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New Solutions for Adrenal Health

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Your Agenda

- Stress – Historical perspective
- General adaptation syndrome
- Brief review of the stress response and adrenal function
- Cortisol
- Vitamin C
- Hormesis
SIKH DIET VERSUS DIET OF POORER CLASS EUROPEAN.

The former diet consisted of whole wheat flour chapatties, butter, whole milk, dhal (legume), fresh raw vegetables ad libitum and fresh meat with bone once a week.

The latter diet consisted of white bread and margarine, tinned meat, boiled vegetables, tinned jam, tea and sugar with a little milk.

Two rats of the same age and initial body-weight: the one (left) fed on the Sikh and the other (right) on the poor European diet.

Two rats of the same age and initial body-weight: the one (left) fed on the Sikh and the other (right) on the poor European diet.

Two rats of the same age and initial body-weight: the one (left) fed on the Sikh and the other (right) on the poor European diet.

The rats shown above are representative of 20 in each group. Duration of experiment: 187 days. Average initial body-weight both groups: 125 grams. Average final body-weight: Sikh, 188 grams; poor European, 118 grams. Common diseases in the latter group were pneumonia and gastro-intestinal ailments.
“The functional perfection of the adrenal glands is dependent upon the balance of the food and upon the quality and quantity of its vitamins”

“An intimate relationship exists between the adrenal glands and the meta-bolic processes of the animal organism”

“Each vitamin exercises a specific influence on the adrenal glands; the effect of their deprivation on these organs is one of the most outstanding features of deficiency disease”
Stress - Historical Context

- Early research by W B Cannon (1871-1945)
- In 1915 coined the term “fight or flight mechanism” to describe associated changes in adrenal gland secretions
- In 1926 coined the term “homoeostasis” to describe the maintenance of physiological variables within certain ranges e.g. blood glucose, $O_2$ tension and core temperature

Goldstein DS, Kopin IL. Stress 2007; 10(2): 109-120
Stress - Historical Context

- Cannon’s work was then extended by Hans Selye (1907-1982)
- Observed that the same characteristics and physiological responses occurred in rats subjected to a variety of intense stimuli
  - adrenal enlargement, thymus and spleen atrophy and GIT ulcers
- Termed the series of responses the General Adaption Syndrome (GAS)

Goldstein DS, Kopin IL. Stress 2007; 10(2): 109-120
General Adaptation Syndrome

SELYE’S STRESS MODEL

normal resistance state

alarm phase
Phase 1

catabolic phase

anabolic phase

resistance phase
Phase 2

exhaustion phase
Phase 3

Phase 1
Phase 2
Phase 3
STRESSORS
stimulate

Hypothalamus

CRH
GHRH
TRH

Nerve impulses
Sympathetic centers in spinal cord

Sympathetic nerves

Anterior pituitary gland

ACTH
TSH
hGH

Adrenal medulla

Visceral effectors

Epinephrine and norepinephrine

Supplement and prolong “fight-or-flight” responses

Key:
CRH = Corticotropin releasing hormone
ACTH = Adrenocorticotropic hormone
GHRH = Growth hormone releasing hormone
hGH = Human growth hormone
TRH = Thyrotropin releasing hormone
TSH = Thyroid-stimulating hormone

Adrenal cortex

Liver

Thyroid gland

Thyroid hormones ($T_3$ and $T_4$)

Mineralocorticoids (Aldosterone)

Glucocorticoids (Cortisol)

STRESS RESPONSES
Increased catabolism of triglycerides
Glycogenolysis

Increased catabolism of glucose to produce ATP

STRESS RESPONSES
Retention of sodium

STRESS RESPONSES
Glucogenesis
Protein catabolism
Sensitize blood vessels
Reduce inflammation

Elimination of $H^+$
Water retention

STRESS RESPONSES
Increased heart rate and force of beat
Constriction of blood vessels of most viscera and skin
Dilation of blood vessels of heart, lungs, brain, and skeletal muscles
Contraction of spleen
Conversion of glycogen into glucose in liver
Sweating
Dilation of airways
Decrease in digestive activities

(a) Alarm reaction (“fight-or-flight” responses)
(b) Resistance reaction
Adrenal Hormones

Mineralocorticoids
- Aldosterone

Glucocorticoids
- Corticosterone
- Cortisol

Adrenal androgens
- DHEA
- DHEA-Sulfate

Catecholamines
- Epinephrine
- Norepinephrine

Zona glomerulosa
Regulated by K⁺

Zona fasiculata
Regulated by ACTH

Zona recticularis
Regulated by ACTH

Chromaffin cells

Medullary veins

Splanchnic nerves

Capsule

Cortex

Medulla

Chromaffin cells

Medullary veins

Splanchnic nerves

Cortisol

Aldosterone

Corticosterone
Cortisol Physiological Function

- In addition to its role as a stress response hormone, cortisol plays many key roles in almost every physiological system:
  - Central nervous system
  - Activity and direction of energy metabolism
  - Maintenance of a proper cardiovascular tone
  - Activity and quality of immune system and inflammatory responses
  - Growth and reproduction

Cortisol Pathophysiology

Glucocorticoids are heavily involved in human pathophysiology and influence life expectancy:

- Anxiety
- Depression
- Insomnia
- Chronic pain and fatigue syndromes
- Obesity
- Metabolic syndrome
- Essential hypertension
- T2 Diabetes
- Atherosclerosis with its cardiovascular sequelae
- Osteoporosis
- Autoimmune disease
- Inflammatory and allergic disorders
- Sickness syndrome

Cortisol Pathophysiology

- HPA axis activity or sensitivity
  - hypothalamus and pituitary
- Cortisol activity or sensitivity
  - Receptor based
  - Enzyme based
- Responsiveness of the target tissues to cortisol is highly variable
Function:
- Alteration of intracellular cortisol concentration
- Organ specific enhancement of cortisol effect

High expression: Liver, adipose tissue, lung, gonads, pituitary, bone, eye
HPA Axis/Cortisol Sensitivity

**Glucocorticoid Sensitivity**

- **HPA Axis**
- **CNS/Liver/Fat/Blood Vessels**

**Free Cortisol**

- **High** → **Low**
- **Low** → **Low**
- **Normal** → **Normal**
- **High** → **High**
- **Low** → **High**

**Glucocorticoid Effects in CNS/Liver/Fat/Blood Vessels**

- **Normal** → **Low**
- **Low** → **Very Low**

Figure 1 C
Central Nervous System

Cortisol excess or hypersensitivity
= Insomnia
= Anxiety
= Depression
= Defective cognition

Cortisol deficiency or resistance
= Fatigue
= Somnolence
= Malaise
= Defective cognition
Blood Vessels

Cortisol excess or hypersensitivity
  = Hypertension

Cortisol deficiency or resistance
  = Hypotension
Adipose Tissue

Cortisol excess or hypersensitivity
  = Accumulation of visceral fat
  = Metabolic syndrome

Cortisol deficiency or resistance
  = Loss of weight
  = Resistance to weight gain
Adrenal Glands & Vitamin C

- When Vit C intake is from food fasting plasma levels don’t exceed 80μmol/L
- Levels in the adrenal gland can be as high as 10 mmol/L (125 times higher)
- How do adrenals concentrate Vit C to such high levels and why?
- In humans, adrenal Vit C secretion is an integral part of the stress response

What Doesn’t Kill You Makes You Stronger!

- Stimulatory or beneficial effects at low doses and inhibitory or toxic effects at high doses
- Hormesis is now the standard terminology used to describe the beneficial adaptive response of cells and organisms to moderate stress
Stress Resistance Proteins
(Heat shock proteins, antioxidants, growth factors)

Area of Hormesis
(Adaptive stress response)
How is Moderate Stress Beneficial?

- Mild stress induces the activation of signalling pathways, leading to intrinsic changes conferring resistance to a more severe stress.
- The stress-inducing agent elicits molecular responses that not only protect the cell against higher doses of the same agent, but also against other agents or even less specific stressors including oxidative, metabolic and thermal stress.
- They can even repair existing damage.
Hormesis

- Major components of the hormetic response include various stress resistance proteins such as heat shock proteins (HSP), sirtuin1, growth factors and cell kinases.
- Classical examples of hormetic stress are exercise and calorie restriction.
- Many phytochemicals consumed in our diet are hormeric:
  - Ferulic acid from tomatoes, sweet corn, rice
  - EGCG from Green tea
  - Curcumin from Turmeric
  - Sulforafane and isothiocyanate from cruciferous vegetables
Hormesis and HSP

- HSP are produced when cells are exposed to stress.
- Their job is to protect (chaperone) other proteins from damage by binding to them and shielding them from attack.
- HSP play an important role in the conservation & maintenance:
  - Protein homeostasis
  - The cellular stress response
  - Aging

Adaptogens and Hormesis

- Adaptogens are herbs that help the body better adapt to stressors by fine-tuning the stress response.
- The stress–protective effect of adaptogens is the result of the adaptation of the organism to the mild stressful effects of the adaptogen.
- Adaptogens are Hormetic.
Adaptogens and Hormesis

The regular consumption of adaptogens gives rise to an adaptogenic or stress-protective effect in a manner analogous to repeated physical exercise, leading to prolonged state of non-specific resistance to stress and increased endurance and stamina under extreme conditions.