The Stress Response

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• This talk is a reorganization of ideas with which we are all familiar
  – So, it’s all basic stuff, but the relationships are “new”
• As it turns out, no matter how you define stress, the end effectors are very similar
  – Enormous overlaps in the psychic stress response, response to acute trauma and long term illness.
Starvation

- Response characterized by conservation of fuel, fluid and minerals
  - Fall in resting energy expenditure

- Energy sources are glycogen, protein and fats
  - Glycogen stores of liver gone in 24h

- Ongoing glucose utilization by CNS results in slight decrease in insulin level
  - Glucagon increases
  - Insulin decreases
• Insulin
  – Major regulator of lipolysis and proteolysis

• Glucagon
  – Stimulation of hepatic glycogenolysis and gluconeogenesis
    • Stimulates uptake of alanine, which is the major substrate for gluconeogenesis
      – Released by way of muscle proteolysis
  – Gluconeogenesis also uses lactate and glycerol
    • Lactate, in Cori cycle, can be converted to glucose
      – Uses energy of oxidation of FFA’s
• This characterizes the first 5-10 days of starvation
  – Lots of protein breakdown…..this has to stop
• So, at this point, the brain switches to the utilization of ketones
  – So less protein needs to be broken down to make glucose
    • Elevated ketones inhibit AA catabolism, leading further to decreased gluconeogenesis
  – Brain can use ketones even when well, but uses glucose preferentially
• We still need some glucose, however
  – Kidney then becomes a significant source of glucose by way of gluconeogenesis
    • Uses glutamine as a substrate, which is also a product of protein catabolism
• In early starvation, 90% of gluconeogenesis occurs in the liver and 10% in kidney
• Later, only 55% occurs in the liver, and 45% in the kidney
So.

- First phase of starvation – rise in glucagon and decrease in insulin
- Second phase – increase in ketone bodies
  - Provide brain with substrate
  - Play a regulatory role in metabolic adaptation – depress gluconeogenesis and thus decrease protein degradation
- Finally, all fat stores exhausted, and the body then turns to protein again
  - Catabolizes heart, lungs, blood etc.
• Why does this matter?
• In the case of extreme stress, nitrogen loss does not necessarily decrease in proportion to energy provision.
• So no great adaptation to relative starvation with progressive nitrogen conservation.
  – The severely stressed patient instead enters a period of increased metabolic activity.....
Stress

• A complex neuroendocrine response
  – Has both an afferent and efferent limb
• Afferent limb
  – Pain and special neurosensory pathways (optohalmic, auditory and olfactory along with visceral sensory pathways)
• Efferent limb
  – Neurological
    • Increased autonomic sympathetic nervous system activity / Epinephrine and Norepinephrine
  – Endocrine
    • Increased pituitary hormones – ACTH, GH and ADH
• Three main effects
  – Release of catechols inhibits insulin secretion and peripheral insulin action, and stimulates glucagon and ACTH production
  – ACTH and ADH increase corticosteroids, inhibit insulin activity and increase aldosterone
  – Water retention and antidiuresis
Afferent Pathway

• Spinal cord and peripheral nervous system are primary afferent limbs for painful stimuli and tissue injury
  – Corticosteroid response to thermal injury in the leg of an anesthetized dog blocked by section of periph nerves or spinal cord
  – ACTH and GH responses of surgical patients blocked by spinal, but not general, anesthesia

• The medulla integrates responses from sympathetic and parasympathetic components of nervous system
  – Responsible for complex reflexes such as regulation of blood sugar and blood pressure.
• The hypothalamus is the highest level of integration of the stress response
  – Regulates the effector mechanisms of the autonomic nervous system and the pituitary gland
    • TSH, GH, PRL, LH, FSH, ADH and ACTH
• Under major stress, other pathways independent of site of injury (like visual or auditory cortex) can stimulate stress response
  – Korean war soldiers involved, but not injured in, combat, had elevated urinary corticosteroids that fluctuated with levels of hostilities encountered
  – Noise, bright light and constant handling have similar effects on newborns in NICU
• Visceral stretch and chemoreceptors
  – Atrial stretch receptors, aortic arch baroreceptors, chemoreceptors of carotid bodies and hypothalamic glucose receptors
  • Signals integrated at medullary and hypothalamic levels
• **Cytokines**
  – Another important afferent system is the response to cytokines
  – Elaborated at site of injury or infection
    • Eg. Mononuclear phagocytes and lymphocytes
  – Major examples are IL-1 and TNF

• **IL-1**
  – Stimulates granulopoiesis, induction of fevers, synthesis of acute phase proteins and hyperinsulinemia
• Tumor Necrosis Factor
  – Made by tissue macrophages, blood monocytes and other cytotoxic cells
    • In response to bacteria, bacterial toxins and endotoxins
  – Activities include:
    • nonspecific host response to inflammation
    • regulation of energy-substrate and protein metabolism in skeletal muscle
    • stimulation of lipolysis
    • stimulation of acute phase reactant proteins
• Both cytokines and afferent nervous system have the capacity to cause the neuroendocrine changes affecting the metabolic response to injury and sepsis

• Afferent system is most important initially, and later, cytokines may play the dominant role
FIGURE 1. Major components of the central and peripheral stress system. The paraventricular nucleus and the locus ceruleus/noradrenergic system are shown along with their peripheral limbs, the pituitary–adrenal axis, and the adrenomedullary and systemic sympathetic systems. The hypothalamic corticotropin-releasing hormone (CRH) and central noradrenergic neurons mutually innervate and activate each other, while they exert presynaptic autoinhibition through collateral fibers. Arginine vasopressin (AVP) from the paraventricular nucleus synergizes with CRH on stimulating corticotropin (ACTH) secretion. The cholinergic and serotonergic neurotransmitter systems stimulate both components of the central stress system, while the γ-aminobutyric acid/benzodiazepine (GABA/BZD) and arcuate nucleus proopiomelanocortin (POMC) peptide systems inhibit it. The latter is directly activated by the stress system and is important in the enhancement of analgesia that takes place during stress. (Reprinted from G.P. Chrousos² by permission.)
Efferent pathway

Hypothalamus and sympathetic nervous system

- After many afferent signals, CNS integrates efferent discharge in hypothalamus
- Major outflow pathways are the efferent sympathetic and parasympathetic pathways and endocrine pathways by way of the pituitary
  - All occur simultaneously
  - Sympathetic nervous system is the main effector
    - Sympathetic ganglion chain is a multiplying system, with a small number of preganglionic fibers synapse with a large number of axons to the periphery.
    - Epinephrine secretions effectively distribute the sympathetic discharge through the entire body by way of the circulation
• CRH
• Stress induces the hypothalamus to release CRH
  – Leads to secretion of epi/norepi, glucocorticoids
• CRH receptors localized in CNS, and also in immune and cardiovascular systems
• Immune CRH, which is secreted locally at inflammatory sites, is of peripheral nerve origin
• So the presence of CRH and CRHr at local inflammatory sites suggests that CRH acts in an axon reflex loop with immune cells.
• Epinephrine, Norepinephrine and glucagon
  – Epinephrine and norepinephrine are elevated in trauma, burns, sepsis and elective surgery
    • Levels correlate with severity of stress, and remain elevated for duration of stress
  – Epinephrine secreted by adrenal medulla and norepinephrine thought to come from “leaks” at sympathetic nerve endings.
• Most prominent effects are those of the “fight or flight” response
  – Increased HR, CO
  – Shunting of blood from spleen and splanchnic bed
  – Etc.
  – In experimental bleeding studies on human volunteers (!), 30% of blood volume can be lost with very little clinical manifestation
• Sympathetic metabolic response
• Insulin
  – Pancreatic islet cells have alpha and beta receptors
    • Beta increase insulin secretion, and alpha decreases it
      – Sympathetic innervation is extensive, and alpha receptors are sensitive, so insulin response is blunted
  – Epi and norepi induce peripheral resistance to cellular uptake of insulin
  – Both mechanisms lead to the hyperglycemia of stress
  – Epinepherine infusions in human volunteers increase glucose and FFA levels and a suppression of rise in insulin
  – Norepi infusions lead to a lower rise in Glc and FFA’s, but without the suppression of insulin
• Glucagon
  – Elevated levels occur in trauma, burns, blood loss and infections
  – Most marked increase in initial period of stress, and then returns to normal as patient recovers
  – Acts on skeletal muscle to mobilize amino acids (notably alanine), that stimulate hepatic glucose production

• The combination on elevated glucagon and suppressed insulin play major role in regulation of hepatic gluconeogenesis and hyperglycemia
Efferent pathway

pituitary hormones

- Six anterior pituitary hormones
  - ACTH, GH, TSH, PRL, FSH and LH
- Increased ACTH and elevated glucocorticoids have been demonstrated in trauma, burns, surgery and infection
  - Correlate directly with magnitude of injury and persist through periods of stress
Glucocorticoids play a more permissive role than previously thought in the post-stress metabolic response

- Important effect on substrate production
  - Acts on adipose tissue to cause lipolysis and release of FFAs
  - Influencing hyperglycemic state:
    - Mobilizes amino acids from skeletal muscle,
    - Stimulates glucagon production
    - Augments catechol induced hepatic glycolysis
- Prevent migration of leukocytes from circulation into extravascular fluid spaces
- Reduce accumulation of monos at inflammatory sites
- Suppress production of many cytokines and their actions
• Corticosteroids are bound to CBG.
  – CBG is a negative acute phase reactant
  – Bound steroids have no biological activity, a decrease in CBG results in more available steroid
  – Synthetic steroids (like decadron) do not bind to CBG, and so have an exaggerated effect.
• Corticosteroid receptors are present on sympathetic nerves
  – Thus augment excitability to Norepi
• Interestingly, repeated induction of steroid secretion can result in hippocampal damage due to the excitatory AA glutamate
  – Decreases adaptation to stress over time
• GH
  – Increased levels in the initial response to trauma and shock
  – Proportional to degree of stress, and short lived
  – Inhibits action of insulin
    • Decreasing glucose uptake in muscle and increasing FFA output by stimulation of lipolysis
• **TSH**
  - Activity changes very little in acute trauma and in prolonged stress such as burns

• **LH, FSH and PRL**
  - Of questionable import, presently
  - Testosterone and LH levels are decreased after major surgery (and fellowship....anyone for some knitting?)
• ADH and renin-angiotensin-aldosterone axis
  – ADH synthesized in supraoptic neurons of the hypothalamus and is secreted directly into the circulation by the posterior pituitary
  – Decreases free water clearance
  – Conditions of stress provide a strong stimulus for ADH release that lasts as long as the stress.
    • Response to trauma is strong enough to override volume and osmotic feedback, leading to SIADH
  – ADH is also a potent vasopressor
  – Increases glucagon release and insulin suppression
– Renin-angiotensin-aldosterone system
  • Usually responds to intravascular pressure
  • controlled by the sympathetic nervous system, the arteriolar perfusion pressure of the JGA, and the sodium flux across the macula densa of the kidney
  • In children with thermal burns, 9x increase in renin activity and 5x increase in serum aldosterone – even when normotensive and normovolemic
    – Sympathetic control overrides feedback controls
      » Increase post trauma can be blunted by propranolol
• Combined effect of posterior pituitary and renin/aldosterone system
  – Reduces urine output in post-trauma patients, contributing to hyponatremia, hypervolemic, edema and alkalosis
**Functional consequences of malnutrition**

- A major effect of the stress response is net catabolism of body protein
  - After major injury, burns or sepsis, as much as a twofold increase in protein degradation
  - Synthesis rates increase, but not as much as degradation rates when patients in a negative nitrogen balance

- Increases in synthesis and degradation increase energy expenditure and constitute a “futile” cycle.
• **Altered hepatic secretory protein output**
  - Acute phase proteins increase in the plasma, mediated, in part, by IL-1 (catechols and steroids may enhance this induction)
    - CRP, which activates complement, enhances phagocytosis and regulates cellular immunity
    - alpha-1 acid glycoprotein, which inhibits platelet activation and phagocytosis
    - Haptoglobin, clears free hemoglobin from plasma
    - Alpha-1 antitrypsin
    - Ceruloplasmin
    - Fibrinogen
  - Transferrin and albumin levels fall
    - Due not only to decreased synthesis…
    - Albumin decreases secondary to increased transcapillary leakage, promoted by TNF and IL-1
      - Contributes to increased extracellular and extravascular water
Secondary Immunodeficiency

- In severe burns, bacteremia and septicemia occur in approximately 75% of patients
- Related to decreased host defenses
- After injury, T and B lymphocytes undergo detrimental changes, affecting cell mediated defenses
- Levels of serum immunoglobulins are markedly decreased post injury, affecting humoral immunity
Almost all injury induced endocrine and mediator changes have been shown to increase levels of 3-5-cyclic AMP in lymphoid cells.

- Increased cAMP is associated with downregulation of immune activity.
- Final common pathway by which hormones, cytokines and other mediators promote stress induced immune dysfunction.
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<th>Effect on cAMP</th>
<th>Effect on immunity</th>
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• Beta adrenergic agonists suppress several immune functions, including chemotaxis, release of inflammatory mediators, proliferation of T lymphocytes and the lytic activity of NK cells
• Many of these are synergistic
  – Eg. Corticosteroids increase beta receptors on all classes of leukocytes, and thus enhance and maintain the immunoinhibitory effects of catechols

• Cyclic GMP directly antagonize effects of increased cAMP

• Cimetidine decreases the cAMP/cGMP ratio, thus correcting injury related immune dysfunction.
• Stress and stress hormones influence the direction of the immune response
  – Predominantly stimulate a TH2 (humoral immunity) and suppress a TH1 (cellular immunity) response.
  – Dexamethasone, norepinephrine, epinephrine and histamine inhibit LPS induced IL-12 production and stimulate IL-10 production
    • IL-12 induces TH1 cells
    • IL-10 stimulates the development of antibody producing B cells
    • Mediated by beta receptors on monocytes
  – Contributes to an increased susceptibility to infectious agents
FIGURE 1. Stress and CRH influence TH1 and TH2 immune responses by stimulating glucocorticoid, catecholamine, and peripheral (immune) CRH secretion and by altering the production of key regulatory cytokines and histamine. IL-12 is a major inducer of TH1 responses, whereas IL-10 antagonizes its effects and favors TH2 responses; both cytokines are predominately produced by activated monocytes/macrophages; histamine and certain cytokines are produced by activated mast cells. Catecholamines and histamine inhibit IL-12 and stimulate IL-10 production, whereas glucocorticoids inhibit IL-12, but do not affect IL-10 production. Thus, both glucocorticoids and catecholamines, peripheral end-products of the stress response, and histamine, a product of activated mast cells, selectively suppress TH1 responses, i.e., cellular immunity, and favor TH2 responses, i.e., humoral immunity. Immune CRH through degranulation of mast cells acutely potentiates certain inflammatory responses, particularly allergic ones. Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; E, epinephrine; IL, interleukin; LC/NE, locus ceruleus/norepinephrine autonomic (sympathetic) nervous system; NE, norepinephrine; TH, T helper lymphocyte.
Psychic Stress

• Interesting to note that the “stress” response and the inflammatory/immune response are inextricably intertwined…..

• The possibility that stress alone may induce an inflammatory response is gaining acceptance
• Substance P is the most abundant neuropeptide in the CNS.
• Functions as a neurotransmitter/neuromodulator and is a known effector of neurogenic and non-neurogenic inflammation
• Elevated in the brain in response to psychological stressors; space flight, parachute jumping and anxiety.
• Acts primarily in the amygdala
  – Projects to the hypothalamus producing a defensive rage in cats
  – Projects to the periaqueductal grey matter which is involved in aversive responses to stress
• Interacts with the HPA axis, resulting in elevations of CRF and ACTH.
  – May act directly or indirectly by increasing ADH (a powerful stimulator of HPA activity)
• SP and SP receptors are present in hypothalamic and brainstem nuclei that control sympathetic vasomotor activity
  – SP enhances pre sympathetic activity involved in cardiovascular regulation
• SP is essential to the maintenance of catechol secretion from the adrenal medulla in times of stress.
• So it is involved in the generation of an integrated cardiovascular, behavioral and endocrine response to nociceptive stimuli and stress
• Lymphocytes, leukocytes and macrophages also have SP receptors.
  – Stimulate production of cytokines
• Stimulates hematopoiesis in the bone marrow with a resultant leukocytosis
• Cytokines
  – Various psychological stressors can induce proinflammatory cytokine secretion (IL-1, IL-6 and TNF)
    • Immobilization stress and open field stress in animals
  – Mental processes can also enhance release of cytokines in response to LPS.
LPS and the Liver

• Both LPS and psychic stress induce IL-6 and fever
  – In fact, repeated LPS inoculations are used to mimic chronic repetitive psychic stress
  – Stress may thus act similarly to an inflammatory stimulus
Theorized that LPS may augment some of the effects of stress in inducing an inflammatory response

- LPS, in an uninfected organism, comes from the GI tract.
- Stress and sympathetic activation decrease splanchnic blood flow
  - Leads to ischemia of the gut, resulting in changes in permeability
  - Results in increased absorption of LPS
  - Activation of the SNS is also known to increase absorption
  - LPS cleared by Kupffer cells
    » Induce cytokine release thus leading to an inflammatory process
Stress and cardiovascular disease

- Stress activates the sympathetic nervous system, the HPA, the renin-angiotensin system.
- Induce a heightened state of cardiovascular activity, injured endothelium) and induction of adhesion molecules which recruit inflammatory cells to the arterial wall
- The acute phase response is activated, characterized by
  - Macrophage activation (and production of free radicals)
  - Production of cytokines
  - And acute phase proteins.
• Stress produces an atherosclerotic lipid profile
  – Steroids, catechols, glucagon and GH lead to lipolysis, leading to production of glycerol, which becomes part of the FA pool
  – These hormones also enhance liver production of triglycerides, which are secreted as VLDL.
  – VLDL secretion accompanied by secretion of apo B…resulting in increased LDL particles
• All of the above add up to enable the atherosclerotic process
FIGURE 2. Diagrammatic representation of the inter-relationships between the hypothalamic-pituitary-adrenal axis and the immune–endocrine responses. Ach = acetylcholine; 5HT = 5 hydroxytryptamine; CRF = corticotrophin-releasing factor; GABA = gamma-aminobutyric acid; A = adrenaline; NA = noradrenaline; IL = interleukin; TNF = tumor necrosis factor. (Modified from Song and Leonard.)
Mind-body medicine

- Constant stress has an measurable impact on health
  - People exposed to chronic stressors have an increased susceptibility to the common cold
  - School examination induced stresses increases susceptibility to viral stresses
  - Stress increases susceptibility to cardiovascular disease
  - Marital dysfunction increases stress hormones in both partners
• The soul sympathizes with the diseased and traumatized body and the body suffers when the soul is ailing
  – Aristotle
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