



Hormones and Systems Connectivity

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1

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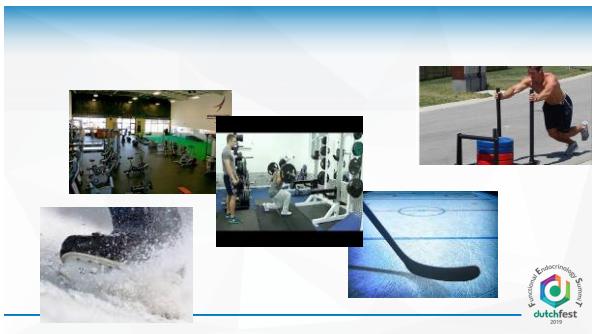
- Integrative Medicine Director Hall of Fame Health Program
- Founder Metabolic Code Enterprises, LLC
- Education CoChair A4M/MMI

2

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3



4

Key Tenants of Aging and Performance

- Oxidative Stress/Inflammation
- Hormonal Balance
- Stress Hormones
- Glucose/Insulin Regulation
- Immune Balance
- Environmental Burden
- Individuality

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5

Exercise

Moderate

- Improves mood/ HPA axis
- Improves sugar metabolism
- Improves oxygenation of tissues
- Increases fat burning enzymatic activity in muscle
- Increases bone density/muscle-fat ratio/basal metabolic rate (BMR)
- Reduces fluid retention –
- Reduces Stress hormones

Intense

- Increase Cortisol
- Increase Dysglycemia response
- Increase Amino Acid deficits
- Increase Mineral and trace mineral deficits
- Increase Immune Stress
- Can create catabolic metabolism
- Increase proneness to injury
- Decrease metabolic efficiency

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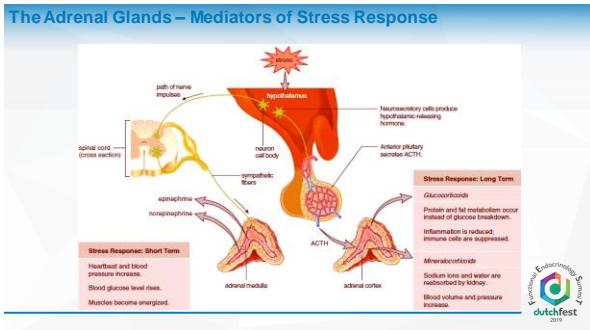
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Immune Function and Intensity

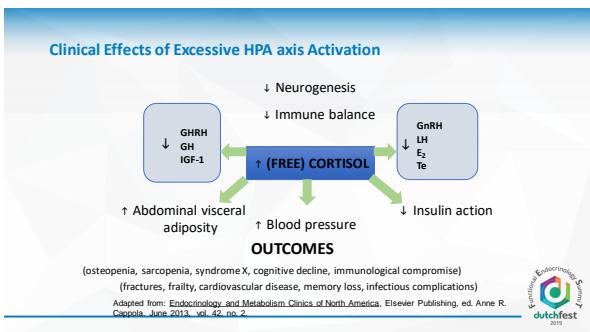
- Moderate exercise is associated with reduced rate of infection
- Prolonged continuous exercise 55-75% max O₂ uptake resulted in longer lasting immune dysfunction.
- TNF alpha, IL-1 IL-6, IL-10 and CRP reported

Gleeson, Michael. Immune Function in sports and exercise. Journal of Applied Physiology. August 2007 vol. 103 no. 2 693-699

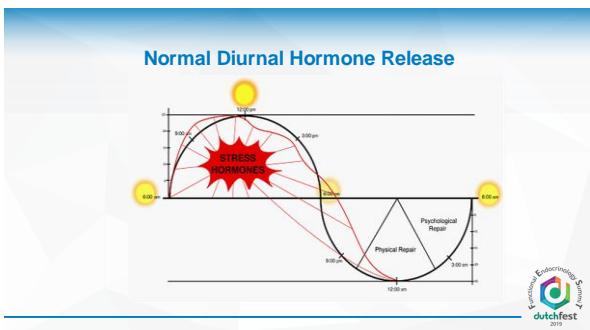
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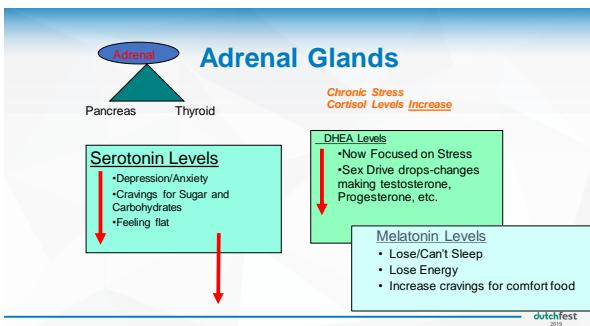
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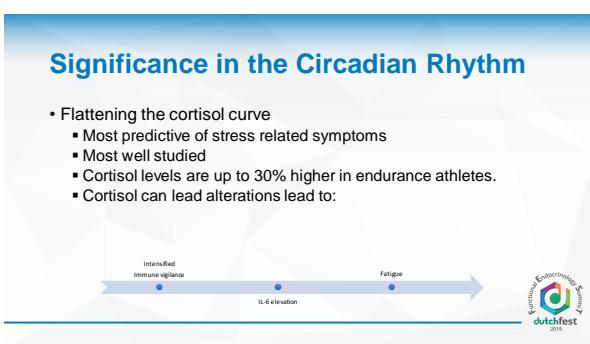
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10



11



12

Diurnal Cortisol and Physical Performance in Aging Males

- Middle aged men (45-59) measured AM and night cortisol
- Tracked twenty years later (65-83)
- Outcome measures walking speed and balance time morning serum and 4 salivary samples for two consecutive days
- Worst Performance in people with poor morning cortisol response & less nocturnal decline.

Outcome: HPA axis dysregulation is associated with worse physical performance later in life.

Diurnal cortisol patterns are associated with physical performance in Caerphilly Prospective Study Gardner, MP, Lightman SL, et al. Int J Epidemiol 2011 Dec;40(6):1699-702. doi: 10.1093/ije/dyq153



13

Testosterone Deficiency in Aging Athletes

- 2010 clinical study (n=183 male athletes, mean age 61.9yrs)
- Severe testosterone deficiency reported in 12%; mild deficiency in 18%
- Those > 70yrs, severe testosterone deficiency in 28%; mild deficiency in 26%
- RESULTS:** A significant percentage of aging male athletes have undiagnosed testosterone deficiency

D Luigi, et al. Prevalence of undiagnosed testosterone deficiency in aging athletes: does exercise training influence the symptoms of male hypogonadism? J Sex Med 2010;7:259-261



14

IF I am So Fit, Why is My testosterone low?

- Free Testosterone/Cortisol Ratio Important Indicator
- Higher the ratio the better the training gains
- As Cortisol raises and Free and Total Testosterone lowers shifts occur
 - More cortisol made from DHEA – less DHEA makes testosterone
 - Immune changes tendency toward more allergies (food & environment)
 - Anabolic drive reduces, gains from training disappear
 - Inflammation signaling increases
 - Gut breakdown becomes more "Leaky"
 - Mood Alters



15

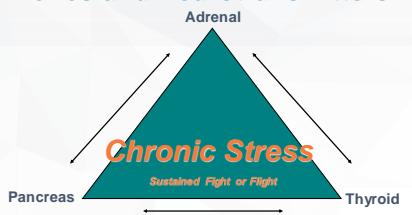
Cortisol and Sex Hormone Imbalances

- Increased cortisol blocks T4 conversion to T3 which causes
- TRH is up-regulated to create more T4
- Increasing TRH will increase prolactin which in turn
- Down regulates LH and FSH production which
- Down regulates testosterone
- As testosterone goes down, so does growth hormone



16

Hormones and Neurotransmitters



17

Thyroid Hormone Conversion

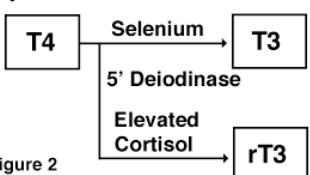


Figure 2

- rT3 Binds to T3 receptors
- Blocks T3 from binding



18

Stress and Thyroid Antibodies

- Reduced glucocorticoid activity is associated with an increased prevalence of ThAbs positivity in older ambulatory subjects.
Tzitzis K, et al. Eur J Endocrinol. 2010;162(2):307-13
- HPA axis (neuro-endocrine) imbalances caused by stress-mediated activation involved in autoimmune thyroid diseases (AITD)
Klecha AJ, et al. Neuroimmunomodulation. 2008;15(1):68-75



19

Cortisol and Thyroid Function

- Adrenal and thyroid function closely linked
- Both under control of hypothalamus and tropic hormones
- Thyroid competes with adrenals for tyrosine
- When tyrosine used to produce cortisol under stress not enough tyrosine left to make thyroid hormones



20

Metabolic Effects of Suboptimal Thyroid Function

- Glucose tolerance
- Rate of glucose absorbed from GI tract and cellular uptake
 - Insulin signaling/receptor problems
 - Reduces target cell insulin binding/number of insulin receptor expressed
 - Decreases metabolism fats and increases serum lipids & availability of cardioprotective essential fatty acids
 - Decreases Inadequate T3 lowers oxygen consumption, contributes to lipids peroxidation and free radical damage

(J Clin Endocrinol Metab. 82 (10) Oct. 1997)

21

Hypothyroidism and Athletes

- Cardiac performance is altered in low thyroid states
 - Changes in: cardiac output, stroke volume and end diastolic volume at rest



(Westhammar S, Kekel-FS, Waitzinger J, Kohler J, Adam W, Stauch M, and Pfeiffer EF. Left ventricular function at rest and during exercise in acute hypothyroidism. *Br Heart J.* 1988 September; 60(3):204-211.)

22

Study - Exercise Intensity and Thyroid Hormones

- 2005 clinical study (n=60 male well trained athletes)
 - Compared thyroid hormone levels at 45%, 70% and 90% of maximum heart rate
 - TSH, T4 and fT4 levels increased at 70 and 90% vs. 45%
 - fT3 and T3 increased at 70%, but fell at 90%
 - Thought to be due to elevations in cortisol



Ciloglu, F., Peker, I. et al; Exercise intensity and its effect on thyroid hormones Neuroendocrinology Letters No.6 December Vol.26, 2005

23

Insulin Resistance and Overtraining

- Overtraining can lead to neuro-endocrine immune imbalance
 - Increase in inflammatory cytokines (TNF-alpha, IL-1, IL-6)
 - Anabolic hormones (i.e. testosterone, growth hormone, IGF-1) and cortisol reported elevated during 15-30° of post-resistance exercise
 - Associated with sleep and mood disturbances, inflammation, immune imbalances, fatigue, IR
 - Moderate, regular exercise improves anti-inflammatory cytokine release



Kraemer WJ, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. *Sports Med*. 2005;35(4):339-61. Review. Main LC, et al. Relationship between inflammatory cytokines and self-report measures of training overload. *Res Sports Med*. 2010 Apr;18(2):127-39. Astrøm RE, et al. Persistent low-grade inflammation and regular exercise. *Front Biotech (Scholar Ed)*. 2010 Jan 1;2:95-105.

24

Bottom Line - Exercise and Metabolism

Higher testosterone to cortisol ratios are correlated to strength gains and tissue anabolism and improved performance and overall well-being in men and women



25

Overtraining- Under recovered



- Overtraining can lead to neuro-endocrine immune imbalance
- Increase in inflammatory cytokines (TNF-alpha, IL-1, IL-6)
- Anabolic hormones (i.e. testosterone, growth hormone, IGF-1) and cortisol reported elevated during 15-30° of post-resistance exercise
- Associated with sleep and mood disturbances, inflammation, immune imbalances, fatigue, IR
- Moderate, regular exercise actually improves anti-inflammatory cytokine release


Kraemer WJ, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. *SportsMed*. 2005;35(4):539-551.
Holmér B, Karlsson M, Karlsson J, et al. Effects of exercise on plasma levels of C-reactive protein. *Acta Endocrinol (Edinb)*. 2010 Apr;160(4):127-39.
Adron RE, et al. Paradox for-grade inflammation and regular exercise. *Funct Biol (Schild Ed)*. 2010 Jan 12;96:105.

26

C-Reactive Protein (CRP)

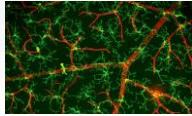
- Atrial fibrillation
- Chronic endurance training can raise CRP and IL-6
- Leads to chronic inflammation and direct AF risk


Swanson, Don. R. Atrial Fibrillation Implicit literature based connections suggest that overtraining and subsequent inflammation may be a contributory mechanism. *Medical Hypotheses*. 2006 Nov;66(5):1049-1052.

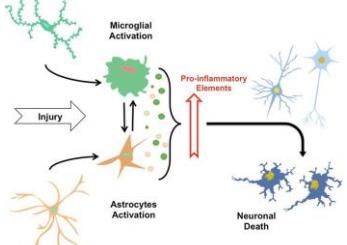
27

Microglia

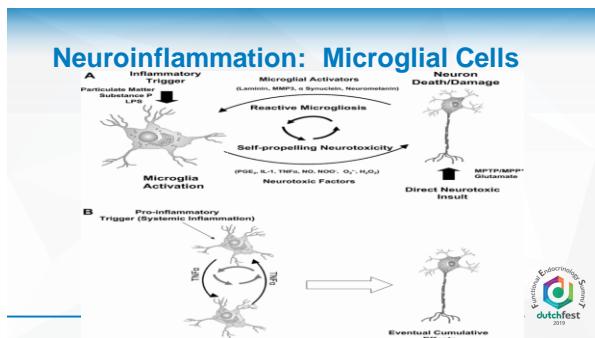
- Glial cell
 - Innate immune cells of CNS
 - Key component in neuroinflammation
 - Activate in response to neural injury
 - Acute inflammation of brain = rapid action of microglia
 - Generates Reactive oxygen species (ROS)



28



29



30

Chronic Microglial Activation

- Sustained release of inflammatory mediators
- Blood Brain Barrier (BBB) becomes permeable to
 - circulating blood components
 - Peripheral immune cells – macrophages, T cells, B cells
- Enter brain space and encounter neurons and glial cells
- Glial cells = express Major histocompatibility complex II molecules II (MHC II)



31

Chronic Microglial Activation

- Results in chronic inflammation
- Chronic up-regulation of microglial cells
- Leading to:
 - Neuronal damage/death
 - Neurobehavioral impairment
 - Chronic neurodegenerative conditions



Hart B, et al. Commentary on [special issue: CDO disease and the immune system]. J Neuroimmunol Pharmacol. 2013;6(1):75-9.

32

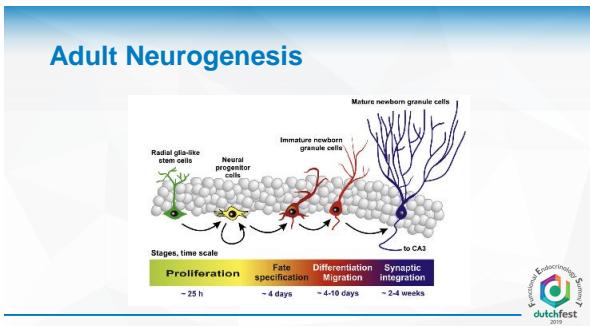
Cortisol and Cognitive Dysfunction

- Elevated HPA axis leads to Hippocampal degeneration
- High plasma Cortisol associated with rapidly increasing dementia (progression vs. severity)

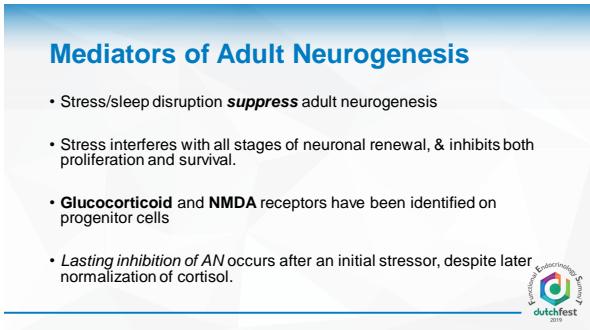


Am J Psychiatry 2008;163:2164-22169

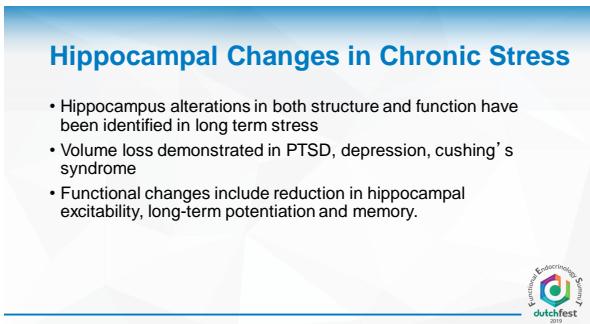
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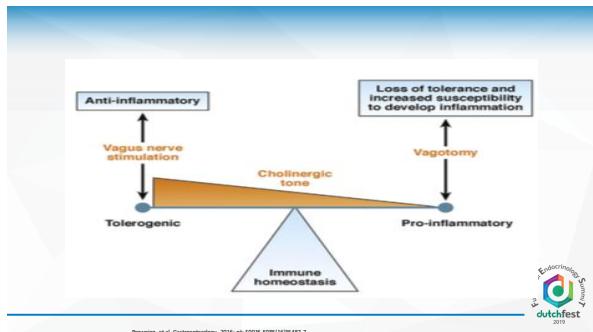
36

Dendritic Retraction of Hippocampus

- Induce shrinkage of the apical dendrites of the CA3 and CA1 pyramidal cells and dentate granule cells
- Changes of neuronal morphology likely to contribute to cognitive deficits
- A functional outcome of dendritic retraction is a disturbance of HPA axis regulation, leading to unregulated glucocorticoid release.
- Increased oxidative stress, neuroexcitation, loss of counter-regulatory control



37


Browning, et al. Gastroenterology. 2010; pt. 2; 140(5):1605-1617.

38

Sympathetic nervous system (SNS)

- Sympathetic nerves contain multiple oscillations
- Sympathetic nerve discharge (SND) bursting pattern influences many physiological functions
 - Regulation of efferent sympathetic nerve outflow
 - Synchronizing or desynchronizing nerve activity innervating different targets
 - Regulation of target organ function
 - Generating differential patterns of sympathetic nerve outflow


Gilbey MP. Sympathetic rhythms and nervous integration. Clin Exp Pharmacol Physiol. 2007;34:356-361.

39

SNS

- Altering efferent SND characteristics leads to regulation of central sympathetic neural circuit's target organ responses

Gilbey MP. Sympathetic rhythms and nervous integration. Clin Exp Pharmacol Physiol. 2007; 34:356–361.

40

Sympathetic Dominance

- Imbalance between sympathetic and parasympathetic nervous systems
- Vagal "brake" not working properly
- PNS and SNS should work in harmony – homeostasis
- PNS/SNS homeostasis declines with age
- Direct innervation of sinus node
- Increased SNS due to affective disorders, chronic stress, neuro-inflammation

Leads to elevation in resting heart rate (RHR)

41

Cholinergic Anti-inflammatory Pathway

- Inflammatory reflex of vagus nerve, inhibits cytokine release and thereby prevent tissue injury and death
- Cholinergic agonists inhibit cytokine synthesis and protect against cytokine-mediated inflammation
- Stimulation and balance of vagal tonicity limits damaging effects of cytokine

Tracey KJ. J Clin Invest. 2007 Feb;117(2):289-98.

42

Vagus Nerve and Neuroinflammation

- Vagus nerve important role in metabolic homeostasis
- Cholinergic signaling
- Controls immune function and pro-inflammatory responses
- Dysregulation of vagus nerve in obesity = chronic inflammation
- Leads to insulin resistance and type 2 diabetes



Pavlov VA, et al. The vagus nerve and the inflammatory reflex – linking immunity and metabolism. Nat Rev Endocrinol. 2012;8(12):743-754.

43

Autonomic nervous system Balance

- Research evidence that indicates resting heart rate is inversely related to Life Span – the slower the HR, the longer life
Poirier P. Exercise, Heart Rate Variability and Longevity. Circulation. 2014;129:2085-87.
- HRV predicts cardiovascular disease mortality in healthy and diseased individuals
Dekker JM, et al. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study—Atherosclerosis Risk in Communities. Circulation. 2000;102:1239–1244.
- High variability leads to increased longevity
 - Indicates more parasympathetic innervation
- A low variability indicates Sympathetic Dominance



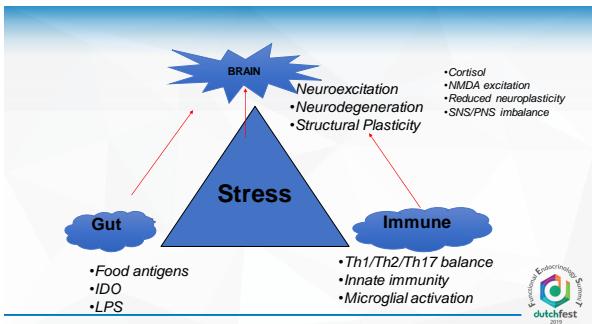
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HRV

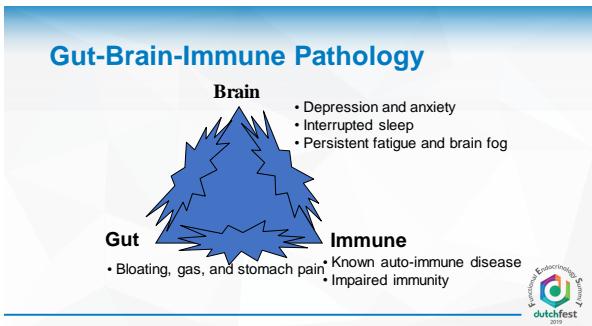
- HRV also indicates psychological resiliency and behavioral flexibility
- Vagally mediated HRV linked to:
 - Self-regulatory capacity
 - Emotional regulation
 - Ability to adapt to social or environmental changes
 - Social interactions
 - Sense of coherence
 - Self-directedness



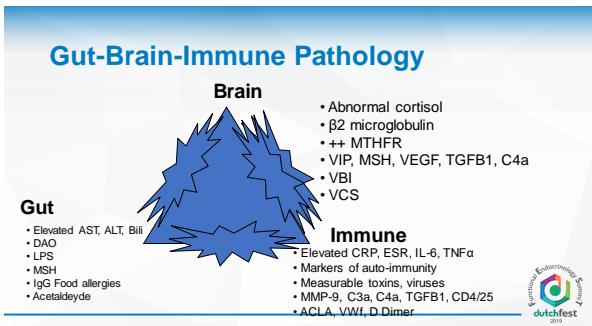
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46



47



48

Immune Function and Intensity

- Moderate exercise is associated with reduced rate of infection
 - Prolonged continuous exercise 55-75% max O₂ uptake resulted in longer lasting immune dysfunction.
 - TNF alpha, IL-1 IL-6, IL-10 and CRP reported

Gleason, Michael, Immune Function in sports and exercise; Journal of Applied Physiology August 2007 vol. 103 no. 2 693-695



49

Clues but not Diagnostic

- Resting Heart Rate changes
 - Changes in % free testosterone
 - Exaggerated post exercise heart rate response.
 - Excess decreased or increased body fat



50

Exercise and Cortisol

- Cortisol levels increase during exercise
 - Various types of exercise producing different levels of cortisol
 - Resistance and strenuous exercise stimulates greatest lactate response and increases in cortisol
 - High volume, intense, short rest intervals resistance = greatest cortisol rise
 - Protocols resulting in high Creatine kinase (CK) 24hr post-exercise also result in significantly elevated cortisol



51

Exercise and Cortisol

- Significant differences in metabolic and hormonal responses to exercise between athletically trained and untrained
 - Cortisol levels at increased workloads reported HIGHER in trained athletes than untrained

Bottom Line

Exercise-induced chronic secretion of cortisol can lead to metabolic imbalances

Bloom SR, et al. Differences in the metabolic and hormonal response to exercise between racing cyclists and untrained individuals. *J Physiol* 1978;258:1-8.
Shirika S, et al. Cortisol response to exercise and post-exercise suppression of blood lymphocyte subset counts. *Int J Sports Med.* 1996;17(8):597-603.



52

Study: Cortisol and Training

- 2012 clinical study (n=304) amateur endurance athletes
 - 190 females and 114 males (38 yo avg)
 - 70 Controls
 - Hair Cortisol Levels Measured
 - Self Reported volume of exercise
 - On average 42% higher cortisol in endurance athletes

Skluda N, et al. Elevated hair cortisol concentrations in endurance athletes. Psychoneuroendocrinology. 2012;37(5):611-7.



53

Cortisol in Endurance

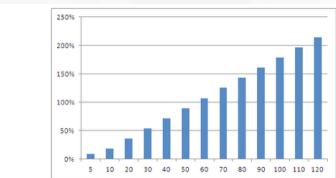
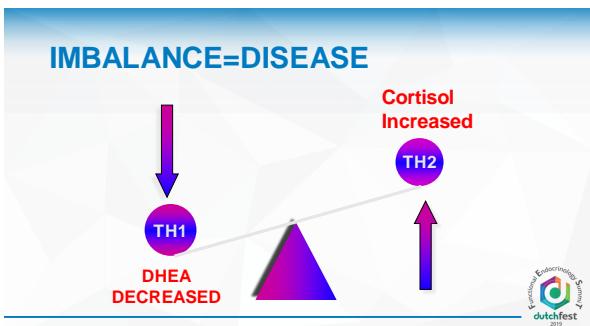


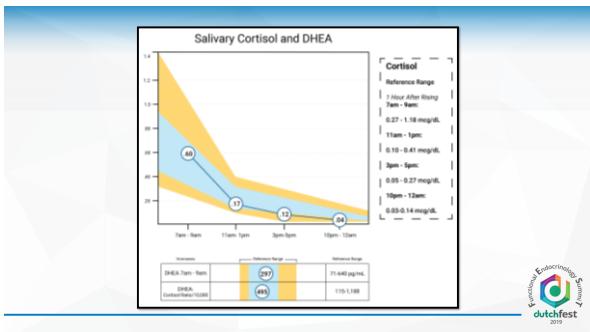
Figure 2: Relative increase in hair cortisol levels of endurance runners in relation to average weekly training load in kilometers (calculation based on a regression with $r=0.32$, indicating a below average precision; Kinschbaum, 2011)



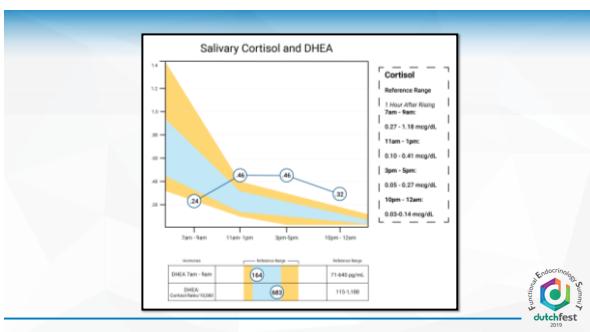
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56



57

Cortisol and Cardiovascular Disease

- 2006 CARDIA study (n=718, av. Age 40)
- Results – the quartile with the flattest diurnal cortisol slopes were approximately 3 & 1/3 times more likely to have coronary calcification
- Results independent upon socioeconomic status and established cardiovascular risk factors

Matthews K, et al. Diurnal cortisol decline is related to coronary calcifications: CARDIA Study. Psychosom Med. 2006;68:657-661.

58

Significance in the Circadian Rhythm

- Flattening the cortisol curve
 - Most predictive of stress related symptoms
 - Most well studied
 - Cortisol levels are up to 30% higher in endurance athletes.
 - Cortisol can lead alterations lead to:

59

HPA axis:Cortisol and Cholesterol Metabolism

- Chronic stress and elevated cortisol are correlated with cholesterol imbalances
 - Decreased HDL
 - Increased triglycerides
 - Increased total cholesterol
 - Increased ox-LDL

Rosmond R, et al. The hypothalamic-pituitary-adrenal axis activity as a predictor of cardiovascular disease, type 2 diabetes and stroke. J Intern Med. 2003;253:189-97.

60

Cortisol and Metabolic Syndrome (MetS)

- 2013 clinical study (n=1258 aged 16-64)
- Hair cortisol analyzed
- A higher prevalence of MetS reported in those with elevated long-term cortisol secretion

Stalder T, et al. Cortisol in hair and the metabolic syndrome. J Clin Endocrinol Metab. 2013;98(2):257-80.



61

Cortisol and Stress F

- Cortisol reported to imbalance acid/base regulation – lactate ↑
- Exacerbation of acid-induced net calcium efflux from bone
- Decreased bone mineral density
- Functional vitamin D deficiency also reported to be correlated with acute stress



Lee P. Best Pract Rev Clin Endocrinol Metab. 2011;26(2):769-81.

Boling EP, et al. Clin Infect Dis. 2004;38(1):174.

62

Cortisol Bone Loss

- Clinical study (n=43) men ages 20-59
- 27 male cyclists (non-weight bearing) and 16 runners (weight bearing)
- Results – cyclists had significantly lower bone mineral density vs. runners
- Cyclists 7x more likely to develop osteopenia of the spine



Rector RS, et al. Participation in road cycling voluntary is associated with lower bone mineral density in men. Metabolism. 2008;57(2):236-32.

63

Other Important Labs to Assess Cortisol Impact

- Blood Pressure >120/80
- pH(salivary and urinary) < 6.8
- Sodium 140 ideal
- RBC Mag 5.8
- Potassium >4.5
- Serum Cortisol 10-15
- Salivary 4 point Cortisol
- Siga varies but should be 3rd quartile
- DHEA 105-700 at least 300
- IGF-1
- Blood Glucose/Insulin
- Resting Pulse <70



64

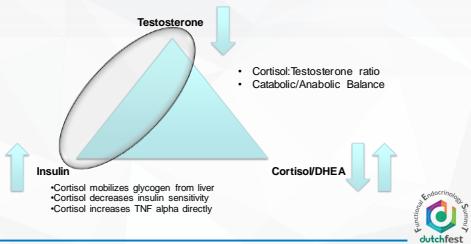
Metabolic Effects of Chronic Cortisol Elevation:

- Increased insulin secretion
- Increased fat deposition
- Alteration in immune function
- Muscle wasting
- Hypothyroidism (adrenal exhaustion)
- Memory loss
- Alteration in sex hormones
- Mental and Emotional instability
- Bone loss/mineral loss
- Sodium and water retention
- Elevated blood lipids
- Loss of REM sleep
- Increase plaque formation
- Increase in cardiovascular risk factors
- Receptor Site activation on Tumor cells



65

To Make Matters Worse: Multiple Hormonal Shifts



66

Coronary Heart Disease

Cortisol, Testosterone, and Coronary Heart Disease
Prospective Evidence From the Caerphilly Study

George Davey Smith, DSC, Yael Ben-Shlomo, BSc, MBBBS, MRCP, FPPIM, PhD; Andrew Bowcock, BSc; John Yarnell, MRCGP, DPH, MSc, MD, MPPIM (ret); Stafford Lightman, MRCGP, PhD, FMedSci; Peter Elwood, DSC, MD, FRCP, FPPIM

Background—There is a popular belief that chronic stress causes heart disease through psychoneuroendocrine mechanisms. We have examined whether an elevated circulating cortisol-to-testosterone ratio increases the risk of ischemic heart disease.

Methods—We used data from the Caerphilly Prospective Study, a population-based study of 1,979 men born in 1911 in Caerphilly, South Wales, with a mean follow-up of 35 years. Subjects underwent a clinical examination and morning fasting blood samples were taken for analysis of cortisol levels, testosterone levels, and other cardiovascular risk factors. The testosteroneto-cortisol ratio was calculated as the ratio of total testosterone to total cortisol. The association between the ratio and risk of coronary heart disease was examined by multivariate logistic regression analysis, adjusted for components of the insulin resistance syndrome ($P<0.001$). A positive linear trend was seen across quintiles of the ratio score, with an odds ratio for incident ischemic heart disease (age-adjusted OR per 1 score change in ratio) of 1.22, 95% CI 1.07 to 1.38, $P=0.003$. This association remained after adjustment for other risk factors of the insulin resistance syndrome (age-adjusted OR per 1 score change in ratio 1.10, 95% CI 0.96 to 1.25, $P=0.18$). There was no association between the ratio and risk of stroke.

Conclusion—This is the first population-based prospective study that has found a specific association between cortisol:testosterone ratio and incident ischemic heart disease, apparently mediated through the insulin resistance syndrome. Whether this reflects the effects of chronic stress, behavioral factors, or genetic influences remains to be determined. (Circulation. 2005;112:332-340)

Key Words: heart disease ■ hormones ■ stress

dutchfest
67
Functional Endocrinology
Lambeth

67

Study: Exercise and Testosterone/Cortisol Ratio

- 2012 Clinical study (n=24) untrained men
- Divided equally into 3 groups
 - Endurance training
 - Resistance training
 - Concurrent training
- 12 week protocol

Shalev N, et al. The effect of different types of exercise on the testosterone/cortisol ratio in untrained young males. Annals Biol Res. 2012;3(3):1452-1459.

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68

Free Testosterone/Cortisol (FTCR)

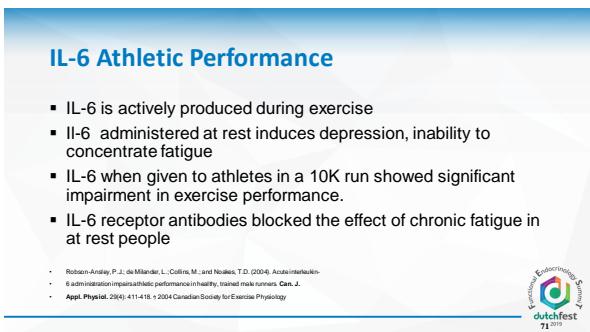
- Free testosterone and cortisol monitored
- Sex Hormone Binding Globulin is elevated in over trained
- Decreased FSH and LH excretion

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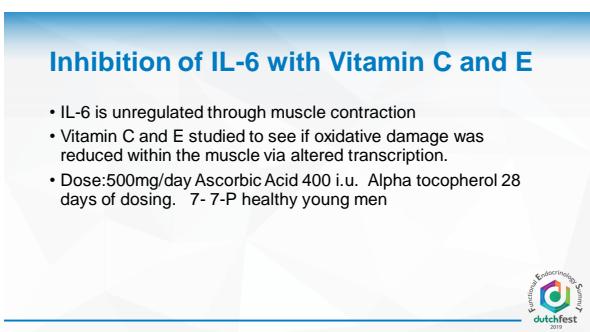
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70



71



72

Results

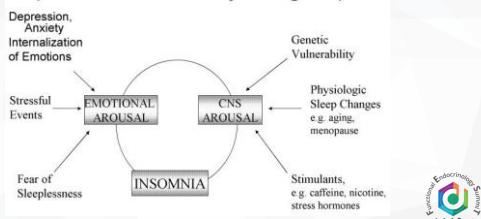
- Control group: ↑50% higher IL-6, cortisol, CRP IL-1ra all higher
- Vitamin C and E attenuated the systemic IL-6 protein release in muscle tissue in response to exercise.

Fischer, Christian, Hiscock, Natalie et al; Supplementation with vitamin C and E inhibits the release of interleukin 6 in contracting human skeletal muscle. Journal of Physiology, July 15 2004;558, 633-645



73

Hyperarousal Hypothesis (Emotional and Physiological)



74

Cortisol and Sleep

- Cortisol release is controlled in slow-wave sleep by decreases in corticotropin-releasing hormone (CRH) and increases in growth hormone (GH)
- Exposure to chronic stressors imbalances HPA axis and disrupts normal diurnal pattern of GH, CRH and ACTH release
- Results in a paradoxical rise in cortisol in evening hours and initial sleep phases
- Nocturnal hypercortisolism* can lead to sleep fragmentation, increasing cortisol even more



75

Insomnia or Disrupted Sleep

- Alters Growth Hormone release
- Increases TNF alpha, IL-6
- Increases insulin resistance
- Contributes to weight gain
- Increases TBG



76

Sleep and Skeletal Muscle

- Sleep – important maintenance of skeletal muscle health
- Sleep deprivation lead to muscle atrophy
- Decreases testosterone, growth hormone, insulin-like growth factor-1
- Increases glucocorticoids (cortisol)
- Leads to decreased protein synthesis and increased muscle degradation
- Resistance exercise reported to minimize muscle atrophy



Monico-Neto M, et al. Resistance exercise: a non-pharmacological strategy to minimize or reverse sleep deprivation-induced muscle atrophy. *Med Hypotheses*. 2013;80(6):701-5.

77

Sleep Deprivation & Weight Gain Linked

- Subjects that avg. 4 hr. sleep/night
↓ Leptin (18%), ↑ Ghrelin (28%)
↑ reported hunger (24%), ↑ carb cravings, especially sweets, salty, and starchy high calorie snacks
- > 1,000 volunteers: those that avg. , 5 hr sleep had ↓ leptin (15.5%), ↑ ghrelin (14.9%), ↑ BMI (3.6%). Results were regardless of the subjects diet and exercise habits (Mignot et al, Stanford School of Medicine Dec. 2004)



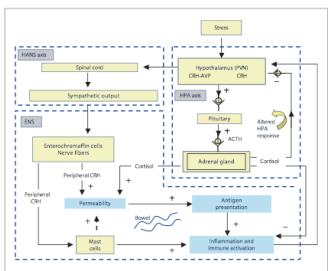
78

Sleep Deprivation & Weight Gain Linked

- Heynsfield and Gangwisch analyzed NHANES I data: Found that subjects with avg. 5hr./night sleep had 73% increased likelihood of obesity over those who slept 7-9 hr/night.
- (Findings reported at the annual scientific meeting of the North American Society for the Study of Obesity Nov. 2004)
- Study showed a linear relationship: reduced amounts of sleep are associated with overweight and obesity (Arch. Intern Med. 2005;165:25-30)



79



80

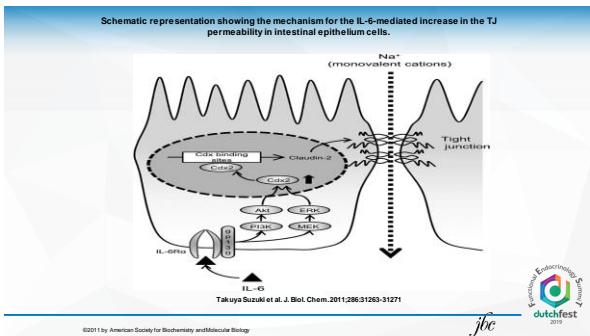
IL-6 regulates Claudin 2 Expression of Tight Junction Permeability in Intestinal Epithelium

- Key immune cytokine in chronic inflammation
- Induced by chronic hypercortisolism and flattening of cortisol curve
- Induced in overtraining in athletes
- Markedly induces expression of Claudin-2
- Disrupts tight junction structure (TJ) multi-protein structure (disrupts protein scaffold cytoskeleton)



Sasaki, Takeshi, Yoshihiko Ni, Teruhiko Saitoh. IL-6 regulates expression of Tight Junction Permeability in the Epithelium. September 9, 2011. The Journal of Biological Chemistry, 286: 31263-31271.

81



82

Endurance & Endotoxin

- Long Duration Exercise induces Endotoxemia due to plasma \uparrow Lipopolysaccharide (LPS) levels
- LPS leads to: \uparrow cytokine release \uparrow oxidative stress and alterations in gut function
- Vitamin C reduced nitrate and LPS serum levels

• Exercise induced Endotoxemia in the effect of ascorbic acid supplementation: Ashton, Tony et al (Free Radical Biol & Med Volume 35) issue 3 August 2003 Pages 284-291 http://dx.doi.org/10.1016/S0898-5889(03)00395

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83

Endurance and Gut

- 93% of athletes in this study had GI complaints
- 2 abandoned the race due to severe GI distress
- Endotoxemia-dizziness nausea and vomiting mimic heat effects

• Relationship between gastro-intestinal complaints and endotoxemia, cytokine release and the acute phase reaction during and after a long distance triathlon in high altitude. Clinical Science (2003) 98, 47-55 (Printed in Great Britain)

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84

Endotoxin LPS Facts

- Has anti-thyroid effects
- Causes blood estrogen levels to rise increases clotting risk
- Intense exercise and fasting increase lactic acid and ammonia production ↑ LPS
- Carrageenan in drinks trigger endotoxin
- Associated with auto immunity



85

Ibuprofen Use in Ultramarathon Competition

- Ibuprofen did not alter muscle damage or soreness
- Elevated endotoxemia and inflammation vs controls
- Elevated C-RP, cytokines (il-6, il 10, il8 iL 1ra, mcp-1)
- Nieminen, S., et al. Ibuprofen use, endotoxemia, inflammation, and plasma cytokines during ultramarathon competition. *Human behavior and immunity* (2008) Volume: 20, Issue: 6, Pages: 579-586.
- Also associated with worsened kidney function post race



86

Eurycoma (*Eurycoma longifolia*) Root

- Tongkat ali or "Malaysian ginseng" - used in SE Asian cultures for improved testosterone levels, libido
- Reported to improve testosterone levels (free and total) in men and women
- Also improves testosterone/cortisol ratio



87

Eurycoma (*Eurycoma longifolia*) Root

- Quassinooids - major phytochemical compounds
- Laboratory studies:
 - Aromatase inhibition
 - At high concentration may also have phosphodiesterase inhibiting properties
- Helps stimulate osteoblast proliferation and osteoclast apoptosis



88

Eurycoma (*Eurycoma longifolia*) Root

- 2013 study (n=25; 13 men, 12 women; ages 52-72)
- 400mg standardized water extract of Eurycoma QD x 5 weeks
- Significant increases in total and free testosterone
- Significant declines in SHBG
- Improved muscular force

Hirsel RR, Wang R, Bassin SH, et al. Tongkat Ali as a potential herbal supplement for physically active male and female seniors-A pilot study. *Phytomedicine* 2013; [Epub ahead of print]



89

Eurycoma (*Eurycoma longifolia*) Root

- 2013 clinical trial
- N=63 men and women
- 200 mg QD standardized water extract for 4 weeks
- 37 % decrease in cortisol levels
- 16% increase in testosterone levels
- Reduced symptoms:
 - -11% stress
 - -15% confusion
 - -12% anger

Talbot SM, Talbot JA, George A, et al. Effect of Tongkat Ali on steroid hormone and psychological mood state in moderately stressed subjects. *J Int Soc Sports Nutr* 2013;10:126.



90

Eurycoma (*Eurycoma longifolia*) Root

- 2012 randomized, double-blind, placebo controlled parallel group study (n=109 men; ages 30-55)
- 300 mg QD *Eurycoma* root standardized water extract for 12 weeks
- Reported improvements in erection, sexual libido, sperm motility and semen volume
- A significant improvement in fat mass was also reported in subjects with a BMI ≥ 25 .

Ismail SB, Wan Mohamed WM, George A, et al. Randomized Clinical Trial on the Use of Plasma-Freeze-dried Water Extract of Eurycoma longifolia for the Improvement of Quality of Life and Sexual Well-Being in Men. *Endocr Pract Alternat Med.* 2012;20(2):426-68.



91

Cordyceps (*Cordyceps sinensis*)

- Caterpillar fungi
- Contains proteins/amino acids/saccharides/sterols/fatty acids/vitamins/minerals (including vitamins B1, B2, B12, vitamin E, vitamin K)



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92

Cordyceps

- More efficient enzyme activity in RBCs - increasing cellular oxygenation
- Enhances kidney function - increased elimination of toxins
- Protects kidneys from aminoglycoside/ cyclosporin toxicity



93

Cordyceps

- Adaptogen
- Increases serum levels of SOD
- Sexual enhancement through sex hormonal system
- Has hypotensive effects through coronary vasodilation

Wang, S. C., Chou, C. J., Lin, L. C., Tsai, W. J., and Kuo, Y. C. Immunomodulatory functions of extracts from the Chinese medicinal fungus Cordyceps sinensis. *J Ethnopharmacol.* 2002;83(1-2):79-85.



94

Cordyceps

- Benefits in chemotherapy/radiation
- Lab studies report increased expression levels of endurance responsive skeletal muscle metabolic regulators AMPK, PGC-1 α and PPAR- δ
- Increased endurance promoting and antioxidant genes like MCT1, MCT4, GLUT4, VEGF, NRF-2, SOD1 and TRX in red gastrocnemius muscle

Kumar et al. Cordyceps sinensis promotes exercise endurance capacity of rats by activating skeletal muscle metabolic regulators. *J Ethnopharmacol.* 2011;136(1):280-4.



95

Cordyceps Clinical Studies

- Reported increase sexual vitality in both men and women and improving male sexual performance
- Possible increases in sex hormone binding capacity, or by directly acting on sexual center of brain/sex organs in parallel with hypothalamic-pituitary-adrenocortical axis

Source: J. Zhu et al., CordyMax CS-4: A Scientific ProductReview *Pharmacy Practice Review Guide* 1997.



96

Cordyceps Clinical Studies

- 2010 clinical trial (n=20 healthy adults aged 50-75 yrs)
- Cordyceps Cs-4 333mg tid or placebo x 12 wks
- Metabolic threshold (above which lactate accumulates) increased by 10.5%
- Ventilatory threshold (above which unbuffered H⁺) stimulates ventilation) increased by 8.5%



Chen et al. Effect of Cs-4 (Cordyceps sinensis) on exercise performance in healthy older subjects: a double-blind, placebo-controlled trial. J Altern Complement Med. 2010; 16(5): 585-8.

97

Rhodiola (*Rhodiola rosea*) Root

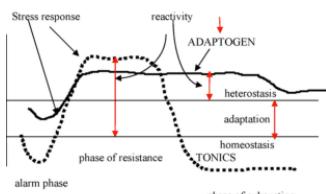
- "Second generation" plant adaptogen
- similar to the adaptogenic effects of the ginsengs
- Studied and used in Russia for over 30 years to combat climatic and environmental stress
- Used to enhance physical and mental performance of athletes and cosmonauts

De Bock K, Eljinde BO, Rasmussen M, Haugel P. Acute Rhodiola rosea intake can improve endurance exercise performance. Int J Sport Nutr Exerc Metab. 2004 Jun; 14(2):208-207.



98

Stress Response and Effects of Adaptogens



Adapted from: Panossian et al. Pharmacology of Schisandra chinensis Baile: an overview of Russian research and uses in medicine. J Ethnopharmacol. 2008;118(2):183-212.

99

Rhodiola (*Rhodiola rosea*) Root

- Initial studies revealed cardioprotective benefits
- Limits adrenergic effects on heart during stress
- Reduces catecholamines during alarm phase of stress and after intense exercise; may increase serotonin by 30%
- May influence levels of monoamines and beta-endorphins



100

Rhodiola (*Rhodiola rosea*) Root

- Lab studies report enhanced stamina and endurance
 - Improved oxygen utilization
 - Improved muscle growth
 - Induces faster recovery and tissue repair



101

Rhodiola (*Rhodiola rosea*) Root

- Pre-Clinical Review
 - Of plant adaptogens, Rhodiola is the only one where a single dose produced effects within 30 minutes and continuing for at least 4-6 h.

Panossian et al. Stimulating effect of adaptogens: an overview with particular reference to their efficacy following single dose administration. Phytother Res. 2005;19(10):819-38.



102

Rhodiola Clinical Study

- 2013 clinical study (n=18, double-blind, random crossover)
- 3mg/kg oral rhodiola standardized extract 1 hour before testing
- Exercise testing consisted of a standardized 10-minute warm-up followed by a 6-mile time trial (TT) on a bicycle ergometer
- Rhodiola significantly decreased HR during warm-up (136 vs. 140 beats/min)
- Improved endurance exercise performance by decreasing the perception of effort

Noreen EE, Buckley JG, Lewis SL, et al. The effects of an acute dose of Rhodiola rosea on endurance exercise performance. *J Strength Cond Res.* 2013;27(3):839-47.



103

Rhodiola Clinical Study

- 2009 Phase III clinical study (n=60, male/female aged 20-55; 576mg daily rhodiola standardized extract for 1 month)
- Conclusion:
 - "Repeated administration of Rhodiola produced an anti-fatigue effect that increases mental performance, particularly the ability to concentrate, and decreases cortisol response to awakening stress in burnout patients with fatigue syndrome."

Orsoni et al. A randomized, double-blind, placebo-controlled, parallel-group study of the standardized extract t-Rh 6 of the roots of Rhodiola rosea in the treatment of subjects with stress-related fatigue. *Planta Medica.* 2009;75(2):105-12.



104

Rhodiola Clinical Study

- 2000 clinical study (n=56, male/female night-shift workers)
- Rhodiola standardized extract for 3 weeks
- 20% improvement in Fatigue Index (mental performance, short-term memory, calculation, concentration, a-v perception)

Darbinian V, Kasper A, et al. Rhodiola rosea in stress-induced fatigue - a double-blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the performance of healthy physicians during night duty. *Phytomedicine.* 2000; 7(5) (Oct 2000): 365-71.



105

Rhodiola Clinical Study

- 2011 review of clinical studies on Rhodiola
- 11 randomized, placebo-controlled clinical studies reviewed
- Conclusion
 - Rhodiola has beneficial effects on:
 - Physical Performance
 - Mental Performance and Mood Stabilization



Hung SK, Pety R, Emia E. The effectiveness and efficacy of Rhodiola rosea L.: a systematic review of randomized clinical trials. *Phytomedicine*. 2011;18(6):235-44.

106

Ashwagandha (*Withania somnifera*)

- “Indian ginseng”
- Herbal adaptogen
- Helps improve performance and decrease fatigue

Sandhu JS, Shah B, Shetty S, et al. Effects of *Withania somnifera* (Ashwagandha) and *Terminalia arjuna* (Arjuna) on physical performance and cardiospiroergometry endurance in healthy young adults. *Int J Ayurveda Res*. 2010;1(3):144-9.



107

Ashwagandha (*Withania somnifera*)

- Reported to help improve thyroid hormone levels, especially T4

Panda S, Kar A. Changes in thyrothormone concentrations after administration of ashwagandha root extract to adult male mice. *J Pharm Pharmacol*. 1998 Sep;50(9):1065-8.



108

Ashwagandha Clinical Study

- 2010 study (n=40, mean age 20.6 yrs)

- Study results:
 - Reported improved physical performance and cardiorespiratory endurance
 - Ashwagandha may help improve generalized weakness and to improve speed and lower limb muscular strength and neuromuscular co-ordination

Sandhu JS, Shah B, Shetty S, et al. Effects of Withania somnifera (Ashwagandha) and Terminalia arjuna (Arjuna) on physical performance and cardiorespiratory endurance in healthy young adults. Int J Ayurveda Res. 2010;1(1):144-5.



109

Ashwagandha Clinical Study

- 2012 double-blind, placebo controlled clinical study (n=64; 300mg standardized Ashwagandha bid x 60d)

- Study results:
 - Ashwagandha reduced markers of stress
 - Significantly reduced serum cortisol (27.9% vs. 7.9% placebo)

Chandrasekhar K, Kapoor J, Anitha S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. Indian J Psychol Med. 2012;34(3):256-62.



110

Schisandra Clinical Studies

- Increased mental performance and decreases stress
- Affects the central nervous, sympathetic, endocrine, immune, respiratory, cardiovascular, and gastrointestinal systems
- Affects levels of nitric oxide and cortisol in the blood
- Improves symptoms of asthenia (lack of strength and energy)

Perevysheva et al. Pharmacology of Schisandra chinensis (Bail.): an overview of Russian research and uses in medicine. J Ethnopharmacol. 2008;118(2):210-212.



111

Magnolia and Philodendron

112

Summary

- It is not about the amount of time you train
- It is about the effort that is made to recovery from intense and regular physical activity
- Diet
- Stress Response Adaptation
- Regular and sound sleep
- Foundational cornerstones to improved performance

113

The image features a banner for the "Functional Endocrinology Summit" and "dutchfest 2019". The logo consists of a stylized green and orange hexagon with a central circle, set against a circular background containing the text "Functional Endocrinology" and "Summit". Below the logo, the words "dutchfest" and "2019" are written in a large, bold, sans-serif font. The banner is overlaid on a photograph of a city skyline at sunset, with a river in the foreground and a bridge spanning the water.

114