NMDF211
Nutritional Biochemistry
Integration of Mind and Body
Session 7
Session Overview

- Overview of HPA axis and role in stress response
- Endocrine system: an overview
- Stress, hormones and health
- Hormonal regulation of biochemical pathways
- Nutrients required for balancing HPA axis
- Lifestyle modifications to modulate stress responses
Overview of HPA axis
HPA axis

- The hypothalamus in the brain produces hormones (along with various other functions such as controlling body temperature). These hormones regulate pituitary hormones which in turn modulate numerous hormones produced by target glands. Examples of such regulatory hormonal cascades include the hypothalamic-pituitary-adrenal (HPA) axis.

- The HPA axis is one of the neuro-endocrine axis that plays an important role in the regulation of the stress-response.

- This cascade is initiated in response to almost any type of physical or psychological stress; during the normal sleep-wake cycle; and in response to certain neurotransmitters.

HPA axis

- The initial step is release of corticotropin-releasing hormone (CRH), that further stimulates the synthesis and release of adrenocorticotropic hormone (ACTH) from the anterior pituitary.

- ACTH is produced from a larger precursor protein (proopiomelanocortin) and stimulates adrenal cortex for synthesis and release of cortisol.

- Physiological glucocorticoid levels follow a circadian rhythm; (an early morning peak just prior to awakening, a rapid decrease over the next few hours, and then a more gradual decline over the course of the day, to very low levels at bedtime)


HPA axis dysregulation and Stress

- The hypothalamus also activates the adrenal medulla via the sympathetic nervous system (SNS), which results in the release of the catecholamines epinephrine and norepinephrine.

- The stress response under normal conditions is dampened via negative feedback loop (ACTH, CRH, and GCs) to maintain body homeostasis.

(Eisenmann, Rorabaugh & Zoladz 2016).

- Interestingly, some hormone systems are controlled by positive feedback mechanisms.
- Modulation of estrogen release during a woman’s menstrual period is one such example.
- Increased blood concentration of estrogen temporarily stimulate, (rather than inhibit), hormone release from the pituitary and hypothalamus, to potentiate increased estrogen levels that ultimately leads to ovulation.
- In order to maintain hormonal balance, at a specific threshold level, the positive feedback loop is turned off.

(Hiller-Sturmhöfel and Bartke 1998)
Overview of Endocrine system
Overview of Endocrine system

- A system of ductless glands that secrete hormones—chemical messengers that are carried for **long distances**.

- Hormones are directly secreted into the extracellular fluid and then carried to their target organs for function.

- Hormones can act on adjacent cells (paracrine action) and on the cell in which they were synthesized (autocrine action) without entering the systemic circulation.

Pic source: (Morley 2019)

(OpenStax 2013, Murray et al 2009)
The diversity of Endocrine system

Hormones can be
- Peptides of various sizes
- Steroids (derived from cholesterol)
- Amino acid derivatives

Several factors determine the response of a target cell to a hormone
- Factors that affect the concentration of the hormone at the target cell
- Factors that affect the actual response of the target cell to the hormone

These hormones are present in small amounts ($10^{-15}$ to $10^{-9}$ mol/L) as compared to other structurally similar molecules (sterols, peptides etc. ($10^{-6}$ to $10^{-3}$mol/L) in the extracellular fluid.

So how does Target cells distinguish between hormones and other compounds?

See Here (Murray et al 2009)
The diversity of Endocrine system

Classification:

Hormones can be classified according to:

- chemical composition,
- solubility properties,
- location of receptors and
- the nature of the signal used to mediate hormonal action within the cell.

(Murray et al. 2009)
The diversity of Endocrine system

Pic source
https://commons.wikimedia.org/wiki/File:Endocrine_central_nervous_en.svg
The diversity of Endocrine system

Hormones are chemically diverse hormones are synthesized from a wide variety of chemical building blocks.

- A large series is derived from cholesterol. These include the glucocorticoids, mineralocorticoids, estrogens, progestins.

- The amino acid tyrosine is the starting point in the synthesis of the catecholamines and of the thyroid hormones tetraiodothyronine (thyroxine; T4) and triiodothyronine (T3).

- Insulin is heterodimer of 21 and 30 amino acids

Can you name another hormone (which is also a vitamin) that is synthesised from cholesterol??

Now also find out names of adrenal steroid hormones that are synthesized from cholesterol. ....
Stress, hormones & health

Watch this video to understand effect of stress on body

https://www.youtube.com/watch?v=WuyPuH9ojCE

Stress, hormones & health

Thus, stress is understood as a state of disharmony, and ideally should be counteracted by stress response of the body via HPA. However, the adaptive response of everyone to stress is influenced by numerous factors mainly:

- genetic,
- environmental and
- developmental.

Ineffective response to stressors and type of stress (acute vs chronic) may translate into diseases.

Prolonged stress response (Chronic stress) or failure to keep a check on this response leads to HPA axis dysregulation that is now associated with various diseases.

Acute stress generally results in an adaptive response to homeostatic changes

(Tsigos et al 2016)
Stress, hormones and health

- Acute stress may play a contributory role in the development of symptoms that are allergic or atopic in nature, vasomotor, gastrointestinal, or psychological.

- Stress is associated with both psychological and biological adaptation.

- Chronic stress, however, impairs adaptation, and may finally contribute to the development of several physical, behavioral and/or neuropsychiatric disorders including anxiety, depression, cognitive dysfunction, immune deficiencies, sleep disorders, digestive problems, cardiovascular disease, obesity, type 2 diabetes mellitus, and osteoporosis.

(Chrousos 2009)
Stress, hormones and health

IMMUNE PERFORMANCE

- NK-cell activity plays a vital role in immune system surveillance against viruses and cancer cells.

- There is considerable clinical data among humans that any type of stress has a detrimental effect on the ability to maintain optimal levels of natural killer (NK) cell cytotoxic activity. A severe life stress may be associated with up to a 50-percent reduction of NK cell activity.

- Reduced ability of the immune system was observed to chronic stress that was induced by acute psychological challenge. A fall in NK cell activity, hence reduces immune performance.

- Higher levels of the catecholamine stress hormone epinephrine are significantly associated with lower IgA concentrations.

(Head & Kelly 2009. Pike etal 1997)
Stress, hormones and health

Intestinal Microflora

- In an interesting discovery, germ free mice were found to have an exaggerated HPA axis response to stress. Introduction of specific *Bifidobacteria* species, reversed these responses!!!! (Sudo et al 2004).
- Catecholamines and other neuroendocrine hormones may directly modulate microbial growth (gut-brain axis)
- Mice models and studies on monkeys have reported lower absolute and/or relative abundance of *Lactobacillus & Bifidobacterium* in the gut microbiota following stress exposure.
- One observational study on undergraduates during a week of exams reported increased stress and reduced abundance of fecal lactic acid bacteria (which include *Lactobacillus*) (Knowles, Nelson & Palombo 2008). However, the data is contradicted in another similar study on students taking medical exams (Kato-Kataoka etal 2016).

(Foster, Rinaman & Cryan 2017, Karl etal 2018)
Stress, hormones and health

Intestinal Microflora

- Various psychological, physical, and environmental stressors may modulate microbiome diversity and numbers.

- Further, microbiota’s response to stress over both the short- and long-term, can potentially be both health promoting (e.g., with cold exposure), health-degrading (e.g., with psychological stress, circadian disruption, and high altitude), or both (e.g., with physical activity and diet).

- Thus microbiome may contribute to stress-associated diseases but may also form basis of modulating these diseases (by moderating stress response).

(Foster, Rinaman & Cryan 2017, Karl et al 2018)
Stress, hormones and health

Stress & the brain-gut-microbiota axis

Stress has been associated with an increase in gut permeability and microbial diversity and growth that in turn may modulate stress response.

Picture source: Kelly et al. 2015
Stress, hormones and health

OBESITY

- Human and animal studies have demonstrated a bidirectional relationship between HPA axis functioning and energy intake.

- The ‘type’ of stressors influences the mode of response. For example, a life-threatening experience may shift to under eating while examination stress may increase energy intake.

- In addition, it has been shown that stressed people that overeat have decreased cerebrospinal CRF levels and HPA axis activity.

- Glucocorticoids interfere with insulin signaling on a peripheral and central level. Centrally, glucocorticoid signaling undermines the antagonizing effect of insulin thereby stimulating energy intake.

  (Lucassen & Cizza 2012, Rutters et al 2012)
Stress, hormones and health

- Among patients of sleep apnea, twice hourly measured plasma cortisol levels were continuously lower over the course of 24 h in obese individuals (mean BMI 35.4 kg/m²) in comparison with non-obese men (mean BMI 26.8 kg/m²) (Vgontzas et al 2007).

- Also, cytokines produced by immune cells or adipocytes can also stimulate the HPA axis (Bose, Oliván & LaFerrère 2009).

- The data on cortisol, BMI and other metabolic markers is inconsistent; Two clinical studies conducted two decades ago reported a significant correlation between postprandial salivary cortisol and BMI, waist-to-hip ratio, fasting glucose, insulin, triglycerides, cholesterol, and blood pressure in men (53 years, n=28; 51-yr-old, n = 284 resp) (Wallerius et al 2003, Rosmond, Dallman & Bjorntorp 1998), while a study on women did not find any change in cortisol (Brydon et al 2008).
Stress, hormones and health

- In a study of 67 University women students, aged 18-25 years investigation was conducted to understand cytokine responses to acute mental stress.

- The study found association of adiposity with larger cytokine responses to stress for abdominally obese women.

- A positive correlation was observed between waist circumference and stress-induced increases in plasma levels of leptin & IL-1 responses (Brydon et al 2008)

Could increased cytokine production could be a mechanism linking stress and abdominal obesity?
Stress, hormones and health

- Ghrelin is a gastric hormone that plays a role in long-term and short-term energy balance and acts centrally to increase food intake.

- Sleep deprivation causes an increase in ghrelin (Dzaja et al 2004)

- An inverse relationship between serum ghrelin and serum cortisol levels during 84 h of fasting is reported suggesting that weight gain due to sleep deprivation may be mediated by cortisol and its effects on ghrelin, or vice versa.

- More studies are necessary to define the relationship between sleep deprivation, cortisol metabolism, appetite-regulating hormones and the development of obesity.

  (Bose, Oliván & Laferrère 2009)
Stress, hormones and health

- Leptin, a key adipokine secreted by adipocytes in proportion to fat mass is responsible for sending signals to the CNS about status of fat stores and when to control food intake. When fat stores are adequate leptin concentrations diminish the drive to feed, while enabling energy production.

- Earliest experiments on mice to understand effect of leptin demonstrated that adrenalectomy obese leptin-deficient ob/ob mice lose weight suggesting a role of glucocorticoids in leptin metabolism (Dubuc & Wilden 1986).

- Administration of dexamethasone in both lean and obese patients increases serum leptin levels, suggesting that glucocorticoids play a role in the control of hyperleptinemia characteristic of obesity (Laferrère et al 2002).

- However, this effect of dexamethasone on leptin levels is seen only under fed conditions or after administration of glucose and insulin, demonstrating an interaction of cortisol, insulin, and positive energy balance on leptin regulation.

(Bose, Oliván & Laferrère 2009)
Stress, hormones and health

- Further, Leptin shows low values during the day and an increase during sleep, suggesting it to have a circadian rhythm.

- It is possible that nocturnal rise in leptin serves to suppress appetite.

- Sleep deprivation has been shown to decrease leptin level that may stimulate food intake and may be a plausible explanation for weight gain and metabolic disease.

(Bose, Oliván & Laferrère 2009)
Stress, hormones and health

- There is also considerable consistence evidence that stress adaptation due to maternal malnutrition during (or before) pregnancy, resulting in low birth weight (less than 2.5kg), may increase the risk for obesity and cardio-metabolic conditions in adulthood (Barker 1997). Also higher maternal BMI & weight along with infant birthweight above 4.0 Kgs is observed to be associated with DNA damage (Dass Singh et al. 2017) and shorter telomere length (Martens et al. 2016).

- HPA axis dysregulation has been associated with other eating disorders such as binge eating disorder, bulimia, and anorexia nervosa.

- Globally during recent times, overnutrition, sedentary lifestyle, and sleep deprivation are commonly observed in developed countries. Corresponding rise in obesity may at least partially be explained by mediation through the complex interplay of HPA axis, genetic polymorphisms, cortisol metabolism, inflammation, leptin, ghrelin, and sex hormones.

- There is scope for further research to elucidate mechanisms that HPA activity dysregulation contributes to obesity and other metabolic complications. (Bose, Oliván & Laferrière 2009)
Relationship between Liver and other organs
Relationship between Liver and other organs

Source: De’Mello & Swain 2011
Relationship between Liver and other organs

- Potential communication pathways between the liver and the brain are vagal afferents that can respond to immune mediators such as TNFα, IL-1β, and IL-6.

- These inflammatory cytokines can interact with their receptors on cerebral endothelial cells.

- These liver-to-brain communication pathways are still being researched but are now known to result in changes in central neural activity and, thereby, behavioural alterations such as fatigue, cognitive dysfunction, mood disorders, and sleep disturbances.

(De’ Mello & Swain, 2011)
Relationship between Liver and other organs

Lung-derived mediators are definitively upregulated by liver tissues in both *in vitro* and *in vivo* models of mechanical ventilation-induced inflammation.

Inflammation initiated in the lung releases inflammatory mediators (light grey arrow, right side) which then translocate to peripheral organs.

Pic Source: Patterson et al (2013)
Relationship between Liver and other organs

Reflect on previous knowledge from session 5 and 6
Activity

- Your client wishes to try intermittent fasting but is confused as has recently read the following online articles.
- Read & critically evaluate these news items reflecting on information learned in this session so far.
- List your recommendations.

https://www.medicalnewstoday.com/articles/321864.php

https://www.noted.co.nz/health/nutrition/michael-mosley-intermittent-fasting-diet-does-it-really-work/
Nutrients required to modulate HPA axis
Nutrients required to modulate HPA axis

- Dietary modification and nutritional interventions can positively influence the stress response.

- There is some evidence that maintaining optimal nutrition and balance of some micronutrients may improve the response of the HPA-axis to stress.

- The studies have mainly investigated effect of nutrient interventions on endocrine response (cortisol) and physiological responses to stress (such as sleep or anxiety).

(Brown 2018, Waladkhani & Hellhammer 2008, Head & Kelly 2009)
Nutrients required to modulate HPA axis

VITAMIN B COMPLEX

- Several human clinical studies have reported positive effects on mood, cognition and general health after multivitamin supplementation containing B-vitamins (B complex, mainly folate, B6 & B12) (Camfield et al. 2013).

- After four weeks supplementation with high dose B vitamins, a sample of 300 healthy adult, self reported on an in-depth assessment tool, an improved stress response in a multiple-dose, double-blind, placebo-controlled, double-centre study.

(Schlebusch et al. 2000)
Nutrients required to modulate HPA axis

Could you suggest mechanism of action of B vitamins on stress response?

See 1 citation found by title matching your search:

The effects of multivitamin supplementation on diurnal cortisol secretion and perceived stress.

Abstract
Recent evidence suggests that dietary intake of vitamins, in particular the B-vitamins including B6, B9 and B12 may have a number of positive effects on mood and stress. Given the effects of stress on a range of biological mechanisms including the endocrine system, it could be reasonably expected that multivitamin supplementation may also affect markers of these mechanisms such as diurnal cortisol secretion. In the current double-blind placebo-controlled study 138 adults (aged 20 to 50 years) were administered a multivitamin containing B-vitamins versus placebo over a 16-week period. Salivary cortisol measurements were taken at waking, 15-min, 30-min and at bedtime, at baseline, 8-weeks and 16-weeks. Perceived Stress (PSS) was measured at baseline, 8-weeks and 16-weeks, while blood serum measures of B6, B12 and homocysteine (Hcy) as well as red cell folate (B9) were also collected at these time points. A significant interaction was found between treatment group and study visit for the Cortisol Awakening Response (CAR). Compared to placebo, at 16-weeks multivitamin supplementation was found to be associated with a near-significant trend towards an increased CAR. No significant differences in PSS were found between groups, with PSS increasing in both groups across the course of the study. Red cell folate was found to be significantly correlated with the CAR response at 16-weeks while Hcy levels were not found to be associated with the CAR response, although Hcy significantly correlated with waking cortisol levels at 8-weeks. A possible interpretation of the elevation in CAR associated with multivitamin supplementation is that this represents an adaptive response to everyday demands in healthy participants.
Nutrients required to modulate HPA axis

OMEGA 3

- Studies have shown that omega-3, including docosahexaenoic acid (DHA), might have beneficial effects on somatic and mental health, possibly through mitigating effects on the immune/inflammation, HPA-axis and the ANS.

  (Thesing, etal 2018, Sculley 2014)

- In a study of 41 women (residing in the Mediterranean region), women with a higher dietary intake of monounsaturated fatty acids and a lower intake of saturated fatty acids were observed to display a normalized decline in cortisol levels from morning to night (Garcia-Prieto etal 2007).
Nutrients required to modulate HPA axis

OMEGA 3

- The Netherlands Study of Depression and Anxiety conducted on 2724 participants, reported significant negative association between n-3 PUFA and higher levels of inflammation markers (C-reactive protein, interleukin-6, tumor necrosis factor alpha), evening cortisol and heart rate. Thus dysregulation of biological stress systems was significantly observed to be associated with lower n-3 PUFA and DHA plasma levels. (Thesing, et al. 2018)

- Additionally, omega 3 supplementation is reported to reduce cortisol in abstinent alcoholics and patients of depression (Brown 2018), anxiety and inflammatory markers in numerous cardiometabolic and mental conditions (anxiety, CVD, depression) (Keenan & Hipwell 2015, Sculley 2014).
Nutrients required to modulate HPA axis

OMEGA 3

- In a randomized, double-blind, placebo-controlled trial, the effects of omega-3 (300mg) with phosphatidylserine or a placebo was studied on perceived chronic stress and psychobiological stress responses to an acute laboratory stress protocol, at baseline and after the treatment period.

- Omega 3 supplementation was observed to attenuate cortisol in highly stressed individuals, and in cortisol low responders, a slight increase in cortisol after omega-3 PS supplementation was noted. Thus, the treatment effects of omega-3 PS may be best understood in terms of a normalization of the stress response (Hellhammer et al. 2012).
Nutrients required to modulate HPA axis

MAGNESIUM

- A strenuous exercise/athletic activity is a form of physical stressor, that activates HPA axis and SNS, thus inducing changes in different hormones levels as well as interleukin 6 (IL-6). IL-6 modulates stress response and could modulate HPA axis and cortisol release from the adrenal glands. A 4-week Mg supplementation (500 mg /d) to rugby players (n=23) lead to significant increase in ACTH reductions in cortisol concentrations attenuated IL-6 level demonstrating influence of Mg supplementation on HPA axis activity. (Dmitrašinović etal 2016)

- Mg supplementation was found to significantly decrease serum cortisol concentration among elderly people with insomnia. (Abbasi etal 2012)

- Mg deficiency is also associated with increased inflammatory stress (higher IL6, IL1, TNF-α and CRP) that may translate into pathological conditions (Nielsen 2018).
Nutrients required to modulate HPA axis

VITAMIN C

- Vitamin C helps reduce both the physical and psychological effects of stress on humans (Brown 2018)

- Treatment with vitamin C has been shown to reduce cortisol reactivity to acute physiological stress (Brody et al. 2002); exercise-induced increase in serum cortisol among marathon runners (Peters, Anderson & Theron 2001), may reduce anxiety (de Oliveira et al. 2015) and inflammatory markers observed in diseases arising from chronic stress (Traber & Stevens 2011).

People who have high levels of vitamin C do not show the expected mental and physical signs of stress when subjected to acute psychological challenges. What’s more, they bounce back from stressful situations faster than people with low levels of vitamin C in their blood!!!!!!!!!!!!!!!

(Psychology today 2003)
Nutrients required to modulate HPA axis

PROBIOTICS

- Intestinal microbiota can affect stress susceptibility and stress-induced symptoms through neural, endocrine, and immune signalling mechanisms.

- Animal data is quite consistent that probiotics can modulate gut microbiota composition strengthen gut epithelium barrier function, and reduce cytokine production. It has also been suggested that gut microbiota-derived peptidoglycan (the cell wall constituent of most bacteria), can translocate into the brain and activate specific pattern recognition receptors of the innate immune system and thereby affect brain development and behaviour (Arentsen et al. 2017, Farzi, Fröhlich, Holzer 2018, Cenit, Sanz, Codoner-Franch 2017).

- A combination of *Lactobacilli* and *Bifidobacterium* is observed to decrease acute stress, cortisol, stress-dependent behavioral disorders & depression in mice. (Azad et al. 2018, Hadizadeh, Hamidi & Salami 2019)
Nutrients required to modulate HPA axis

PROBIOTICS

- The probiotic *Lactobacillus casei* (Shirota) has been shown to have positive psychological effects by improving mood disturbances in the elderly and reducing anxiety symptoms in patients with chronic fatigue syndrome.

- Academic stress-induced increases in salivary cortisol levels of medical students (N=149) and the incidence rate of physical symptoms were significantly suppressed in the supplemented group compared with the placebo group after 8 weeks intervention, possible through vagal afferent signalling to the brain and reduced stress reactivity (Takoda et al. 2017).

*However it cannot be overlooked that the study was sponsored by the producers of Yakult brand.*
Integration of mind and body

Mindful activity with music
Integration of mind and body

- There is accumulating evidence on diverse types of mind–body practices/training (MBT) and their impact on chronic stress and stress management.

- Most common MBT’s are yoga, Nei Yang Gong (also known as Dejian), mindfulness, meditation, mindfulness-based cognitive therapy, mindfulness-based stress reduction, guided imagery, breathing exercises, progressive relaxation, Tai Chi Chuan, and mindfulness-based positive behaviour support (Muehsam et al 2017, Morgon et al 2014).

- There is evidence-based discussions on including these practices in clinical settings to ensure wellness and support positive health outcomes though there is paucity of homogenous studies and consistent results (Goyal et al 2014).
Integration of mind and body

- A cross-sectional study showed that high vs. low mindfulness was associated with improvements in markers of cardiovascular health, including smoking, body mass index, fasting glucose and physical activity (Muehsam et al. 2017).

- A systematic review and meta-analysis of randomized controlled trials (42 studies) reported that practices of yoga is associated with improved regulation of the SNS & HPA axis in various populations (Pascoe, Thompson & Ski 2017).

- Yogic practices may reduce anxiety and stress though more robust studies and consistent data is required (Li & Goldsmith 2012).
Integration of mind and body

Biological mechanisms of mind Body therapies.

Picture source: Muehsam et al. (2017)
## Integration of mind and body

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mindfulness</td>
<td>Being aware of the present moment and present thoughts in a nonjudgmental way. Often taught by a trained instructor in sessions for several weeks in conjunction with home practice.</td>
</tr>
<tr>
<td>Mindful parenting</td>
<td>Parents learn meditation and mindfulness skills that they can exercise when interacting with children.</td>
</tr>
<tr>
<td>Yoga</td>
<td>A movement-based therapy that incorporates physical poses and attention to breath. Taught by a trained instructor.</td>
</tr>
<tr>
<td>Nei Yang Gong</td>
<td>A movement-based therapy that uses a sequence of slow movements, mental exercises, and breathing exercises. Similar to qigong or t’ai chi, it also incorporates the Chinese theory of qi.</td>
</tr>
<tr>
<td>Acceptance Commitment Therapy</td>
<td>A type of cognitive–behavioral therapy that includes mindfulness aspects. It emphasizes a nonjudgmental stance when monitoring thoughts. The commitment component is an active process on identifying life values and promoting behaviors that work toward them.</td>
</tr>
</tbody>
</table>

(Muehsam et al. 2017)
Integration of mind and body

- While the broad diversity of study designs and MBTs studied presents a patchwork of results requiring further validation through replication and longitudinal studies, clear themes emerge for MBTs as immunomodulatory, with effects on leukocyte transcription and function related to inflammatory and innate immune responses, and neuromodulatory, with effects on brain function and morphology relevant for attention, learning, and emotion regulation.

- Further studies among large group of humans is required to establish health benefits of MBT’s.

(Muehsam etal 2017)


References


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