Epigenetic response to Stress

Early experiences have life-long effects

- Deprived environment ➔ stress ➔
  cognitive and behavioral difficulties throughout life
- Deprived maternal care
- Stress
- hypothalamic-pituitary-adrenal axis
Hypothalamic-pituitary-adrenal axis

- Controls reactions to stress
- Also regulates immune system, digestion, mood, emotions, sexual responses, energy storage
Hypothalamic-pituitary-adrenal axis

What is stress? Anything that causes a rise in ACTH and glucocorticoid concentrations.

CRH changes with stress and in a circadian fashion to promote wakefulness.

Psychological stressors may alter but this might be a learned response. Varies between individuals.

HPA is activated by stress: hunger, thirst, trauma in a way that disturbs homeostasis.

Hypothalamus
- corticotrophin-releasing hormone (CRH)
- suprachiasmatic nucleus enforces circadian rhythmicity on the animal establishes rhythms high ACTH in early morning

Hypothalamus
- inhibits Hippocampus
- inhibits anterior Pituitary gland

anterior Pituitary gland
- adrenocorticotropic hormone (ACTH)
- binds ACTH receptors on adrenocortical cells of the adrenal cortex

adrenocortical cells of adrenal cortex
- ACTH stimulates synthesis of glucocorticosteroids and mineralcorticosteroids
- cortisol is the major glucocorticoid hormone

Cortisol is the major glucocorticoid hormone

Hippocampus
- inhibits

CRH changes with stress and in a circadian fashion to promote wakefullness

What fight or flight, focus attention, regulates immune system, digestion, mood, emotions, sexual responses, energy storage
Stress Response

Nerves connect the brain to every organ and tissue. Challenging or threatening situations arouse the brain's stress response, which involves the release of hormones that stimulate physiological arousal and regulate the immune system. Key components in this stress response are the hypothalamus and locus ceruleus in the brain, the pituitary gland, the sympathetic nervous system, and the adrenal glands.

Immune Response

The immune system operates as a decentralized network, responding automatically to anything that invades or disrupts the body. Immune cells generated in the bone marrow, lymph nodes, spleen, and thymus communicate with one another using small proteins. These chemical messengers can also send signals to the brain, through either the bloodstream or nerve pathways such as the vagus nerve and nuclei of the tractus solitarius.

Anatomy of Stress and Immune Systems Scientific American 1997

Hypothalamus-Pituitary-Adrenal (HPA) Axis

HPA Axis is a central component of the brain's neuroendocrine response to stress. The hypothalamus, when stimulated, secretes corticotropin-releasing hormone (CRH) into the hypophyseal portal system, which supplies blood to the anterior pituitary. CRH stimulates the pituitary (red arrows show stimulatory pathways) to secrete adrenocorticotropic hormone (ACTH) into the bloodstream. ACTH causes the adrenal glands to release cortisol, the classic stress hormone that readies the body to meet a challenging situation. But cortisol then modulates the stress response (blue arrows indicate inhibitory effects) by acting on the hypothalamus to inhibit the continued release of CRH. Also a potent immunoregulator, cortisol acts on many parts of the immune system to prevent it from overreacting and harming healthy cells and tissue.
Hypothalamus

Pituitary

Anterior Pituitary gland

Adrenocorticotropic hormone (ACTH)

Binds ACTH receptors on adrenocortical cells of the adrenal cortex

Adrenal cortex

ACTH stimulates synthesis of glucocorticosteroids and mineralocorticosteroids

Cortisol is the major glucocorticoid hormone

Suprachiasmatic nucleus enforces circadian rhythmicity on the animal, establishes rhythms high ACTH in early morning

Corticotrophin-releasing hormone (CRH)

Arginine vasopressin (AVP)

Hypothalamus inhibits Hippocampus inhibits

Hippocampus inhibits

Anterior Pituitary gland

Adrenocorticotropic hormone (ACTH)

Binds ACTH receptors on adrenocortical cells of the adrenal cortex

Adrenal cortex

ACTH stimulates synthesis of glucocorticosteroids and mineralocorticosteroids

Cortisol is the major glucocorticoid hormone

Hypothalamus inhibits

Hippocampus

What is stress?

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Hippocampus inhibits

Glucocorticoids

Mineralcorticosteroids

Fight or flight, focus attention, regulates immune system, digestion, mood, emotions, sexual responses, energy storage.

Receptors in limbic structure (including hippocampus)
Cortisol

- a glucocorticoid
- secreted by adrenal cortex
Increased cortisol secretion

- Fight or flight, focus attention
- Convert stored energy to usable energy substrates
  - Increase blood sugar - promotes hyperglycemia
- Increase rate and strength of the heart contractions
- Sensitizes blood vessels to norepinephrine, blood pressure up
- Anti-inflammatory agent prevents overreaction to injury which could enhance damage
- Inhibit bone formation
- Inhibit sleeping, feeding, digestion, breeding
- Suppress sexual responses
- Stimulates memory of traumatic experience, long term will damage hippocampus
Glucocorticoid hormones are a family.

- Glucocorticoids
  - a class of steroid hormones that includes Cortisol, Corticosterone and others.
  - Family members have similar and overlapping effects (but 100% identical) and bind glucocorticoid receptor.

- Scientists often manipulate two specific glucocorticoids. They are:
  - Cortisol (hydrocortisone) is a type of glucocorticoid. It is released in response to stress. Increases blood sugar (opposite effect to insulin), suppresses the immune system, is an antidiuretic, stimulates flash bulb memory. Produced by adrenal cortex
  - Cortisone is a type of glucocorticoid hormone. Has similar effects to cortisol. It is released in response to stress. It is structurally similar to cortisol. Produced by adrenal gland.

- Other family members exist.
Arginine vasopressin (AVP)

• increases water reabsorption by the kidneys - antidiuretic

• affects vascular smooth muscle tone - causes vasoconstriction that raises blood pressure

• has targets in the brain

• Enhances pair-bonding (monogamy hormone?)
hypothalamic-pituitary-adrenal axis and mood disorders

• Inappropriate responsiveness of HPA axis is associated with
  • post-traumatic stress syndrome,
  • depression,
  • bipolar disorder,
  • alcoholism,
  • anxiety disorders and more.
Epigenetic response to Stress - ground breaking papers


• Two strains of rats.
  • High licking grooming
  • Low licking grooming

• High licking grooming over 1st week of life have reduced adrenocorticotropic hormone (ACTH) and corticosterone responses to acute stress as adults.

• Licking grooming reduces response of HPA to stress in adulthood

• Female children of high licking grooming mothers become high licking grooming mothers and vice-versa

• Cross-fostering shows that this is the product of the experience during the first week of life.
High and Low LG rat mothers show different LG only during the first post-natal week.

Video courtesy of Frances A. Champagne
Cortisol

- A molecule secreted by adrenal cortex that binds a transcription factor inside the cell.
**GR is a Type I Hormonal transcription factor**

* How do they activate transcription?
  - Bind a co-activator complex.
  - Includes CBP/p300
  - Acetylates histones.

Binds as a dimer.

- glucocorticoid receptor
- androgen receptor
- mineralcorticoid receptor
- progesterone receptor
Change in glucocorticoid receptor expression in the hippocampus

**Adult offspring of high licking/grooming mothers**

1. **Hippocampus**
   - Inhibits
2. **Hypothalamus**
   - Inhibits corticotrophin-releasing hormone (CRH)
   - Arginine vasopressin (AVP)
   - Results in increased expression of Glucocorticoid Receptor
3. **Anterior Pituitary gland**
   - Inhibits adrenocorticotropic hormone (ACTH)
4. **Adrenal Cortex**
   - Produces glucocorticoids and mineralocorticoids
   - Glucocorticoids inhibit receptors in limbic structure (including hippocampus)
   - Mineralocorticoids: Fight or flight, focus attention, regulates immune system, digestion, mood, emotions, sexual responses, energy storage

**Adult offspring of low licking/grooming mothers**

1. **Hippocampus**
   - Inhibits
2. **Hypothalamus**
   - Inhibits corticotrophin-releasing hormone (CRH)
   - Arginine vasopressin (AVP)
3. **Anterior Pituitary gland**
   - Inhibits adrenocorticotropic hormone (ACTH)
4. **Adrenal Cortex**
   - Produces glucocorticoids and mineralocorticoids
   - Glucocorticoids inhibit receptors in limbic structure (including hippocampus)
   - Mineralocorticoids: Fight or flight, focus attention, regulates immune system, digestion, mood, emotions, sexual responses, energy storage
Glucocorticoid receptor

in hippocampus

A) Maternal LG or Tactile stimulation (pup LG)

B) GR Promoter 17 Sequence

NGFI-A Binding site
NGFI-A

• In high licking & grooming and low licking & grooming animals on day P1 the CpGs of the NGFI-A site are the same. They are both methylated.

• Licking & grooming causes demethylation by P6.

• Active demethylation! in non-mitotic cells.