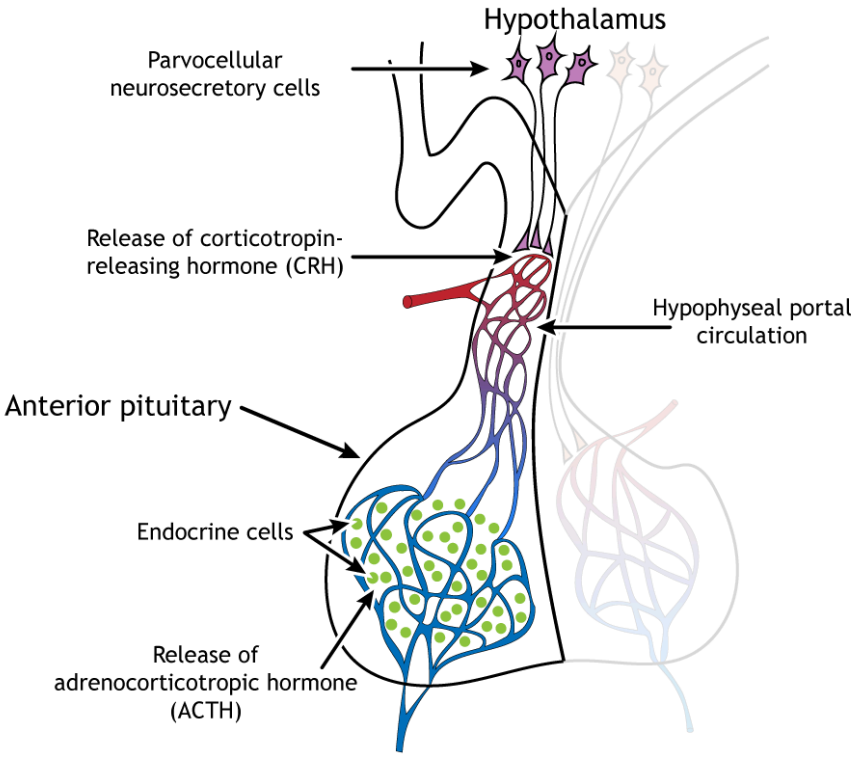


Figure 30.3. In response to stress, the hypothalamic parvocellular neurosecretory neurons release corticotropin-releasing hormone (CRH) into the hypophyseal portal circulation, causing the hormone-releasing endocrine cells in the anterior pituitary to release adrenocorticotropic hormone (ACTH). 'CRH and ACTH Release' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The ACTH travels through the circulatory system and can act on the adrenal cortex, a gland located on top of the kidney. The adrenal cortex releases cortisol, a glucocorticoid hormone, into the blood stream. Cortisol travels throughout the body and has many effects that prepare the body for either fleeing or fighting the stressor. Promotion of energy use (for a quick escape or for defense) occurs through the release of glucose, the sugar the body uses for energy.

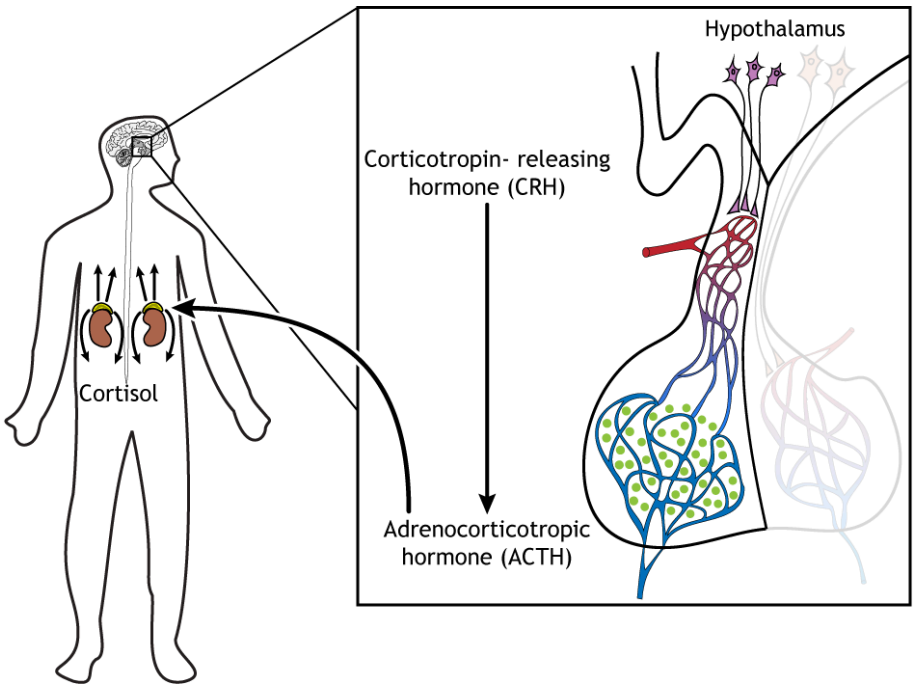


Figure 30.4. The adrenal glands, which sit on top of the kidney, release cortisol into the bloodstream in response to release of ACTH by the anterior pituitary. 'HPA Axis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Hormone Action

Cortisol is a steroid hormone; steroid hormones are synthesized from cholesterol and are able to cross the phospholipid bilayer because they are lipid soluble. Glucocorticoid receptors are located in the cytoplasm of many cell types across the body. The receptors dimerize after cortisol binds, and the dimer moves to the nucleus where it can alter DNA transcription.

A video element has been excluded from this version of the text. You can watch it online here: https://openbooks.lib.msu.edu/neuroscience/?p=698

Animation 30.1. Cortisol can cross the phospholipid bilayer and bind to glucocorticoid receptors.

The receptors dimerize, move to the nucleus, and interact with DNA, altering transcription of certain genes. 'Cortisol Action' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Negative Feedback

Once the stress response has been initiated, and cortisol enters the circulation, cortisol itself is able to act on the hypothalamus and pituitary and inhibit production of CRH and ACTH. This is called a negative feedback loop; the active hormone (cortisol) can shut off its own production. Negative feedback is possible because neurons in the hypothalamus and pituitary express glucocorticoid receptors that are activated by cortisol.

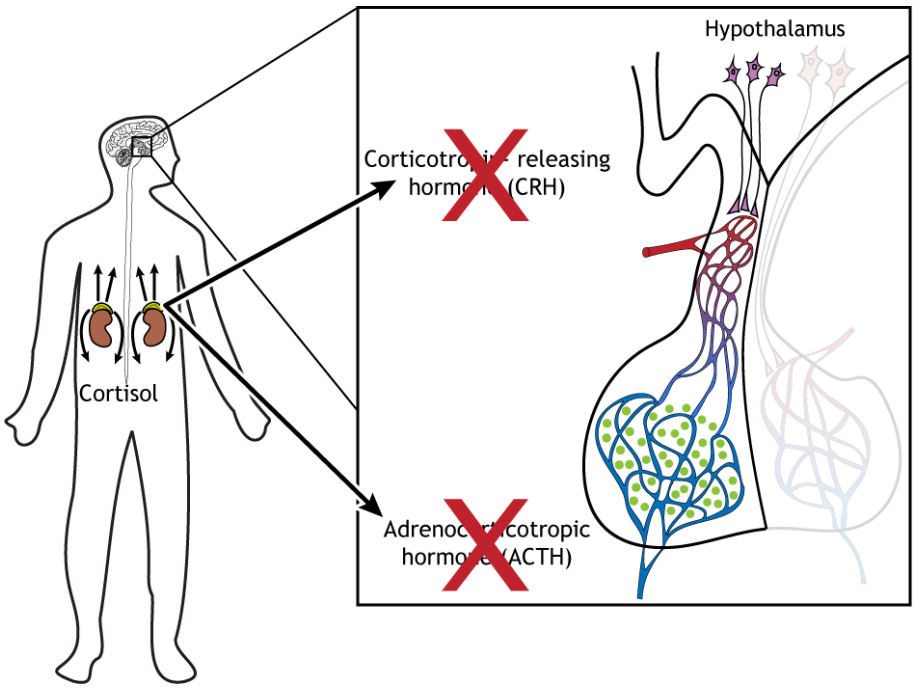


Figure 30.5. Cortisol released by the adrenal cortex inhibits the synthesis and release of CRH and ACTH from the hypothalamus and pituitary, respectively. via a negative feedback loop. 'Cortisol Feedback' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

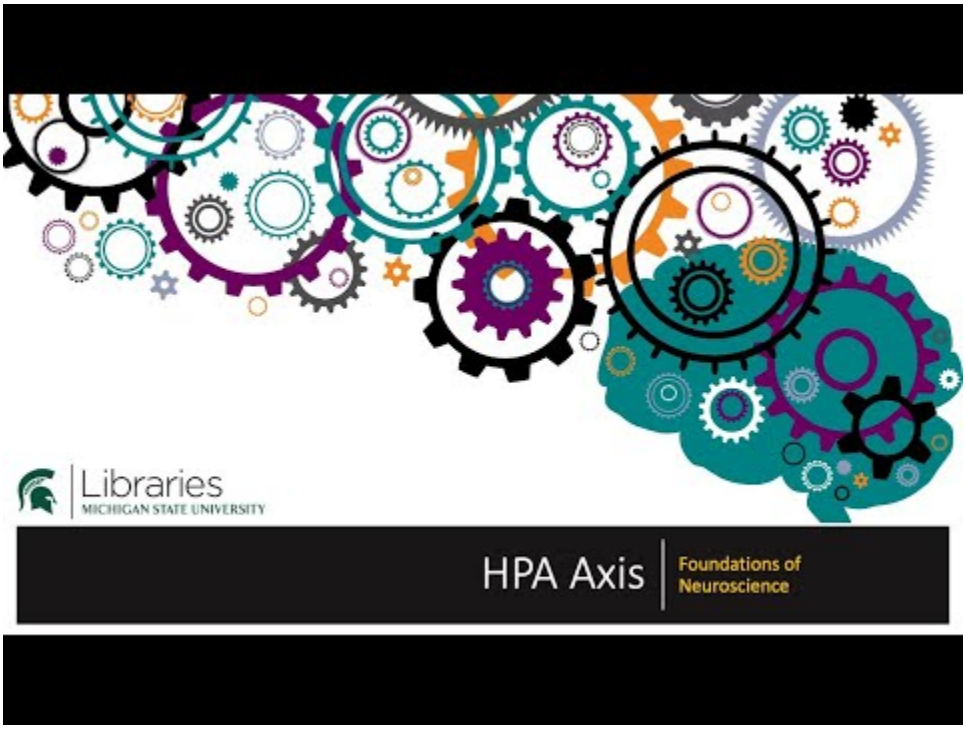
Chronic Stress

While this cortisol response to stress is particularly important in certain situations, like moments of danger, chronic stress is an unhealthy scenario which can put people at risk for heart disease and other illnesses. Chronic stress can cause structural and functional changes, like cell death or alterations in the dendritic arbor, within the cortical regions that play a role in control of the HPA axis due to long-lasting exposure to cortisol.

Key Takeaways

- The hypothalamus directly controls the stress response by controlling hormone release from the anterior pituitary
- The hypothalamus releases corticotropin-releasing hormone (CRH)
- The anterior pituitary releases adrenocorticotropic hormone (ACTH)
- The adrenal cortex releases cortisol
- Cortisol binds to receptors and alters DNA transcription
- Cortisol can shut off its own production via a negative feedback loop

Video Version of Lesson



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31.

HPG AXIS

Control of gonadal hormone release relies on activation of the hypothalamic-pituitary-gonadal (HPG) axis. Gonadal hormones are important for development of the body and brain, changes during puberty, and the activation of some behavior in adulthood like reproductive behavior and aggression.

Resources

- Key Takeaways
- Video Version

Hypothalamus

As a refresher, the hypothalamus, which is located inferior to the thalamus, integrates information from many regions of the central nervous system and maintains homeostasis in the body. They hypothalamic regulation of gonadal hormones and sex behavior is managed via hormone release by the pituitary gland.

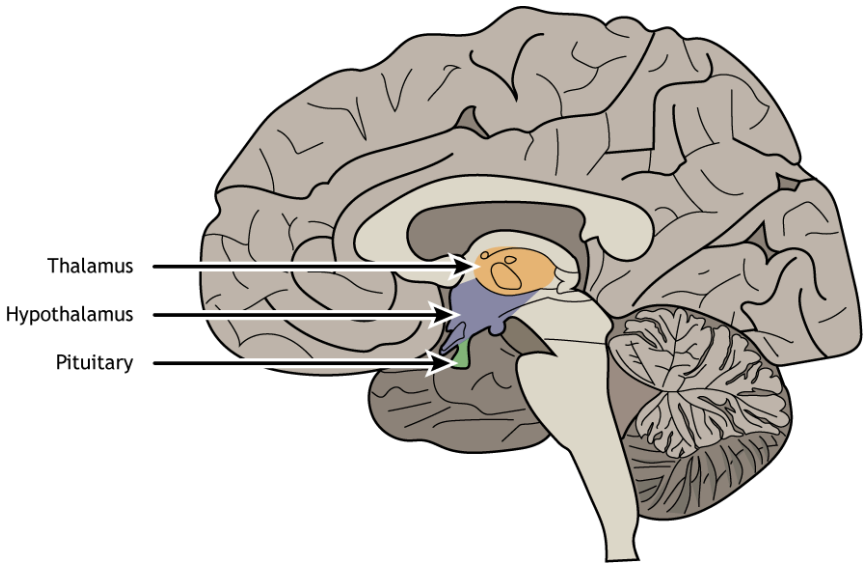


Figure 31.1. The pituitary, shown in green in a mid-sagittal section, lies inferior to the hypothalamus, shown in blue. 'Hypothalamus and Pituitary' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the hypothalamus using the BrainFacts.org 3D Brain

View the pituitary using the BrainFacts.org 3D Brain

Hormone Release

Gonadal hormone release relies on anterior pituitary function. In the hypothalamus, the parvocellular neurosecretory cells release a hormone called gonadotropin-releasing hormone (GnRH) into the hypophyseal portal circulation. When GnRH reaches the anterior pituitary, it causes the endocrine cells of the pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH) into the general circulation.

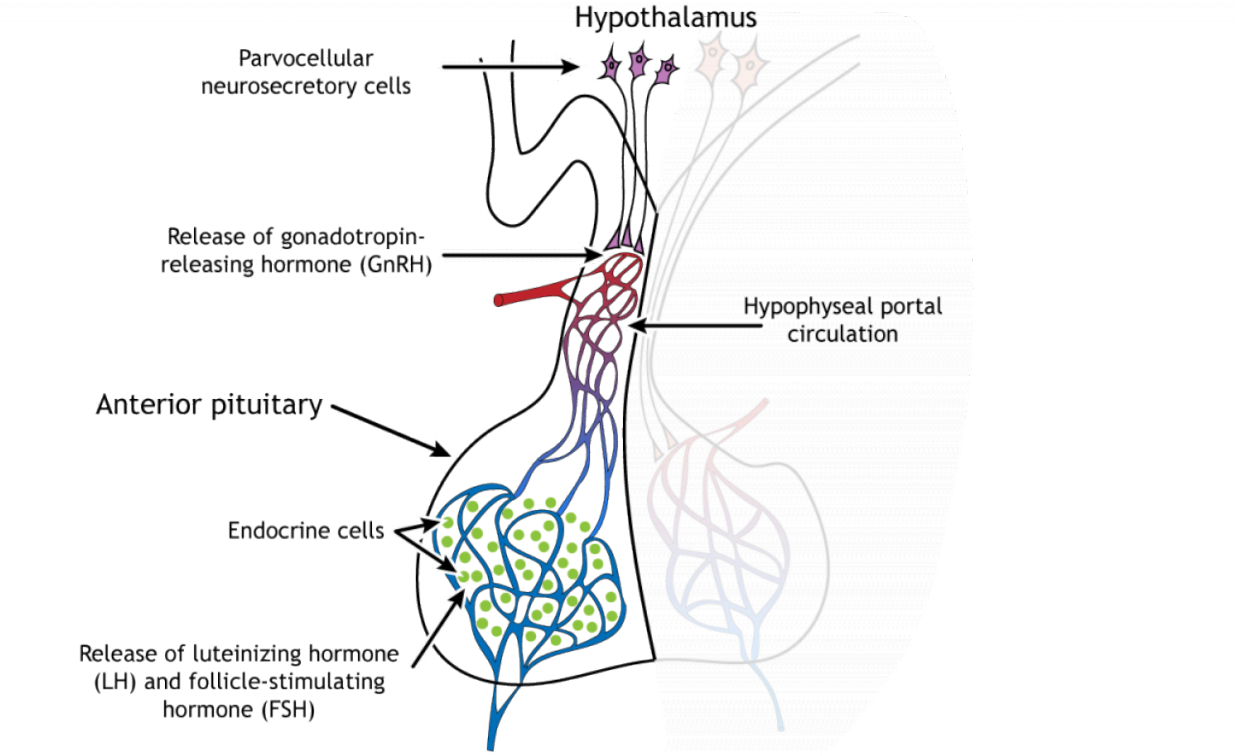


Figure 31.2. In the HPG axis, the hypothalamic parvocellular neurosecretory neurons release gonadotropin-releasing hormone (GnRH) into the hypophyseal portal circulation, causing the hormone-releasing endocrine cells in the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). 'LH and FSH Release' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The LH and FSH travel through the circulatory system and can act on the gonads, either the testes in males or ovaries in females. In response to the pituitary hormones, the testes release testosterone, an androgen, and the ovaries release estradiol, an estrogen, into the blood stream. After puberty, the LH and FSH are also critical for the maturation of sperm and egg cells.

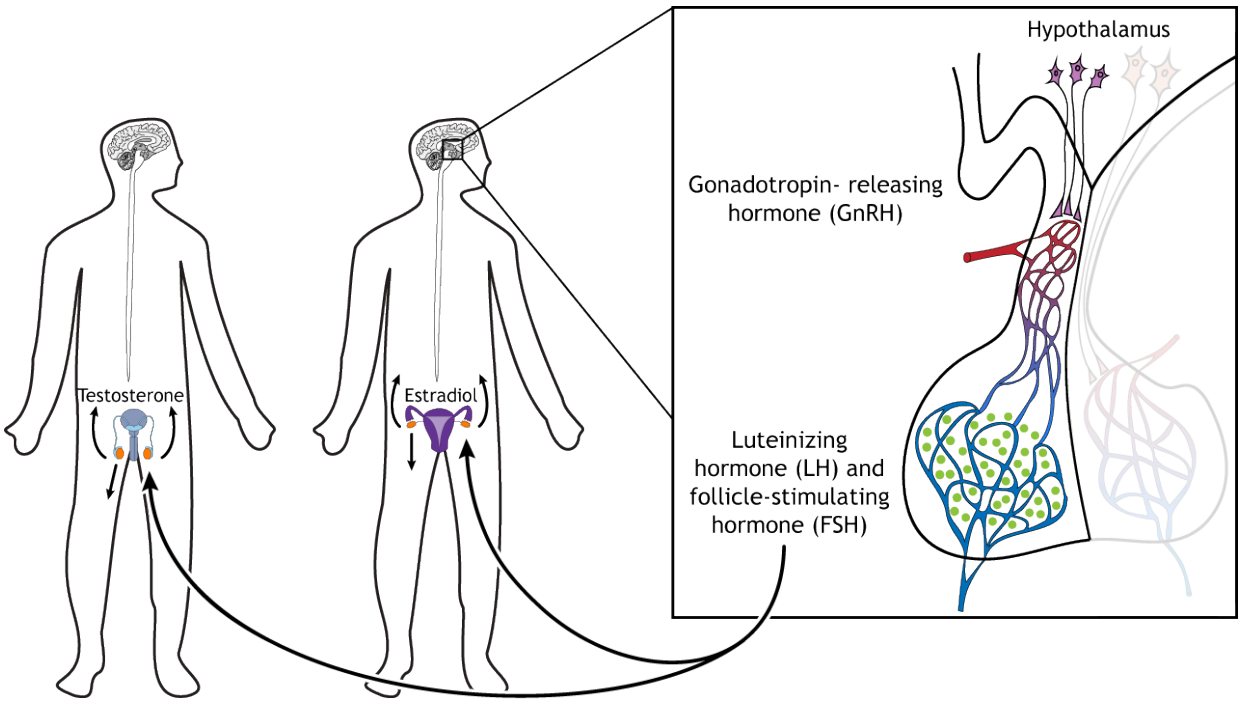


Figure 31.3. The gonads release either testosterone (testes) or estradiol (ovaries) into the bloodstream in response to release of LH and FSH by the anterior pituitary. 'HPg Axis' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Hormone Action

Once the gonadal hormones enter the circulation, they are able to act on cells that express either androgen receptors or estrogen receptors. Like cortisol, testosterone and estradiol are steroid hormones and can cross the phospholipid bilayer. Inside the cell, the hormones bind to receptors which then dimerize and move to the nucleus The receptors can bind to DNA at special promotor regions and act as transcription factors, turning on specific genes.

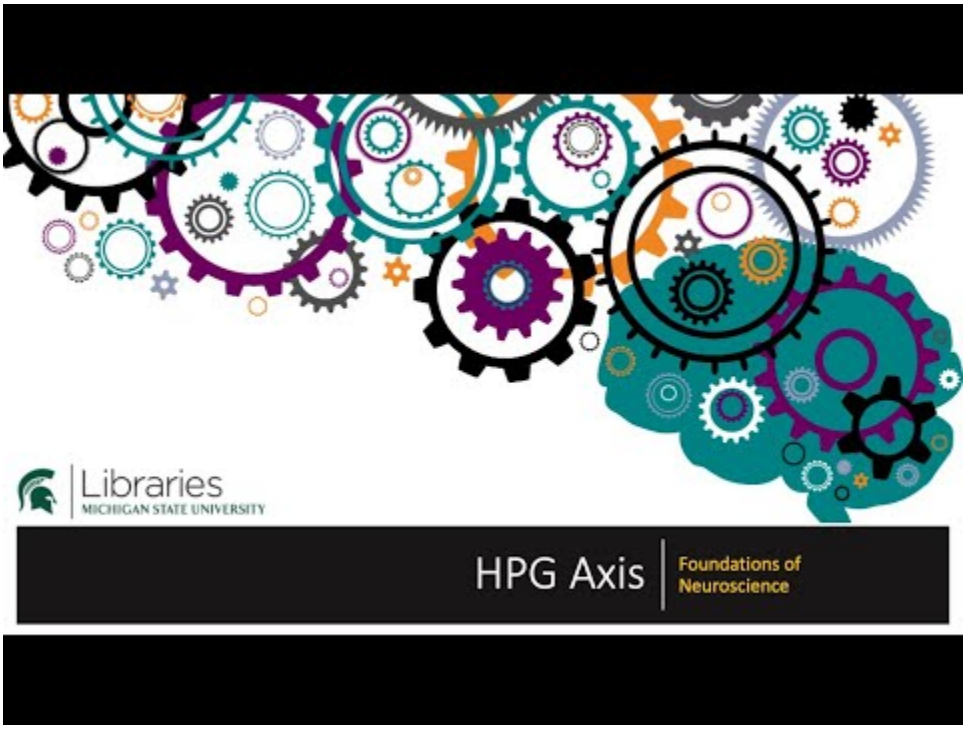
A video element has been excluded from this version of the text. You can watch it online here: https://openbooks.lib.msu.edu/neuroscience/?p=1401

Animation 31.1. Steroid hormones can cross the phospholipid bilayer and bind to hormone receptors. The receptors dimerize, move to the nucleus, and interact with DNA, altering transcription of certain genes. 'Estradiol Action' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- The hypothalamus directly controls release of gonadal hormones by controlling hormone release from the anterior pituitary
- The hypothalamus releases gonadotropin-releasing hormone (GnRH)
- The anterior pituitary releases luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
- The ovaries release estradiol
- The testes release testosterone
- Gonadal hormones bind to receptors and alter DNA transcription

Video Version of Lesson



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32.

SEXUAL DIFFERENTIATION

Sexual differentiation is the process by which a person develops into either a male or a female. For the purpose of this chapter, the content will be based on a male / female binary to introduce the basic concepts of reproductive development. However, it is important to recognize that in real life, chromosomal sex, physical sex, and gender exist on a continuum and cannot always be simplified into a two-structure system.

Resources

- Key Takeaways
- Video Version

During development, the body and the brain undergo either A) feminization and de-masculinization or B) masculinization and de-feminization. In most cases, the differentiated brain will lead to behaviors that correspond appropriately to the differentiated gonads.

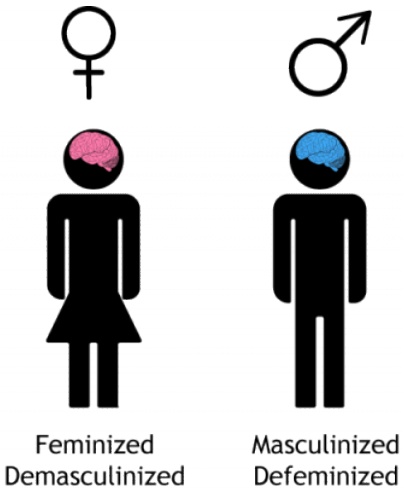


Figure 32.1. In most cases, human females have feminized and desmasculinized brains and bodies whereas human males have masculinized and defeminized brains and bodes. 'Gender Icons' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Chromosomal Sex

In humans, DNA is organized into 46 chromosomes. One set of 23 chromosomes comes from the mother and the other set comes from the father. Twenty-two pairs are called autosomal chromosomes. These chromosome are similar in length and have the same genes present at the same location regardless of if they are received from the mother or father. However, for all genes, the allele, or version, present for each gene may be different from each parent. The last pair of chromosomes is responsible for determining if an individual becomes a male or female; these are called the sex chromosomes. In humans the sex chromosomes are named either X or Y.

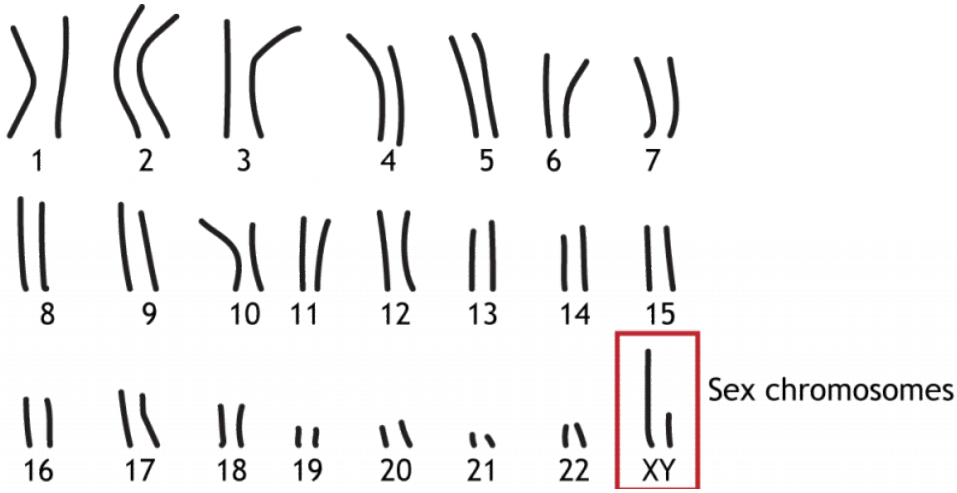


Figure 32.2. Humans have 23 pairs of chromosomes, making 46 total. 22 pairs are called autosomal and have similar structure from each parent. The final pair are the sex chromosomes and determine if the individual is a male or female. Sex chromosomes are named either X or Y. 'Chromosomes' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Fertilization occurs when a sperm cell from the father fuses with an egg cell from the mother. All egg cells contain one X sex chromosome. Sperm cells contain either one X or one Y chromosome, which means chromosomal sex in humans is determined by the sperm. If a sperm carrying an X chromosome fertilizes an egg, the resulting fetus will be XX and a female, whereas if a sperm carrying a Y chromosome fertilizes an egg, the resulting fetus will be XY and a male.

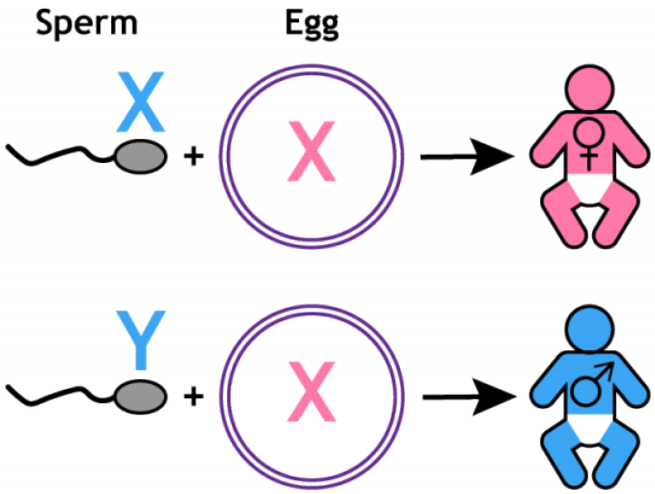


Figure 32.3. The combination of an X-containing sperm cell and an X-containing egg cell will result in a XX individual who will develop as a female. The combination of a Y-containing sperm cell and an X-containing egg cell will result in a XY individual who will develop as a male. 'Fertilization' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Gonadal Differentiation

On the Y chromosome is a gene called the sex-determining region (SRY) of the Y chromosome. The SRY gene is required for masculinization of the embryonic gonads. The SRY gene encodes for a protein called the testis-determining factor (TDF), which causes the embryonic gonads to differentiate into the testes. The testes then begin secreting both testosterone and a hormone called the Müllerian inhibiting substance (MIS). Testosterone causes Wolffian ducts to develop into the vas deferens, seminal vesicles, and epididymis. MIS causes the Müllerian ducts to degenerate. The presence of testosterone also results in the development of the prostate gland and penis.

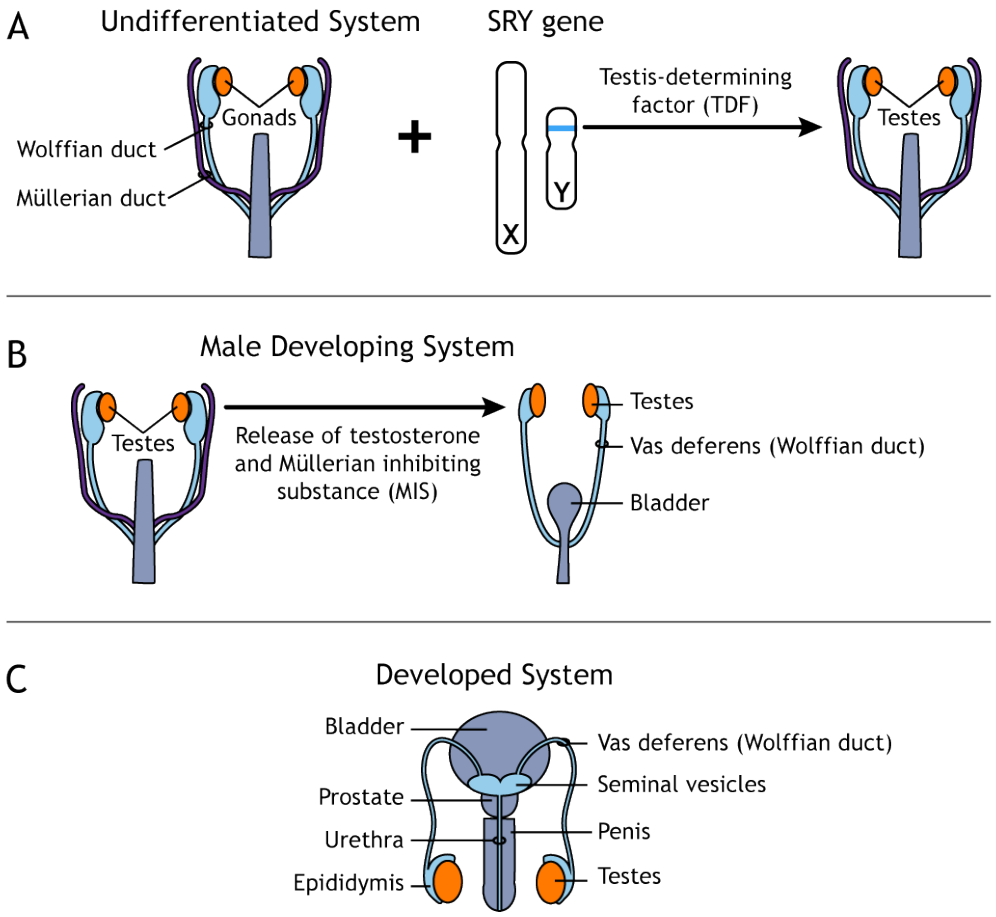


Figure 32.4. A. The undifferentiated gonadal system is the same for both sexes. In males, the SRY gene, located on the Y chromosome, is activated during development, producing testis-determining factor, which results in the gonads becoming testes. B. The testes begin releasing testosterone and Müllerian inhibiting substance, which cause the Wolffian ducts to become the vas deferens, seminal vesicles, and epididymis and cause the Müllerian ducts to degenerate. C. The presence of testosterone also causes the development of the penis and prostate gland in the fully developed system. 'Male Gonad Differentiation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

In females, when the SRY gene and secreted hormones are absent, the gonads differentiate into the ovaries, the Müllerian ducts develop into the fallopian tubes, uterus, and vagina, and the Wolffian ducts degenerate.

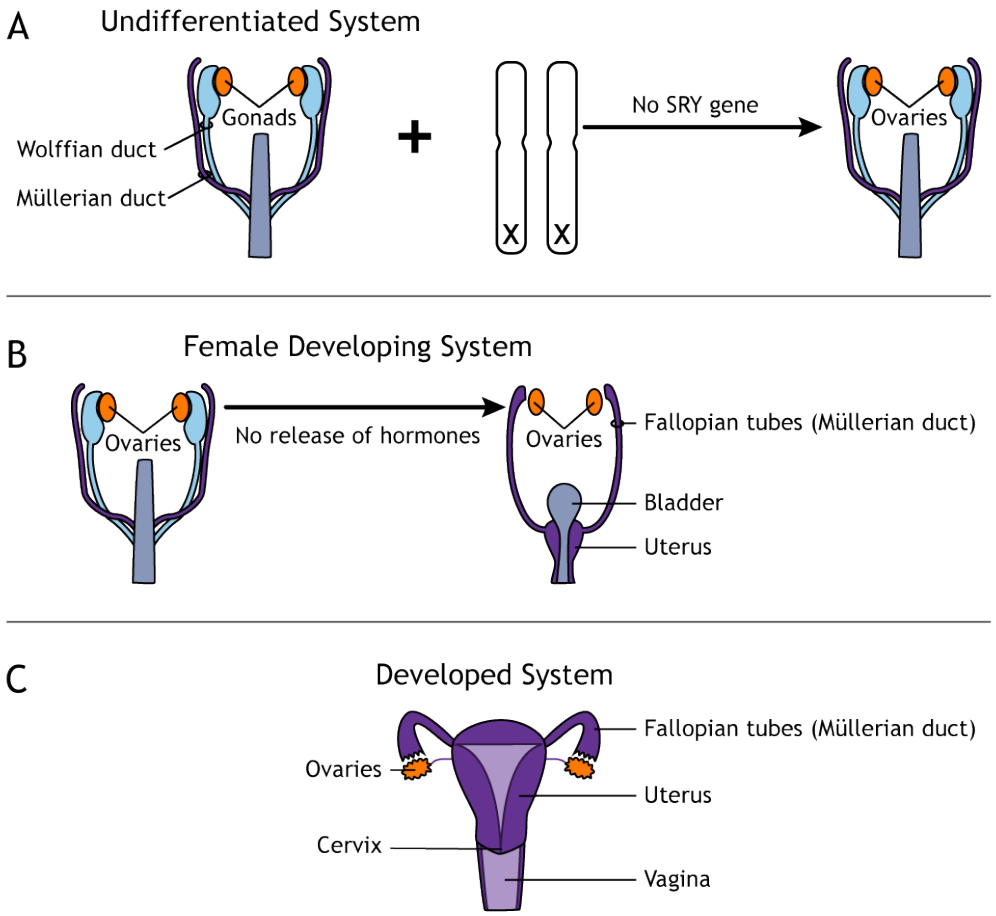


Figure 32.5. A. The undifferentiated gonadal system is the same for both sexes. In the absence of the SRY gene during the 6th to 12th week of gestation, the gonads become the ovaries. B. The ovaries do not produce any hormones during development which causes the Müllerian ducts to become the fallopian tubes, uterus, and vagina, and the Wolffian ducts degenerate. C. In the fully developed system, the cervix is the lower part of the uterus, which separates the uterus from the vagina. 'Female Gonad Differentiation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Hormones During Development

In addition to differentiating the reproductive duct system, the presence or absence of gonadal hormones during development also differentiates the rest of the body, including the brain. Testosterone causes the brain, body, and behavior of the individual to be masculinized and defeminized. The quiescent ovaries do not release hormones which causes the brain, body, and behavior of the individual to be feminized and demasculinized.

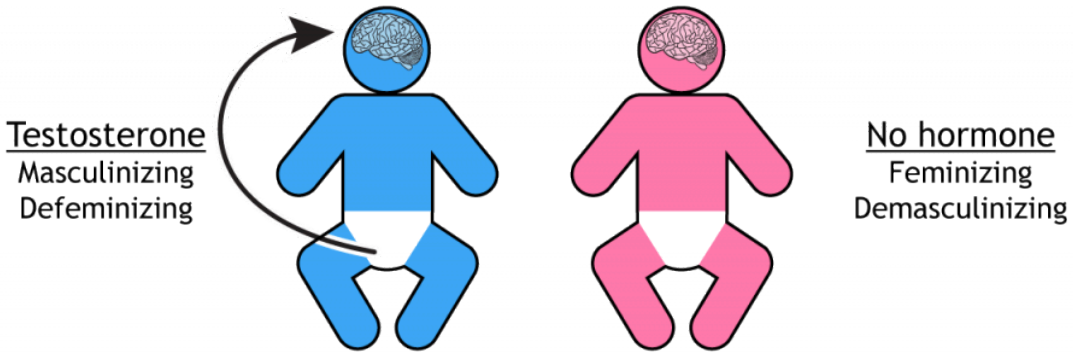


Figure 32.6. Testosterone presence during development masculinizes and defeminizes the brain, body, and behavior. No hormone exposure during development feminizes and demasculinizes the brain, body, and behavior. 'Developmental Hormones' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Critical Period

These hormonal effects of secreted testosterone on the brain must take place during a specific time in development, called a critical period. This early role of testosterone is called an organizational effect and results in a permanent change in the nervous system and therefore behavior. Organizational effects of hormones lead to major, generally irreversible, aspects of cell and tissue differentiation. Organizational effects take place during critical periods like prenatal development and puberty.

In adulthood, the same hormones trigger physiological or behavioral responses like inducing reproductive behavior or ovulation, but these influences, called activational effects, are reversible and short-lived. Removal of the activating hormone will cause the behavior to stop, but replacement later will cause the response to begin again because the brain has previously been organized to produce those behaviors when hormones are present.

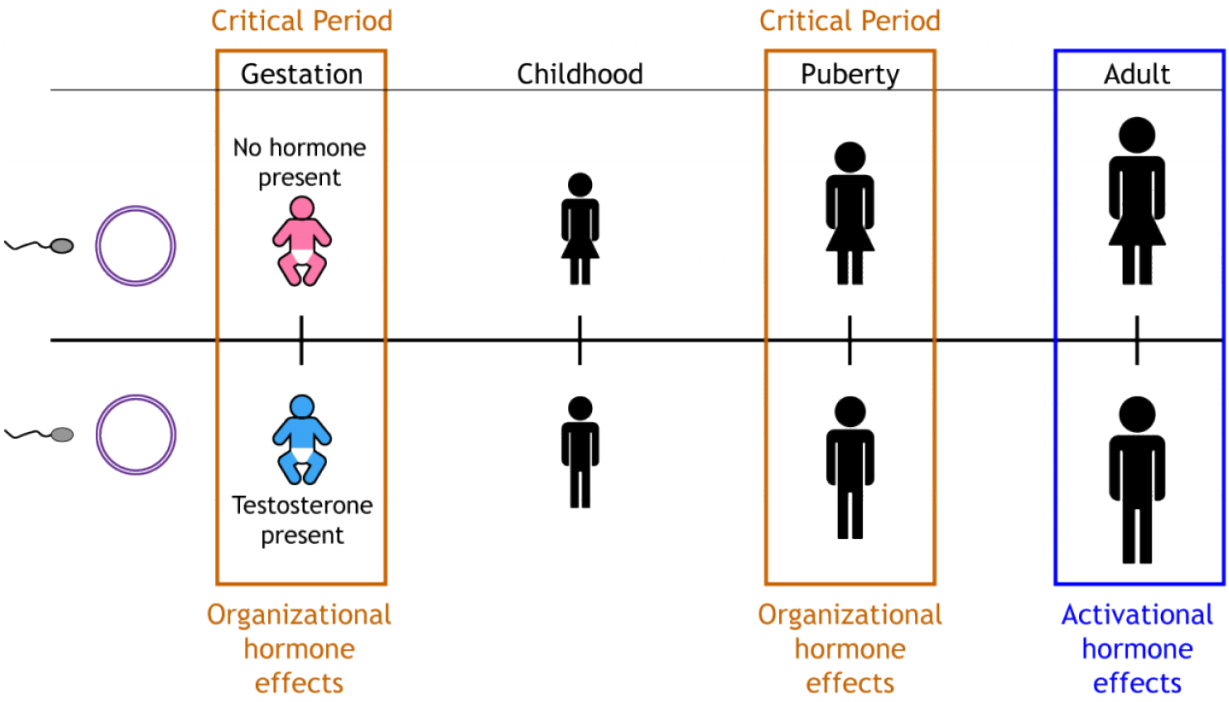


Figure 32.7. Hormones can have long-lasting, organizational effects when present during critical periods such as during the prenatal period or puberty. During these critical periods, hormones will alter the structure of the nervous system, setting up cells and circuits needed to display sex-typical behaviors later in life. Those sex-typical behaviors are then activated in adulthood by the presence of gonadal hormones. 'Organizational versus Activational' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The role of activational hormones can be demonstrated by adult castration in male rats. Healthy males with intact testes will show sexual behavior when placed with a female rat. Castration, the removal of the testes, will cause males to stop showing sexual behavior because the activating hormone, testosterone, is no longer present. However, if the castrated males receive testosterone replacement, they will resume showing sexual behavior. The sexual behavior brain circuit was organized during development by exposure to gonadal hormones, and in adulthood that circuit can be activated by testosterone. The adult behavior can only be seen when the activating hormone is present.

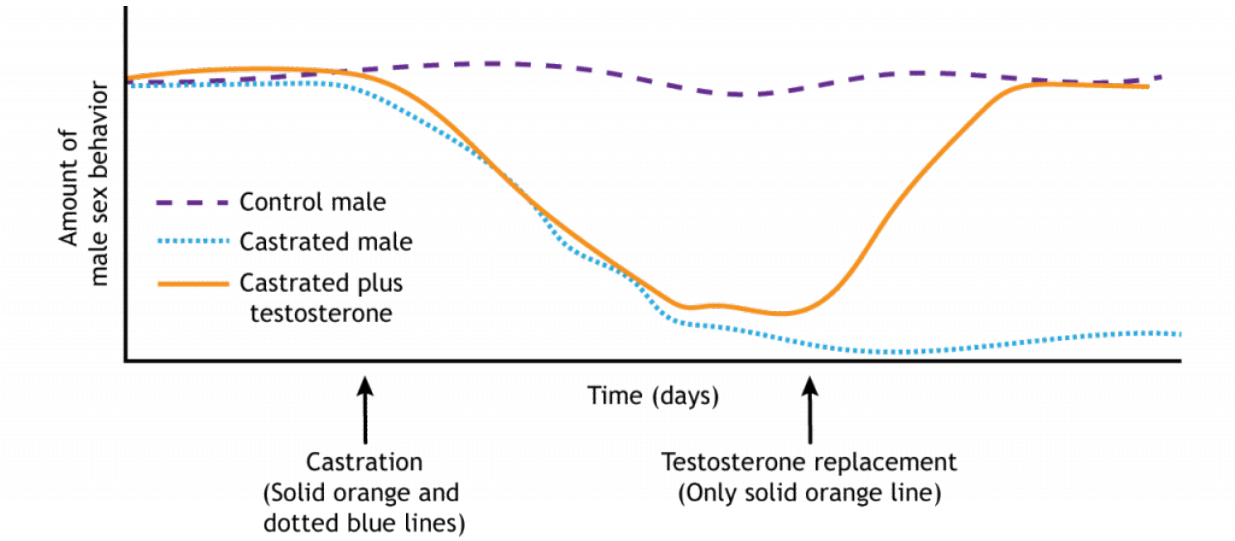


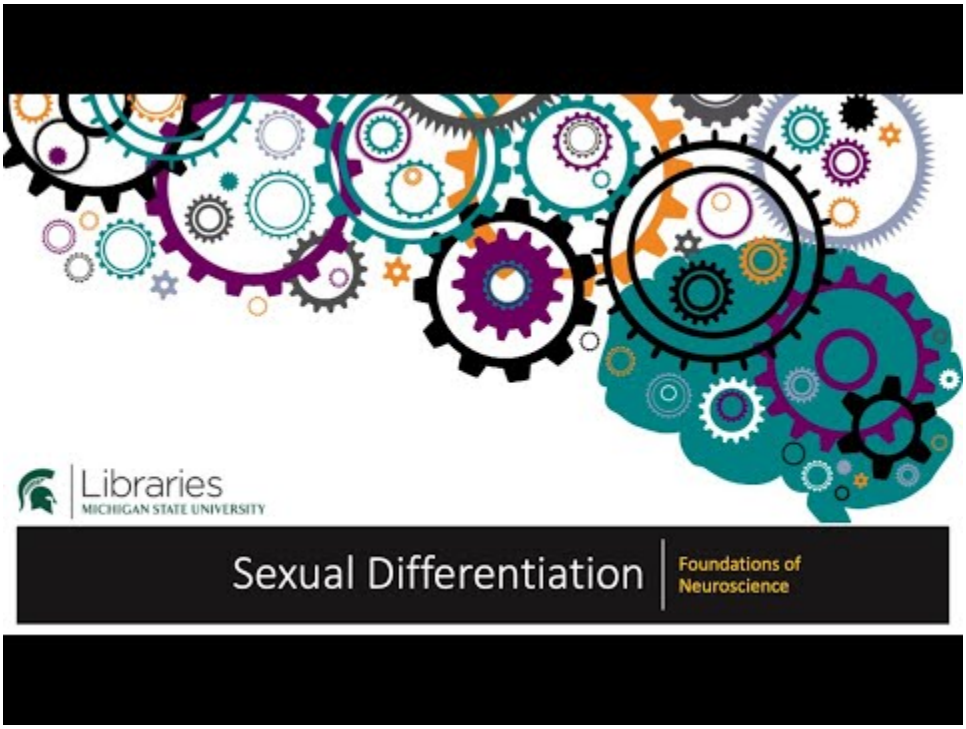
Figure 32.8. Removing testosterone by castrating an adult male rat will decrease the amount of sexual behavior displayed because the hormone can no longer activate sexual behaviors (solid orange and dotted blue lines). However, if the castrated animal is treated with testosterone, sexual behavior returns (solid orange line). 'Castration Effects' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- During development, the body and the brain undergo either A) feminization and de-masculinization or B) masculinization and de-feminization
- The sex chromosomes, X and Y, make up one pair of the 23 total pairs of chromosomes in humans
- Females are genetically XX and males are genetically XY
- The SRY gene on the Y chromosome is responsible for the development of the male reproductive system
- In the absence of hormones, the female reproductive system develops
- Organizational, long-lasting hormone effects take place during critical periods in

development
- Activational, short-lasting hormone effects "activate" the circuits organized by hormones in development

Video Version of Lesson



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33.

MASCULINIZING EFFECTS OF ESTROGEN

Resources

- Key Takeaways
- Video Version

Steroid hormones like testosterone and estradiol are able to pass through the phospholipid membrane of a neuron. Some neurons express receptors for these hormones. Androgen receptors bind androgens like testosterone while estrogen receptors bind estrogens like estradiol. When a hormone binds to a receptor in the neuron, the hormone-receptor complex dimerizes and moves into the nucleus where it can bind to specific sites on the DNA and act as a transcription factor to turn on or off certain genes.

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Animation 33.1. Steroid hormones, like testosterone and estradiol, can cross the cell membrane without assistance. In the cell, the hormones can bind to hormone receptors, which dimerize, move to the nucleus, and act as transcription factors on the DNA. 'Testosterone Action' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Testosterone Pathways in the Cell

When the testes secrete testosterone during the prenatal critical period, the effect is to masculinize and defeminize the brain, body, and behavior, and this is accomplished through the transcription of a specific set of genes. However, many of those genes are not transcribed by the action of androgen receptors interacting with the DNA. When testosterone enters the cell, it does not always bind to androgen receptors. Some neurons also express proteins that can break testosterone down into its metabolites. 5-alpha reductase converts testosterone into dihydrotestosterone, or DHT, another androgen that is able to bind the androgen receptor. The enzyme aromatase converts testosterone into estradiol, an estrogen that can bind to the estrogen receptor.

Estrogen Effects

In some mammals, like rodents, this conversion of testosterone to estradiol is the main process by which neurons and the brain are masculinized. The estrogen receptors cause the transcription of masculinizing genes. Therefore, somewhat surprisingly, even though estrogen is typically thought of as a female hormone, its actions during development are responsible for much of the masculinization that occurs in the brain in some animals. It should be noted, though, that estrogen does not appear to have these same masculinizing effects during human development.

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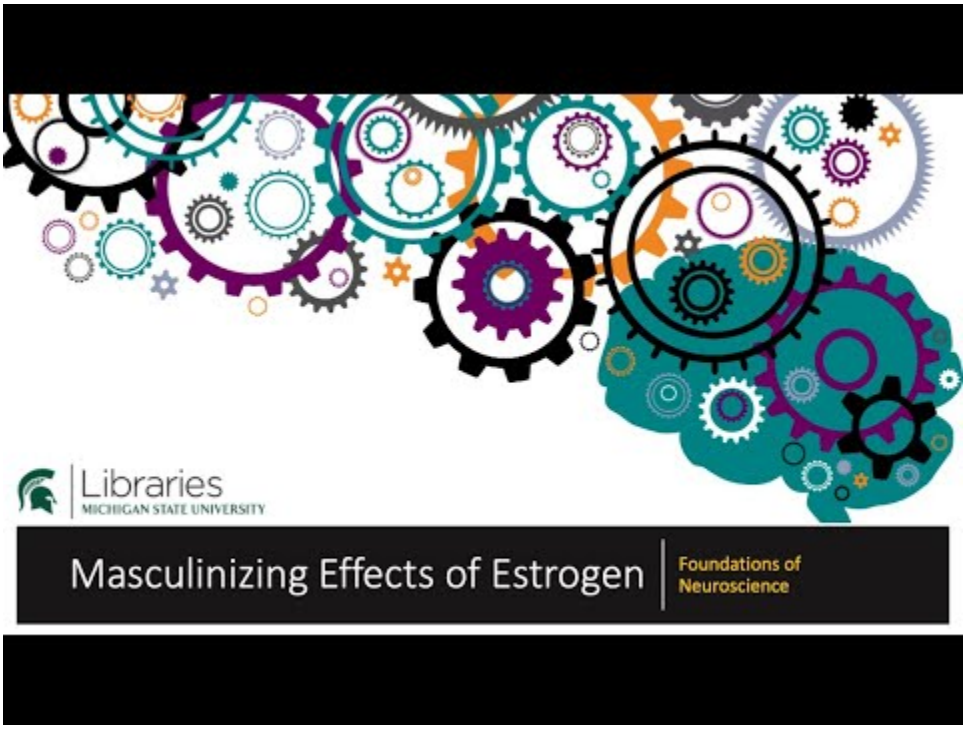
Animation 33.2. After testosterone enters the cell, if it does not bind to an androgen receptor, it can be metabolized by enzymes in the cell. 5-alpha reductase converts testosterone into dihydrotestosterone. DHT, like testosterone, can bind to an activate androgen receptors. The enzyme aromatase converts testosterone into estradiol. Estradiol is an estrogen and can bind to and activate estrogen receptors. During developmental critical periods, the aromatization of testosterone to estradiol leads to the transcription of masculinizing genes in some animals like rodents. 'Aromatization' by Casey Henley is

Key Takeaways

- Steroid hormones can cross the phospholipid bilayer
- Hormone receptors dimerize, move to the nucleus, and act as transcription factors
- In the cell, testosterone can
    - Bind to androgen receptors
    - Be converted to dihydrotestosterone by 5-alpha reductase
    - Be converted to estradiol by aromatase
- In some animals, estradiol action is responsible for the transcription of masculinizing and de-feminizing genes

Video Version of Lesson



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34.

MOTIVATION AND REWARD

Resources

- Key Takeaways
- Video Version

Motivated behaviors are voluntary behaviors that individuals find rewarding or pleasurable. Certain behaviors or stimuli, like food or sex, are naturally rewarding because they are necessary for the survival of a species; they are adaptive, and the nervous system has evolved to make these behaviors pleasurable. Rewarding stimuli increases brain activation in brain regions that comprise the reward circuit.

Reward Circuit

The reward circuit depends on the action of dopamine. Dopamine is synthesized and released by neurons located in the ventral tegmental area (VTA), a midbrain region adjacent to the substantia nigra (remember the substantia nigra from the basal ganglia chapter).

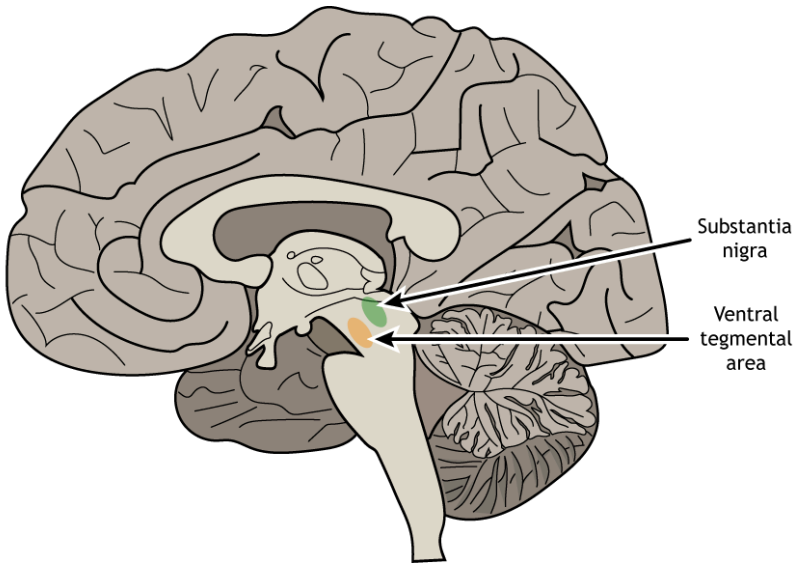

Figure 34.1. The ventral tegmental area (orange region) is located in the midbrain region near the substantia nigra (green region). Both regions release dopamine onto downstream targets. 'Ventral Tegmental Area' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

There are two primary pathways from the VTA that are important for reward. The mesolimbic pathway connects the VTA to the nucleus accumbens, a region located in the ventral striatum (again, remember the basal ganglia chapter). The mesocortical pathway connects the VTA with the prefrontal cortex.

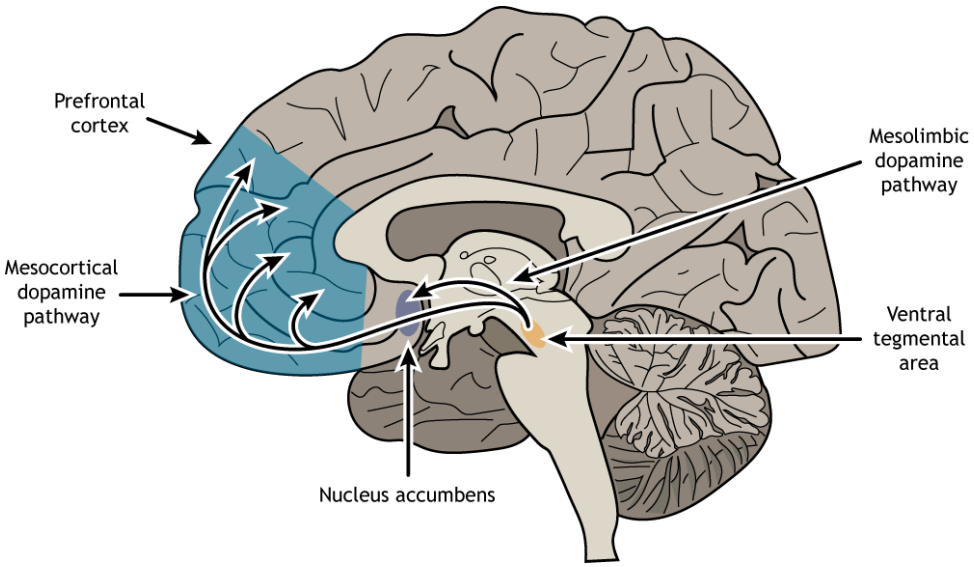

Figure 34.2. The ventral tegmental area (orange region) releases dopamine into the nucleus accumbens (purple region) via the mesolimbic pathway and releases dopamine into the prefrontal cortex (blue region via the mesocortical pathway. 'Mesolimbic and Mesocortical Pathways' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

View the amygdala using the BrainFacts.org 3D Brain

View the amygdala using the BrainFacts.org 3D Brain

Early experimental studies showed that rodents with an electrode placed along these dopaminergic pathways will complete tasks, like a bar press, to self-stimulate the regions. Often the animals would forgo other behaviors, like eating, to continue pressing the bar. Treatment with drugs that block the receptors for dopamine reduce the self-stimulating behavior, indicating that dopamine is the critical neurotransmitter involved in making the stimulation of these brain regions rewarding.

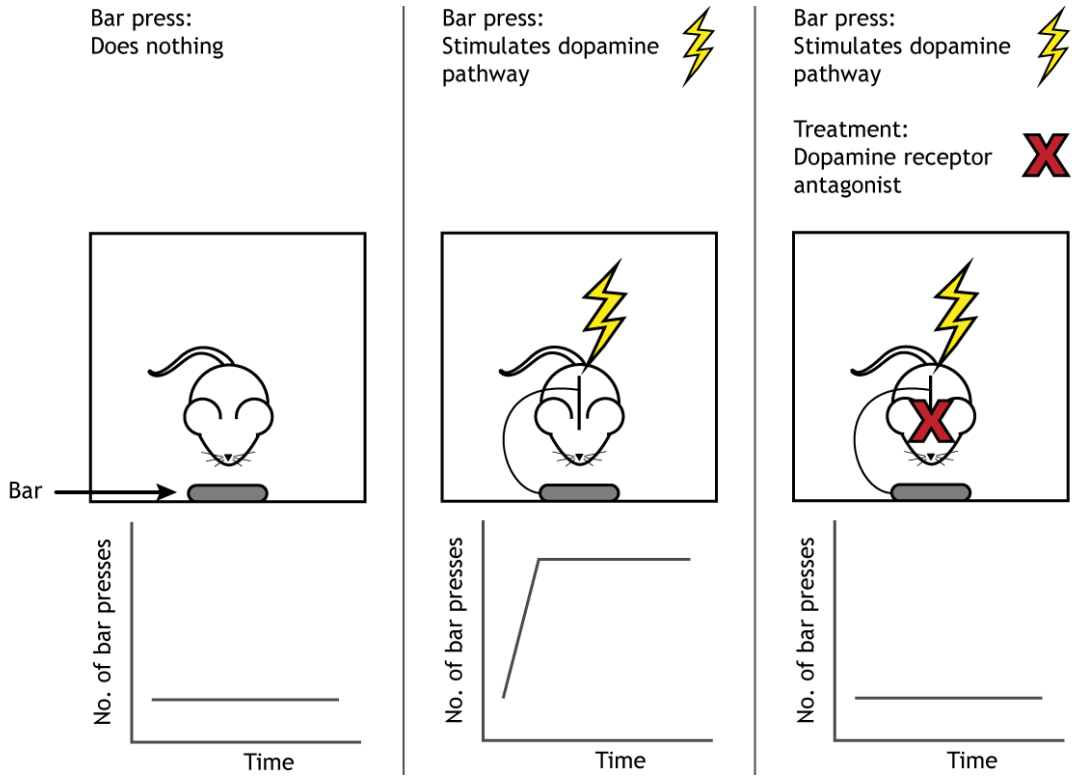

Figure 34.3. When an activity like bar pressing is paired with stimulation of the reward system circuitry, rats will show a marked increased in the behavior (center panel) compared to controls (left panel). If a dopamine receptor antagonist is given in addition to the bar press stimulation, the behavior decreases, presumably because dopamine cannot have its reward effect (right panel). 'Dopamine Pathway Stimulation' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

However, continued research suggests the connection between dopamine release and reward may not be as simple as the self-stimulation studies imply. It appears that it is not the reward itself that increases dopamine, but the predicted expectation of the reward . Dopamine signaling increases during anticipation of a predicted reward. If the level of reward is more than predicted, reward learning occurs, and dopamine signaling and motivation to repeat that behavior increases. If the level of reward is less than predicted, then dopamine signaling decreases as does motivation to repeat the behavior.

Rewarding stimuli

Natural rewards that increase survival and fitness of a species activate the reward circuit. These behaviors and stimuli include certain food (like those containing high sugar or fat levels), social bonding, parental bonding, and sex. Most drugs of abuse also activate the reward circuit and dopamine signaling, which plays a critical role in the formation of addiction. For example, cocaine blocks dopamine reuptake into presynaptic VTA terminals; heroin and nicotine increase dopamine release from the VTA. These alterations increase dopamine effect on neurons in the nucleus accumbens.

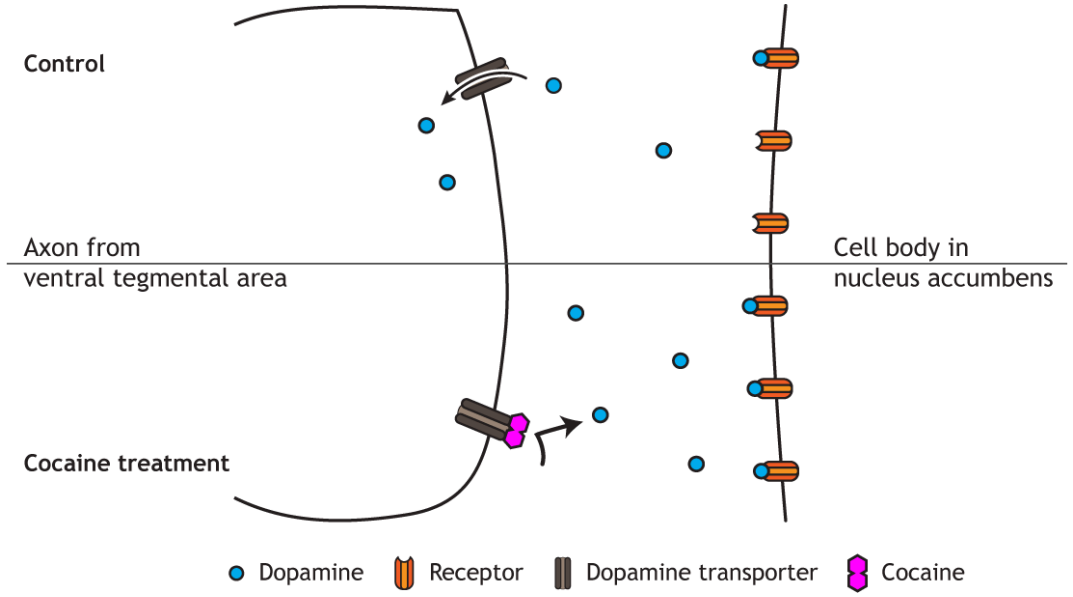

Figure 34.4. Control (top) panel: Dopamine effects are typically terminated by reuptake into the presynaptic terminal via the dopamine transporter (DAT). Cocaine treatment (bottom) panel: Cocaine blocks DAT, preventing reuptake of dopamine. The increased action of dopamine on the nucleus accumbens leads to increased activation of the reward circuit, a mechanism underlying addiction to the drug. 'Cocaine Effects' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- The reward circuit involves dopamine release from the ventral tegmental area into the nucleus accumbens and prefrontal cortex.
- Self-stimulation experiments demonstrate the role of dopamine and the reward circuit
- Dopamine signaling likely predicts reward value and can be altered if predicted outcomes differ from actual outcomes
- Drugs of abuse act upon the reward circuit

Video Version of Lesson

A YouTube element has been excluded from this version of the text. You can view it online here: https://openbooks.lib.msu.edu/neuroscience/?p=1427

35.

SOCIAL BONDING

Long-term attachment, which includes pair bonding with a sexual partner and parental bonding with offspring, are naturally rewarding behaviors in some species of mammals.

Hormone control

The hypothalamus is a critical region for the formation of social bonds. Magnocellular neurosecretory cells, the larger type of neurosecretory cell compared to parvocellular neurons, send axons from the hypothalamus down to pituitary stalk where they terminate on capillaries of the general circulation located within the posterior pituitary. Therefore, unlike the control of stress and gonadal hormones, where the hypothalamic neurons release hormones onto anterior pituitary endocrine cells, release of hormones from the posterior pituitary comes directly from hypothalamic neurons.

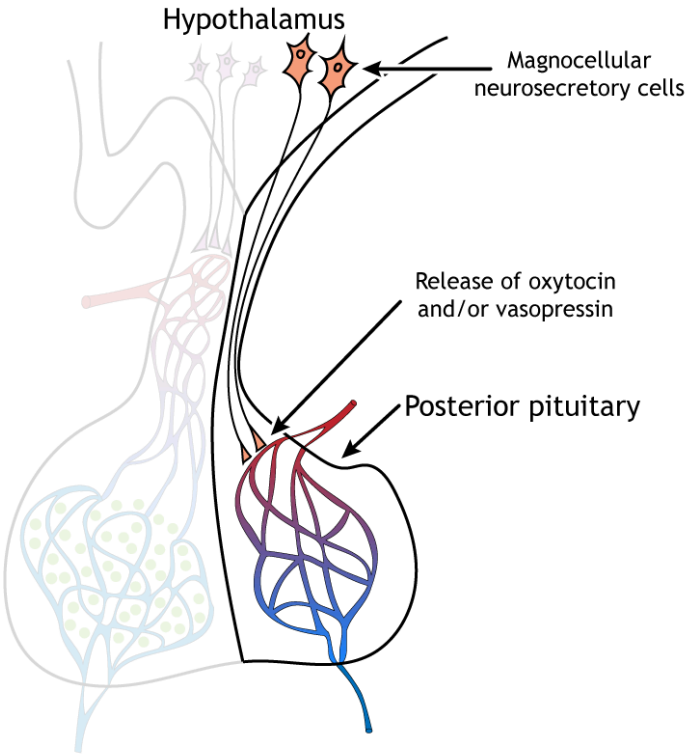

Figure 35.1. The hypothalamic magnocellular neurosecretory neurons release oxytocin and/or vasopressin into the general circulation via capillaries located in the posterior pituitary. 'Oxytocin and Vasopressin Release' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

The magnocellular neurons synthesize and release oxytocin and vasopressin, two neuropeptides, into the blood. Oxytocin, often referred to as the love hormone, promotes social bonding. It is released during reproduction and alsocauses uterine contractions during labor and the milk letdown reflex after birth. Vasopressin, also called antidiuretic hormone, plays a role in regulating salt concentration in the blood by acting on the kidneys to promote water retention and decrease urine production. Vasopressin has also been shown to be involved in bonding, parenting, territoriality, and mate guarding in some animals.

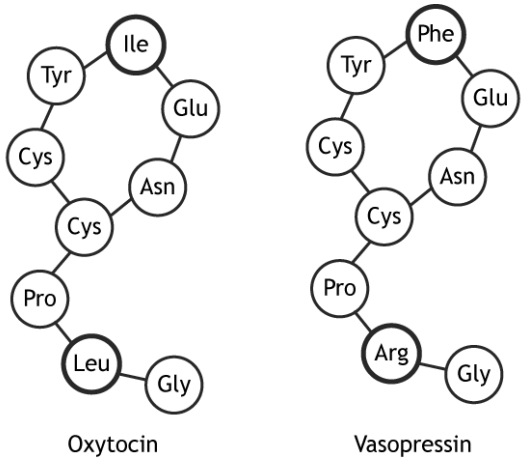

Figure 35.2. Amino acid sequences of oxytocin and vasopressin. The amino acids that are different between the two neuropeptides are bolded. 'Oxytocin and Vasopressin' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Animal Model

Much of the research on social attachment has been done using voles as the animal model. Voles are useful because there are closely related species that display considerably different reproductive behavior. The prairie vole is a monogamous rodent, with males and females displaying strong pair bonds and both sexes showing parental behavior. The montane vole, on the other hand, is a non-social species. Pair bonds are not formed, and only the female cares for the young. Differences in brain and behavior can be studied between these species.

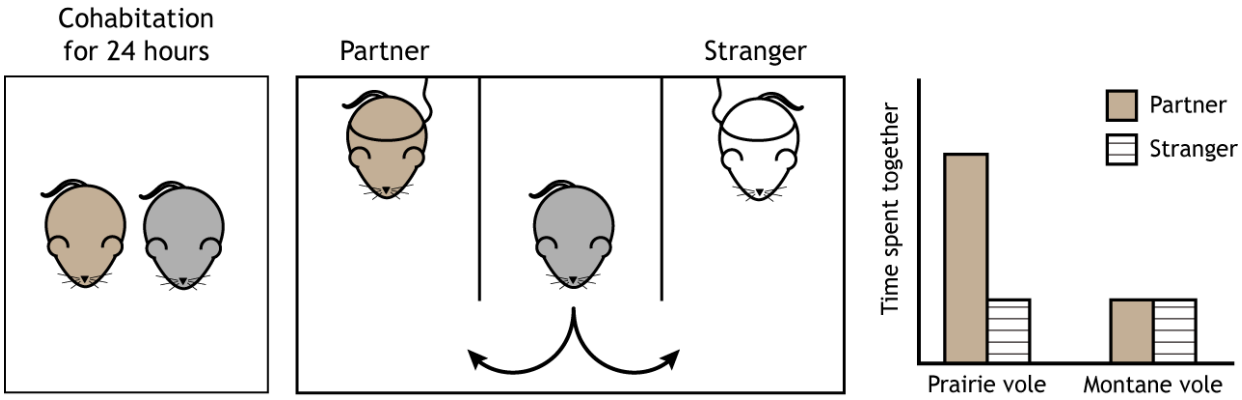

Figure 35.3. Partner preference tests can be conducted to examine social bonds in voles. First, voles are allowed to cohabitate and mate for 24 hours. Then, one of the pair is placed into a preference testing chamber and is allowed to spend time with either the partner animal or a novel stranger. In social voles like the prairie vole, mating will induce a strong preference for the partner animal over a stranger. This effect is not seen in non-monogamous voles like the montane vole. 'Vole Preference' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

In social voles, oxytocin and vasopressin are released by the hypothalamus in response to mating and act on regions of the reward and limbic systems. Female prairie voles express higher levels of oxytocin receptors in the nucleus accumbens compared to montane voles, whereas male prairie voles express higher levels of vasopressin receptors in the ventral pallidum compared to montane voles. The nucleus accumbens (also called ventral striatum) and ventral pallidum are both located in the basal ganglia and are involved in the limbic loop, which is responsible for processing of emotions, rewards, and motivation.

Human bonding

Oxytocin, vasopressin, and the reward system also appear to be important for bonding in humans. When presented with pictures of either their own children or partners, subjects in an fMRI show increased activation in regions like the ventral tegmental area and striatum compared to when viewing pictures of friends. These regions are also known to express oxytocin and vasopressin receptors, and the hormones are released during times of bond formation, like breastfeeding and intercourse.

36.

STUDYING FEAR

Scientists have long realized there are at least two distinct types of fear:

- Innate fear in which subjects avoid certain stimuli such as snakes or spiders even though they may never have seen them before
- Learned fear in which a stimulus or situation causes arousal or anxiety because it has been associated with a painful or negative experience in the past

There are two important protocols used to examine learned fear: fear conditioning and conditioned defeat.

Fear Conditioning

One of the best studied laboratory models of fear comes from the work of John LeDoux who studied the brain circuit that mediates learned or conditioned fear in laboratory rats. In these studies, LeDoux used a classical conditioning procedure to induce what he called "conditioned fear". In classical conditioning (think Pavlov's dogs), a neutral stimulus that normally would not cause any physiological response (called a conditioned stimulus, e.g., a ringing bell) is paired with a meaningful stimulus (called an unconditioned stimulus, e.g., the presence of food) that elicits a behavioral response (unconditioned response, e.g., drooling). Eventually, the behavior (drooling) occurs in response to the conditioned stimulus (bell) alone.

Instead of pairing the conditioned stimulus with a positive unconditioned stimulus like food, LeDoux paired the conditioned stimulus with an electrical shock. After pairing the shock to the stimulus multiple times, the animals responded to the conditioned stimulus alone (no shock) in the same way they did to the electrical shock alone. This is referred to as the conditioned emotional response.

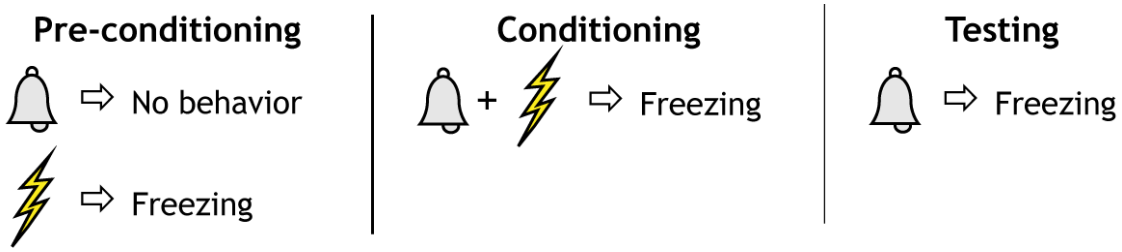

Figure 36.1 Fear conditioning. Left panel: Prior to conditioning, the conditioned stimulus (an auditory tone) has no effect on behavior. The unconditioned stimulus (shock) leads to startle-like behaviors that researchers refer to as "freezing". Middle panel: During fear conditioning, the tone is paired with the shock and freezing behavior is seen. Right panel: After successful fear conditioning, the tone alone can elicit freezing behavior. 'Fear Conditioning' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Conditioned Defeat

In this model the experimental subject (the animal whose behavior is being examined) is placed in the home cage of a larger, resident animal. This typically results in aggressive behaviors displayed by the resident animal toward the experimental subject. The resident animal will usually win the encounter because it is larger and in its own territory. The experimental animals will show submissive and defensive posturing and does not attack or threaten its opponent.

Experiencing this defeat has major long-lasting effects on the experimental subject. Following defeat, the animal rarely shows aggression even to non-aggressive hamsters placed in the subject's home cage (an intruder would typically cause aggression). Because this paradigm has parallels with the earlier fear conditioning studies that paired an acoustical tone with electrical shock to the feet, it is often referred to as "conditioned defeat;" the experimental subject has been conditioned to respond to all other hamsters with submissive defensive postures.

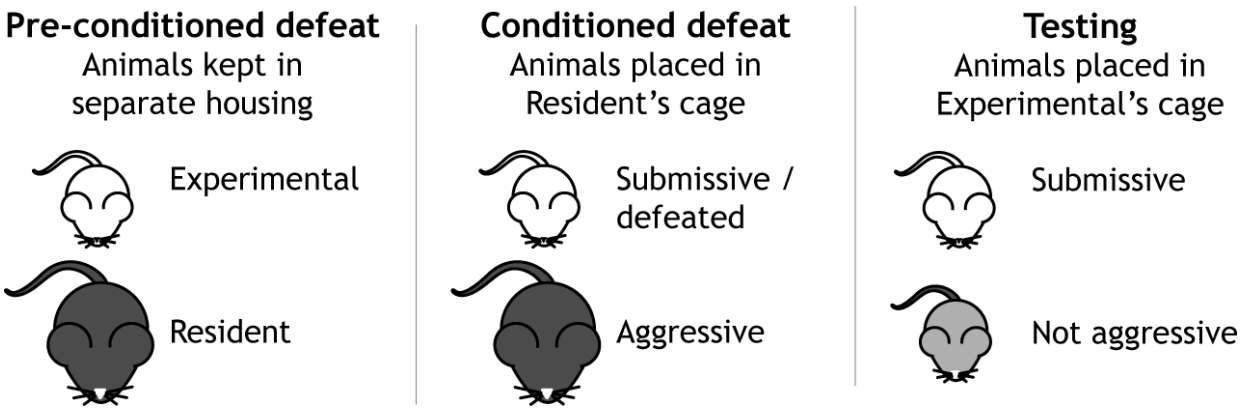

Figure 36.2. Conditioned defeat. Left panel: Prior to defeat, the experimental subject and resident animal are kept separate, and behavior is normal. Middle panel: During the conditioned defeat trial, the experimental animal is placed into the home cage of the larger, resident animal. The resident will defend its territory, acting aggressively toward the smaller, experimental animal. The experimental animal will show submissive and defensive behaviors. Right panel: After defeat, the experimental animal will show submissive behaviors even toward non-aggressive animals placed into the experimental animal's home cage. 'Conditioned Defeat' by Casey Henley is licensed under a Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Key Takeaways

- Learned fear can be studied using either fear conditioning or conditioned defeat tests
- Fear conditioning pairs a neutral stimulus, like a light or a tone, to a harmful stimulus, like a shock
- Conditioned defeat submits an experimental animal to aggressive behaviors from another animal, after which the experimental animal will continuously show submissive behaviors to others