When Neuroendocrinology and Immunology Meet: Practical Considerations

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Objectives

• Illustrate how the immune system controls endocrine organs and function

• Understand the impact of antibodies directed to G-protein coupled receptors

• Review the role of androgens in chronic conditions, inflammation, and immunity

• Demonstrate how sex steroids control neuroinflammatory processes in the brain and show the complexity of the stress response
Let’s get physical

No Gain without Pain

Target Group

- Longterm moderate-intensity exercise
  - improves psychological and physiological well-being
  - Reduces anxiety and depression
  - Decreases cortisol
  - Increases DHEA, GH, IGF-1

Cotman & Berchtold 2002
Petruzzello et al. 1991
Barbour et al. 2007
Muscular strength in male adolescents and premature death: cohort study of one million participants

Objectives To explore the extent to which muscular strength in adolescence is associated with all cause and cause specific premature mortality (>5 years).

Design Prospective cohort study.

Setting Sweden.

Participants 1,425,989 Swedish male adolescents aged 16–19 years were followed over a period of 24 years.

Main outcome measures Baseline examinations included knee extension, handgrip, and elbow flexion strength tests, as well as measures of diastolic and systolic blood pressure and body mass index. Cox regression was used to estimate hazard ratios for mortality according to muscular strength categories (tertiles).

This study provides strong evidence that a low level of muscular strength in late adolescence, as measured by knee extension and handgrip strength tests, is associated with all cause premature mortality to a similar extent as classic risk factors such as body mass index or blood pressure. Muscular strength is also associated with premature mortality due to cardiovascular disease but not due to cancer. Finally, our data suggest that low muscular strength is associated with an increased risk of mortality due to suicide, supporting the notion that physically weaker people might also be mentally more vulnerable. Low muscular strength should be considered an emerging risk factor for major causes of death in young adulthood.

Editorial: A Healthy Body in a Healthy Mind—and Vice Versa—The Damaging Power of “Uncontrollable” Stress

George P. Chrousos and Philip W. Gold
National Institutes of Health
Bethesda, Maryland 20892

Stress and disorders of the stress system

[Diagram showing stress system and associated disorders]
Role of emotional stress in the pathophysiology of Graves' disease

The role of stress in the pathophysiology of Graves' disease is suggested by several clinical observations, by recent advances in immunology and by better understanding of autoimmune diseases which provides new insights into potential effects of stress hormones on T helper cell imbalance involved in the pathogenesis of autoimmune diseases. Stress management should therefore be an important part of the treatment of Graves' disease, as stress reduction may improve the effect of therapy. However, this field still requires interventional data to support stress management in the treatment of Graves' disease.

Figure 1 Proposed role of stress hormones in Graves' disease pathophysiology. The major Th cells involved in Graves' disease are Th2. Recently, Th17 has been described both in mice and humans to favor the production of the pathogenic antibody directed against the TSH receptor by B lymphocytes. Stress hormones can induce production of IL4, IL6, and IL12 by DC. Stress hormones can induce direct stimulation of Th2, and Th17 or Th1. Immature DCs induce apoptosis in Treg cells. Treg cells could not act like regulators of Th2 and Th17 effector cells that are supposed to both be pathogenic in Graves' disease: i) Treg cells have been found to be low in patients with untreated Graves' disease and inversely correlated to serum concentration of TSH receptor antibodies; and ii) intrathyroidal steroid treatment could restore their function.

The Effects of Salsalate on Glycemic Control in Patients With Type 2 Diabetes
A Randomized Trial

Allison B. Goldfine, MD; Vivian Pomerance, MD; Kathleen A. Jablonski, PhD; Lanzo Pyle, MS; Myrtle A. Slaten, MD; and Steven L. Shoelster, MD, PhD, for the TWINAL-T2D (Targeting Inflammation Using Salsalate in Type 2 Diabetes) Study Team*

Patients: Persons aged 18 to 75 years with fasting plasma glucose concentrations of 12.5 mmol/L or less (≤225 mg/dL) and hemoglobin A1c (HbA1c) levels of 7.0% to 9.5% treated by diet, exercise, and oral medication at stable doses for at least 8 weeks.

Intervention: After a 4-week, single-masked run-in period, patients were randomly assigned to receive placebo or salsalate in doses of 3.0, 3.5, or 4.0 g/day for 14 weeks (27 patients each) in addition to their current therapy.

Conclusion: Salsalate lowers HbA1c levels and improves other markers of glycemic control in patients with type 2 diabetes and may therefore provide a new avenue for treatment. Renal and cardiac safety of the drug require further evaluation.

Primary Funding Source: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.


www.amjals.org
Myths, Presumptions, and Facts about Obesity

CONCLUSIONS
False and scientifically unsupported beliefs about obesity are pervasive in both scientific literature and the popular press. (Funded by the National Institutes of Health.)

<table>
<thead>
<tr>
<th>Table 3: Facts about Obesity</th>
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<tbody>
<tr>
<td>Fact</td>
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<tr>
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<tr>
<td>Although genetic factors play a large role, heritability is not destiny; caloric content and physical activity are important.</td>
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<tr>
<td>Diet (i.e., reduced energy intake) very effectively reduces weight, but trying to go on a diet or recommending that someone go on a diet generally does not work well in the long term.</td>
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<tr>
<td>Regardless of body weight or weight loss, an increased level of exercise increases health.</td>
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<td>Physical activity or exercise in a sufficient dose aids in long-term weight maintenance.</td>
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<td>Continuation of conditions that promote weight loss promotes maintenance of lower weight.</td>
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<tr>
<td>For overweight children, programs that involve the parents and the home setting promote greater weight loss or maintenance.</td>
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<tr>
<td>Some pharmacological agents can help patients achieve clinically meaningful weight loss and maintain the reduction as long as the agents continue to be used.</td>
</tr>
<tr>
<td>In appropriate patients, bariatric surgery results in long-term weight loss and reductions in the risk of incident diabetes and mortality.</td>
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</table>

Endocrine hypertension: What is new?

Christian A. Koch
Rev Port Endocrinol Diabetes Metab. 2012;7(2):52-61

Obesity is a global health problem, most of which can probably be improved by changing dietary habits, with less consumption of processed and preserved foods and by increasing physical activity to combat the various hormonal imbalances that have developed in many individuals. Among the factors responsible for, or observed in, endocrine hypertension, are excessive increases in the action of hormones, including aldosterone, mineralocorticoids, cortisol, and catecholamines (or by their action through the sympathetic nervous system), growth hormone, thyroid hormone, and parathyroid hormone. On the other hand, insulin resistance and deficiency of growth hormone, testosterone, vitamin D, and thyroid hormone may also be seen to contribute in patients with endocrine hypertension. A review is presented of recent advances in the traditional adrenal causes of endocrine hypertension and some non-traditional aspects of endocrine hypertension are illustrated, including our hypothesis that addiction to food, sweets, and salt are the main issues in many societies, and should be approached holistically and by the ancient philosophical method that a healthy mind will lead to a healthy body.

areas. Dopamine plays an important role in addictive behaviors, including compulsive shopping, eating, sodium appetite, gambling, and hypersexuality. Enkephalin surges in an anteromedial quadrant of the dorsal neostriatum have recently been found to contribute to generating intense consumption of palatable food. like aspartame can affect perceived taste. German researchers have recently shown that obese children (age 6 to 18 years) have less sensitive taste buds when undergoing a paper strip test with the taste qualities, sweet, sour, salty, bitter and umami (savory). In that study, obese children rated sweet samples consistently as less sweet than did the normal-weight children. A sixth basic taste
Testosterone Deficiency as a Risk Factor for Cardiovascular Disease

Ullah et al., Horm Metab Res 2011
Sleep and Immune Function

Blockade of mineralocorticoid receptors (spironolactone) enhances naïve T-helper cell counts during early sleep in humans (Brain Behav Immunol Oct 2012)

Circadian Integration of Metabolism and Energetics

Joseph Sass, et al.
Science 330, 1348 (2010)
Quetiapine-induced sleep-related eating disorder-like behavior: a case series

Sadeka Tamanna, M. Rehmat Ali, Chelle R Pope, Garland Holtzman, and Christian A Koch

Figure 1: Potential mechanism of quetiapine-induced SRED and somnambulism. SRED: sleep-related eating disorder. SWS: slow wave sleep. VLPO: ventrolateral preoptic nucleus.

Tamanna et al. Journal of Medical Case Reports 2013, 6:380

Review Article

Neuroendocrine Alterations in Obese Patients with Sleep Apnea Syndrome

Fabio Lanfranco, Giovanna Motta, Marco Alessandro Minetto, Matteo Baldi, Marcella Balbo, Ezio Ghigo, Emanuela Arvat, and Mauro Maccario

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Volume 2010, Article ID 474531, 11 pages

tdoi:10.1155/2010/474531

Obstructive sleep apnea syndrome (OSAS) is a serious, prevalent condition that has significant morbidity and mortality when untreated. It is strongly associated with obesity and is characterized by changes in the serum levels of secretory patterns of several hormones. Obese patients with OSAS show a reduction of both spontaneous and stimulated growth hormone (GH) secretion coupled to reduced insulin-like growth factor-I (IGF-I) concentrations and impaired peripheral sensitivity to GH. Hyperinsulinemia and chronic sleep fragmentation could affect the sleep-entrained prolactin (PRL)-rhythm. A disrupted Hypothalamus-Pituitary-Adrenal (HPA) axis activity has been described in OSAS. Some derangement in Throid-Stimulating Hormone (TSH) secretion has been demonstrated by some authors, whereas a normal thyroid activity has been described by others. Changes of gonadal axes are common in patients with OSAS, who frequently show a hypogonadotropic hypogonadism. Altogether, hormonal abnormalities may be considered as adaptive changes which indicate how a local upper airway dysfunction induces systemic consequences. The understanding of the complex interrelations between hormones and OSAS may allow a multi-disciplinary approach to obese patients with this disturbance and lead to an effective management that improves quality of life and prevents associated morbidity or death.
Complex multidirectional interactions between testosterone and obesity, metabolic syndrome, and type 2 diabetes mediated by cytokines and adipokines leading to comorbidities such as ED and increased CVD risk.

Wang C et al. Diab Care 2011;34:1669-1675
ANDROGENS AND CORONARY ARTERY DISEASE
Chapter 16
Carolyn A Allan, Department of Obstetrics and Gynaecology, Monash University, Clayton, Victoria 3168, Australia Moulinath Banerjee, Cardiovascular Research Group, Manchester University, 43 Grafton Street, Manchester M13 9NT
Fredrick C.. Wu, Department of Endocrinology, Manchester Royal Infirmary, University of Manchester, Oxford Road, Manchester M13 9WL, United Kingdom
Revised 24 JAN 2011
http://www.endotext.org/male/male16/maleframe16.htm

The hepatic expression and activity of both HL and SR-B1 was shown to be upregulated by testosterone and downregulated by estradiol. In addition, estradiol up-regulates the hepatic expression and secretion of apoA-I. These actions of testosterone and estradiol are in good agreement with their lowering and increasing effect on HDL cholesterol, respectively. In addition, both testosterone and estradiol stimulate SR-B1 expression in macrophages and thereby cholesterol efflux from these cells onto lipidated HDL.

**Figure 1** Pathways of HDL metabolism and regulation by testosterone and estradiol

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**Conclusion**

Sex differences in CAD cannot be explained on the basis of ambient testosterone exposure

Androgens can exert both beneficial and deleterious actions on myriad factors implicated in the pathogenic mechanisms of atherosclerosis and CAD

It is not possible to determine the net effect of testosterone on CAD

http://www.endotext.org/male/male16/maleframe16.htm

Differentiate between

1. The concern for the possibility of cardiovascular side effects in androgen treatment of endocrine and non-endocrine conditions
2. Whether testosterone may be used for the prevention or even treatment of CAD

One cannot extrapolate from cross-sectional observational data examining cardiovascular risk factors, or in vitro data studying isolated mechanisms with pharmacological doses of androgens, to assume manipulation of the sex steroid milieu will result in clinical benefits in a complex multifactorial condition such as CAD
Conclusion

Randomized controlled interventional studies recently have **not confirmed estrogens to be effective in primary or secondary prevention of CAD in women**

In the **absence of such information on testosterone and DHEA in men** at present, **priority should be established modes of intervention with a proven effect in preventing and treating CAD, i.e. weight reduction, smoking cessation, exercise, aspirin, antihypertensives, etc.**

In men with established testosterone deficiency, there are **no good data to suggest that physiological testosterone replacement therapy is associated with increased cardiovascular risk**

**Androgen deprivation therapy in treating men with prostate cancer does increase cardiovascular risk.** Such men should have cardiovascular risk factors identified and treated.

http://www.endotext.org/male/male16/maleframe16.htm

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**Mixed Forms of Hypogonadism**

(mainly in men age >30)

- **Aging**
  - Weight change of > 15% = change in T and free T
  - 2,736 men age 40-79 y
  - European male ageing study
  - Eur J Endocrinol 2013; Feb, 445

- **Alcoholism**

- **Glucocorticoid therapy**

- **Type 2 diabetes**
  - Can men prevent diabetes with testosterone boost?
  - T4DM = Testosterone 4 the prevention of DM
  - 1,500 men aged 50-74, Victoria, Western Australia, University of Adelaide

- **Cardiovascular disease**

- **Hemochromatosis**

- **Systemic illness (sickle cell, liver failure, chronic kidney disease, HIV)**

- **etc.**
High Prevalence of Testosterone Deficiency
= check serum testosterone

- Small testes (< 5 ml)
- Infertility
- Erectile dysfunction
- Type 2 diabetes (strongest link !, 50% of men > 45 y)
- Metabolic syndrome
- Osteoporosis and low trauma fracture
- Moderate / severe COPD
- Obstructive sleep apnea
- Inflammatory arthritis
- Medications (i.e. glucocorticoids, opioids)
- End-stage renal disease
- HIV
- Hemochromatosis
Lipids

Glycemic control

Inflammatory markers

- IL-6 ↓ after 3-16 wks of testosterone
- CRP ↓ after 3 wks – 3 mo
- TNFα↓ and IL-1β↓ after 4 wks
Is testosterone immunosuppressive in a condition-dependent manner? An experimental test in blue tits

The effects of T on immunity can be either immune-enhancing or immunosuppressive, depending upon the condition of the individual, its life history stage, as well as on the immune challenge employed.

Table 1. Means and standard errors of immune responses of male blue tits by dietary and testosterone treatment during moult 2006 and in spring 2007

<table>
<thead>
<tr>
<th></th>
<th>Dietary treatment</th>
<th>Testosterone (T) treatment</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Enhanced</td>
<td>Standard</td>
<td>High T males</td>
<td>Control males</td>
</tr>
<tr>
<td>Moult 2006</td>
<td>0.32±0.04</td>
<td>0.33±0.04</td>
<td>0.33±0.04</td>
<td>0.33±0.04</td>
</tr>
<tr>
<td>Anti-PHA response (units)</td>
<td>0.81±0.06</td>
<td>0.78±0.06</td>
<td>0.78±0.37</td>
<td>0.80±0.63</td>
</tr>
<tr>
<td>Anti-5SRP antibody response</td>
<td>0.9±0.42</td>
<td>0.6±0.02</td>
<td>0.5±0.50</td>
<td>0.3±0.40</td>
</tr>
</tbody>
</table>

For details of statistical tests, see text. PHA, phytohaemagglutinin; SPBC, sheep red blood cell; T, testosterone.

The Journal of Experimental Biology 212, 1811-1818

Hyperandrogenism exerts an anti-inflammatory effect in obese women with polycystic ovary syndrome

weight and IL-6 were related to the rise in CRP. We propose that hyperandrogenism in PCOS may exert an anti-inflammatory effect when obesity is present, but may not promote inflammation in the disorder; and that circulating androgens have a pleiotropic effect on inflammation depending on the combination of PCOS and weight status in a given individual.

Table 4. CRP levels at baseline (0 month) and after 3 and 6 months of GnRH agonist treatment in women with PCOS, and in control subjects

<table>
<thead>
<tr>
<th></th>
<th>CRP (mg/l)</th>
<th>GnRH agonist treatment months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>PCOS</td>
<td>2.0±0.3</td>
<td>1.5±0.6</td>
</tr>
<tr>
<td>Obese</td>
<td>3.9±0.9</td>
<td>11.5±4.3</td>
</tr>
<tr>
<td>Controls</td>
<td>1.7±0.7</td>
<td>0.5±0.2</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SE. FFA free fatty acids; IL-6 interleukin-6; CRP C-reactive protein; GnRH gonadotropin-releasing hormone agonist

Concentrations in 3 ml units: CRP <5.24 (normal), IL-6 <1.5 (normal), P<0.05

* Obese PCOS, 0 vs. 6 months, P<0.05

Endocrinology
DOI 10.1007/s00120-012-2326-6
High-Grade Prostate Cancer and Biochemical Recurrence After Radical Prostatectomy Among Men Using 5α-Reductase Inhibitors and Alpha-Blockers

BACKGROUND. Two clinical trials have shown that users of 5α-reductase inhibitors finasteride and dutasteride (5-ARIs) have reduced overall prostate cancer risk, while the proportion of high-grade tumors is increased. We studied tumor characteristics, risk of biochemical recurrence and mortality after radical prostatectomy in 5-ARI and alpha-blocker users.

RESULTS. The proportion of high-grade (Gleason 7–10) tumors was significantly elevated among men who had used 5-ARIs for 4 years or longer compared to the non-users (83.3% vs. 53.3%, respectively). Survival curves for biochemical relapse-free survival differed

CONCLUSIONS. Long-term users of finasteride or dutasteride had more often high-grade prostate cancer. Our results suggest also worse progression-free survival. The association

| TABLE II. Risk of Biochemical Relapse and Death From Any Cause after Radical Prostatectomy Among Men Using 5α-Reductase Inhibitors Compared to the Non-Users |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                | No. of relapses                | Age-adjusted HR (95% CI)        | Multivariable adjusted HR (95% CI) | No. of deaths                  | Age-adjusted HR (95% CI)        | Multivariable adjusted HR (95% CI) |
| 5-ARI usage                    | Non-users                       | 367                             | 1.30 (1.29–1.35)                   | 116                             | 0.82 (0.80–0.85)                   | 0.79 (0.77–0.80)                   |
|                                | Ever-use                        | 37                              | 1.00 (0.90–1.10)                   |                                  | 1.00 (0.90–1.10)                   |                                  |
| Cumulative number of DODs      | 1–200                           | 16                              | 0.99 (0.89–1.10)                   | 5                               | 1.11 (0.95–1.29)                   | 1.03 (0.88–1.22)                   |
|                                | 301 or more                     | 21                              | 1.21 (1.08–1.37)                   | 3                               | 0.56 (0.48–1.62)                   | 0.59 (0.49–1.66)                   |
|                                | Duration of usage               |                                 |                                  |                                  |                                  |                                  |
|                                | Less than 4 years               | 15                              | 1.08 (0.75–1.56)                   | 7                               | 0.80 (0.42–1.53)                   | 0.79 (0.36–1.75)                   |
|                                | 4 years or longer               | 24                              | 1.62 (0.89–2.97)                   | 1                               | 0.45 (0.07–2.63)                   | 0.50 (0.07–3.66)                   |
|                                | P_trend (differences)           | 0.18                            | 0.50                            | 0.21                            | 0.28                            |
Antiinflammatory effect of androgen receptor activation in human benign prostatic hyperplasia cells

Figure 3: Effect of DHT treatment on cytokine/chemokine/growth factor secretion by BPH cells. hBPH cells were cultured for 24 h with serum-free medium alone (untreated) or DHT (30 nM). Culture supernatants were analyzed with a bead-based multiplex assay. Experiments were performed in triplicate using four different hBPH cell preparations. Data are expressed as percentage of variation vs untreated. *P<0.05 vs untreated.

Journal of Endocrinology (2012) 214, 31–43

Antiinflammatory effect of androgen receptor activation in human benign prostatic hyperplasia cells

Journal of Endocrinology (2012) 214, 31–43

prevented by testosterone supplementation. We now investigated whether, in humans, hypogonadism was associated with more severe BPH inflammation and the in vitro effect of the selective androgen receptor agonist dihydrotestosterone (DHT) on cultures of stromal cells derived from BPH patients (hBPH). Histological analysis of inflammatory infiltrates in prostatectomy specimens from a cohort of BPH patients and correlation with serum testosterone level was performed. Even after adjusting for confounding factors, hypogonadism was associated with a fivefold increased risk of intraprostatic inflammation, which was also more severe than our data demonstrate that DHT exerts an immune regulatory role on human prostatic stromal cells, inhibiting their potential to actively induce and/or sustain autoimmune and inflammatory responses.
Testosterone treatment stimulates the formation of new myelin and reverses myelin damage in chronic demyelinated brain lesions.

The remyelinating actions of T could be mimicked by 5alpha-DHT (not converted to estrogens) and blocked by flutamide (androgen receptor antagonist).

Knockout of the AR in neurons and macroglial cells prohibits T from stimulating new myelin formation.

7alpha-methyl-19-nortestosterone (T analogue, developed for long-term male contraception and androgen replacement therapy in hypogonadism) does not stimulate prostate growth and promotes myelin repair.

Males with Multiple Sclerosis?

MS occurs 3 times more frequently in females.

MS is considered Th1-mediated.

Estrogens (17-beta E2) enhance T regs.

ERalpha is important to prevent axonal loss and monocyte infiltration into the CNS.

Pregnancy increases IL-10 and improves MS.

Sex hormones control neural growth factors: BDNF, GDNF, IGF-1, VEGF.

Progesterone (ERbeta ligand) is neuroprotective on oligodendrocyte differentiation.
Neurology, 2013 Jan 30. [Epub ahead of print]

Childhood obesity and risk of pediatric multiple sclerosis and clinically isolated syndrome.

RESULTS: We identified 75 newly diagnosed pediatric cases of MS or CIS, the majority of which were in girls (n = 41, 55%), age 11-18 (n = 54, 72%). Obesity was associated with a significantly increased risk of MS/CIS in girls (p = 0.005 for trend) but not in boys (p = 0.93). The adjusted odds ratio and 95% confidence intervals for CIS/MS among girls was 1.58 (0.71-3.50) for overweight compared to normal weight (reference category), 1.78 (0.70-4.49) for moderately obese, and 3.76 (1.54-9.10) for extremely obese. Moderately and extremely obese cases were more likely to present with transverse myelitis compared with normal/overweight children (p = 0.003).

??? – E2 from fat vs. pro-inflammatory state

CONCLUSION: Our findings suggest the childhood obesity epidemic is likely to lead to increased morbidity from MS/CIS, particularly in adolescent girls.
A proposed model of the role of different hormones in regulation of innate, and Th1 and Th2 cytokine profiles during pregnancy. The placenta also secretes IL-10 that may stimulate humoral and suppress cellular immunity.

Estradiol might amplify the effects of cortisol and NE. This hormonally induced Th2 shift may suppress Th1-related diseases such as RA and MS during pregnancy.

www.endotext.org, chapter 28

Effects of different hormones, neurotransmitters or neuropeptides on type 1/pro-inflammatory and type 2/anti-inflammatory cytokine production, the Th1/Th2 balance, and cellular vs. humoral immunity

Solid lines represent stimulation, while dashed lines inhibition.

Elenkov. www.endotext.org, chapter 28
**SLE**

- 90% of patients are women
- 7 of 286 men with SLE had Klinefelter's (Acta Paediatr 2011)
- SLE is modulated by estrogens
- Androgens may be protective but are not an appropriate therapy
- DHEA therapy was abandoned
- Oral contraceptives are safe
- Postmenopausal HRT is safe (cave: procoagulant activity)
Postulated Effects of Gonadal Steroids on B Lymphocytes

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Regulation</th>
<th>Potential Consequences</th>
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<tbody>
<tr>
<td>B lymphopoesis</td>
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<tr>
<td>Estrogens</td>
<td>Suppression</td>
<td>Unknown</td>
</tr>
<tr>
<td>Androgens</td>
<td>Suppression</td>
<td>Unknown</td>
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<tr>
<td>Checkpoints for autoreactivity</td>
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<td>Estrogens</td>
<td>Impairment</td>
<td>Increased propensity for autoimmunity</td>
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<tr>
<td>Androgens</td>
<td>Enhancement</td>
<td>Diminished propensity for autoimmunity</td>
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<td>Immunoglobulin class switching</td>
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<td>Estrogens</td>
<td>Enhancement</td>
<td>Enhancement of vaccine responses</td>
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<tr>
<td>Androgens</td>
<td>Inhibition</td>
<td>increased propensity for pathogenic autoimmunity</td>
</tr>
<tr>
<td>Progestins</td>
<td>Inhibition</td>
<td>increased propensity for pathogenic autoimmunity</td>
</tr>
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Sakiani et al., Nat Rev Endocrinol January 2013

- Estrogen and progesterone exert immune-modulatory and anti-inflammatory actions in the brain
- Both are neuroprotective in acute ischemic and demyelination brain damage
- Progesterone improves neuronal dysfunction after traumatic brain injury
- The brain is capable of steroidogenesis – neurosteroids (Baulieu 1981)
- Hippocampus-derived estrogen is remarkably higher than plasma estrogen
- Steroids also enter the brain from the peripheral circulation
"Neurosteroid": Baulieu 1981
DHEAS synthesized in the brain
Androstenedione, Pregnenolone,
DOC, tetrahydrometabolites of progesterone

"Neuroactive Steroid": can modify neural activities (independent of their origin), bind / modulate receptors, i.e.
• GABA
• NMDA
• AMPA
• 5-HT3

Neuroactive steroids and neurosteroids are proposed for treating epilepsy, head injury, posttraumatic stress disorder, depression, neurocognitive deficits

Neurosteroid-mediated regulation of brain innate immunity in HIV/AIDS: DHEA-S suppresses neurovirulence

Maingat et al., FASEB J 2013 (Feb)
DHEAS in “HIV”-like queens improves neurobehavioral performance

Differential genomic (nuclear) and nongenomic (extranuclear, cytoplasmic) actions of progesterone and endogenous steroid hormones

MPA + norethindrone (NET)

In genomic actions, all progestogens bind to the PR and act as agonists.

MPA is a partial to full agonist for the GR and AR

Norethindrone is a partial to full agonist for the AR

Progesterone is a weak agonist for the GR and AR, and a full antagonist for the MR

Maingat et al., FASEB J 2013 (Feb)
Prevalence and Impact of Hypogonadism in Cancer Patients with Muscle Wasting in a Phase IIb Enobosarm Trial

- Up to 50% of men with advanced cancer are hypogonadal at or during treatment
- 159 pts (men > 45 y, postmenopausal women), > 2% wt loss in prior 6 months
  BMI < 35; NSCL, colorectal cancer, NHL, CLL, or breast cancer
  T < 300 ng/dL
- 60% of men were hypogonadal at randomization
- Randomized to oral (1 or 3 mg) enobosarm or placebo daily for 16 wks
- Stair climb power higher among eugonadal men compared to hypogonadal
  (85 Watts vs 71 Watts)
- Enobosarm significantly improved physical function, more so in hypogonadal subjects

Dobs et al. Endocr Rev 2012; Abstract SUN-261
G Protein Coupled Receptors

An estimated 70% of prescription drugs are targeting GPCRs

Drugs can be GPCR agonists, antagonists, allosteric modulators/GPCR ligands
   (i.e. calcimimetics / CaSR modulators)
   Muscarinic receptors
   Serotonergic GPCRs

“orphan” GPCR (no knowledge of respective physiologic agonist)

GPR91, GPR99 – renin release
GPR40 – expressed in beta cells
GPR54 – hypogonadism

Hudson BD et al., Curr Top Med Chem 2013
Future therapy for Graves’ orbitopathy?
see Neumann S et al., Thyroid 2012, on drug-like TSHR antagonists in Graves’ orbital fibroblasts
G Protein Coupled Receptors

**Loss of function** mutations in GPCRs and disorders:

**Resistance** to normal agonist action, i.e.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Disorder</th>
</tr>
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<tbody>
<tr>
<td>Melanocortin 4</td>
<td>obesity</td>
</tr>
<tr>
<td>CaSR</td>
<td>familial hypocalciuric hypercalcemia</td>
</tr>
<tr>
<td>TSH</td>
<td>familial hypothyroidism</td>
</tr>
<tr>
<td>LH</td>
<td>male pseudohermaphroditism</td>
</tr>
<tr>
<td>GPR54</td>
<td>hypogonadotropic hypogonadism</td>
</tr>
<tr>
<td>GHRH</td>
<td>familial GH deficiency</td>
</tr>
<tr>
<td>V2 vasopressin</td>
<td>nephrogenic DI</td>
</tr>
</tbody>
</table>

**Gain of function** mutations in GPCRs and disorders, i.e.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>familial nonautoimmune hyperthyroidism</td>
</tr>
<tr>
<td>CaSR</td>
<td>familial hypocalcemic hypercalciuria</td>
</tr>
<tr>
<td>V2 vasopressin</td>
<td>nephrogenic inappropriate antidiuresis</td>
</tr>
<tr>
<td>LH</td>
<td>familial male precocious puberty</td>
</tr>
</tbody>
</table>
Octreoscan
• Sarcoidosis
• Graves’
• Medullary thyroid cancer
• Metastatic pheochromocytoma
• GEP-NET
• Breast cancer
• Prostate cancer
• and other conditions
Endocrine and Autoimmune Aspects of the Health History of John F. Kennedy

Leo R. Mandel, MD, MPH

At the age of 43 years, John F. Kennedy was the youngest man ever elected president. Throughout both his campaign and his presidency, he was portrayed as the epitome of youth and vigor. In fact, he had the most complex medical history of anyone to occupy the White House. The recent opening of his White House medical records has provided researchers greater insight into the multiple medical conditions that afflicted Kennedy. A review of these records, coupled with other available sources, allows new understanding of his health history that can now be explained in the context of a unifying autoimmune endocrine disorder.

Figure: John F. Kennedy's medical profile.

The time of diagnosis of gastrointestinal symptoms, adrenal insufficiency, and hypothyroidism are plotted against Kennedy's body weight at various ages. Arrows indicate the timing of each event, and the references from which body weight information was obtained:
* Sibling of PT 330, August 1943.
† Addison disease diagnosed, September 1947.
‡ Hypothyroidism diagnosed, December 1964.
§ Suspended castration of gonadotropes, July to August 1960.
Antipituitary antibodies in patients with autoimmune and non-autoimmune thyroid disease

- 1290 patients with thyroid disorder
  - 961 autoimmune, 329 non-autoimmune
- 135 controls
- 11.4% of patients with AITD (Graves and Hashimoto) had APA
- Of 110 APA-positive AITD patients, 20 (18%) had autoimmune polyglandular syndrome
- 36 patients of 110 APA-positive (35%) had growth hormone deficiency after dynamic pituitary testing

Manetti L et al., J Clin Endocrinol Metab 2007

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**TABLE 3. Criteria for defining a disease as autoimmune**

1. According to Witebsky et al. (36)
   - Demonstration of circulating autoantibodies and/or cellular immuno-mediated events
   - Demonstration of lymphocytic infiltration in the target organs
   - Identification and characterization of autoantigens
   - Induction of the disease in animal models with the injection of autoantigens and passive transfer by serum or lymphocytes

2. According to Rose and Bona (37)
   - Direct proof (such as transfer of the disease by either pathogenic autoantibody or autoreactive T cells)
   - Indirect evidence (based on reproduction of the autoimmune disease in experimental animals)
   - Circumstantial evidence (lymphocyte infiltration of the affected organs, association with other autoimmune diseases, correlation with major histocompatibility complex genes and benefit from immunosuppressive therapy)

Betterle C et al., Endocrine Rev 2002
### TABLE 4. Prevalence of clinical autoimmune diseases in a cumulative population of 1240 patients with autoimmune adrenal disease

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>3.7–32</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>2.0–22.7</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>25</td>
</tr>
<tr>
<td>Chronic candidiasis</td>
<td>0.8–21</td>
</tr>
<tr>
<td><strong>Diabetes mellitus (type 1)</strong></td>
<td>1.2–20.4</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>1.2–20</td>
</tr>
<tr>
<td><strong>Hypergonadotropic hypogonadism</strong></td>
<td>4.5–17.6</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>0.8–16</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0.8–12</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>1.2–8</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>0.8–6</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>3.7</td>
</tr>
<tr>
<td>Inflammatory bowel diseases</td>
<td>2.4</td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
<td>2.4</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>1.6–3</td>
</tr>
<tr>
<td>Lymphocytic hypophysitis</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Betterle C et al., Endocrine Rev 2002

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**Key points**

- The type 1 autoimmune polyglandular syndrome results from mutations in the AIRE gene, which modulates transcription of peripheral self-antigens in the thymus presented by human leukocyte antigen (HLA) molecules to maturing T cells.
- The type 2 autoimmune polyglandular syndrome is the most frequent autoimmune polyglandular syndrome, with underlying pathologies that develop years to decades apart in an affected individual.
- Patients with Addison disease have a 50% risk of developing a second autoimmune disease during their lifetime.
- Mutations in HLA genes, which encode the MHC (major histocompatibility complex) class II molecules expressed by antigen-presenting cells, contribute to the targeting of specific tissues by autoreactive T cells.
- **Non-HLA genes** contribute to the risk of autoimmune disease, as they may reduce the threshold of autoimmunity or influence the organs affected in type 2 autoimmune polyglandular syndrome.
- IPEx (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) syndrome results from mutations in the forkhead box protein P3 (FOXP3) gene, which is necessary for normal function of regulatory T cells.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>APS-1</th>
<th>APS-2</th>
<th>IPEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>Rare</td>
<td>Common</td>
<td>Very rare</td>
</tr>
<tr>
<td>Onset</td>
<td>Infancy</td>
<td>Adulthood</td>
<td>Infancy</td>
</tr>
<tr>
<td>Relatives at risk</td>
<td>Siblings</td>
<td>Multiple generations</td>
<td>None</td>
</tr>
<tr>
<td>Genetics</td>
<td>Monogenic with AIRE gene mutations, autoimmune recessive</td>
<td>Polygenic associated with HLA-DR3 and HLA-DQA1 and/or HLA class II genes (MICA, HLA-DRB1, CTLA4, NPYR)</td>
<td>Monogenic with FOXP3 gene mutations, X-linked</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>Asplenia,</td>
<td>None</td>
<td>Immune dysregulation</td>
</tr>
<tr>
<td></td>
<td>multicellular candidiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1A diabetes</td>
<td>1.8%</td>
<td>20%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>100% anti-thyroid autoantibodies</td>
<td>Steroid 21-hydroxylase, TPO, Tg, Insulin, IA-2, GAD, ZnT8, Tg, others</td>
<td>Present depending on disease manifestations</td>
</tr>
<tr>
<td>Common phenotype</td>
<td>Candidiasis, Addison disease, hyperparathyroidism</td>
<td>Addison disease, autoimmune thyroid disease, type 1A diabetes mellitus, celiac disease</td>
<td>Enteropathy, type 1A diabetes mellitus</td>
</tr>
</tbody>
</table>

Abbreviations: APS, autoimmune polyglandular syndromes; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; FOXP3, forkhead box P3 gene; GAD, glutamic acid decarboxylase; HLA, human leukocyte antigen; IFNs, immune deficiency, polyendocrinopathy, enteropathy, X-linked (IPEX); MICA, MHC class I-related gene A; IL2, interleukin 2; PTPN22, protein tyrosine phosphatase, non-receptor type 22; TPO, thyroid peroxidase; TG, thyroglobulin; Tg, tissue transglutaminase; NPYR, variable number tandem repeat in the 6' promoter of the insulin gene; ZnT8, Zn Nr3 transporter.

Check serum IgG4
### Table 2. Antidepressants, Neurotransmission and Cytokines

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Pharmacodynamics</th>
<th>Neurotransmission</th>
<th>Cytokines</th>
<th>Th1/Th2 Balance</th>
<th>Hypothetical Shift</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNRIs: Paroxetine, Sertraline, Fluoxetine, Escitalopram</td>
<td>NET inhibition (+ NET antagonism: paroxetine, HITC antagonism: Fluoxetine, DAT inhibition: Escitalopram)</td>
<td>Demonstration of neurotransmission: 5-HT1A receptor (5-HT1A(AC) receptors) → 5-HT firing reduced a decrease in 5-HT terminal receptors (a hyperstimulation of the receptors and demonstration of the 5-HT1 receptor) → NS firing (increased) NS in the PFC and hippocampus and DA release enhanced in PFC (only at high dose)</td>
<td>INF-γ, TNF-α, IL-12, IL-6 (low dose) IL-8 (high dose)</td>
<td>Th1 shift (low dose)</td>
<td>Th1 shift (high dose)</td>
<td>Vollenweider et al., 2004 [395] (others)</td>
</tr>
<tr>
<td>SNRIs: Duloxetine</td>
<td>NET inhibition + NET inhibition (only at high dose)</td>
<td>Demonstration of neurotransmission: 5-HT1A receptor (5-HT1A(AC) receptors) → 5-HT firing reduced a decrease in 5-HT terminal receptors (a hyperstimulation of the receptors and demonstration of the 5-HT1 receptor) → NS firing (increased) NS in the PFC and hippocampus and DA release enhanced in PFC</td>
<td>INF-γ, TNF-α, IL-12, IL-6, IL-8 (high dose)</td>
<td>Th1 shift (low dose)</td>
<td>Th1 shift (high dose)</td>
<td>Vollenweider et al., 2004 [395] (others)</td>
</tr>
</tbody>
</table>

### Immunomodulation Mechanism of Antidepressants: Interactions between Serotonin/Norepinephrine Balance and Th1/Th2 Balance

and cytokine production. The considerations on neuro-immunomodulation could represent an additional aid in the study of pathophysiology of psychiatric disorders and in the choice of specific antidepressants in specific clusters of symptoms, especially in comorbidity with internal pathologies. Furthermore limited data, reviewed here, have shown the effectiveness of some antidepressants as pure immunomodulators. However, these considerations are tentative and require experimental confirmation or refutation by future studies.

| SNRIs: Desvenlafaxine | NET inhibition + DAT inhibition (a NACH receptor agonist) | Demonstration of 5-HT terminal mono- and heteroreceptors (a hyperstimulation of the receptors and demonstration of the 5-HT1 receptor) → NS firing enhanced (increase in PFC and hippocampus) and DA release enhanced in PFC and in nucleus accumbens | INF-γ, TNF-α, IL-12, IL-6, IL-8 | Th1 shift | Stronkhorst et al., 2008 [358] |
| SNRIs: Venlafaxine | NET inhibition + NET inhibition (only at high dose) | Demonstration of 5-HT1A receptors (a hyperstimulation of the receptors and demonstration of the 5-HT1 receptor) → NS firing (increased) NS in the PFC and hippocampus and DA release enhanced in PFC (only at high dose) | INF-γ, TNF-α, IL-12, IL-6, IL-8, IL-10 | Th1 shift | Stronkhorst et al., 2013 [338] |

The while mechanisms and interactions between nerve, immune, and inflammatory processes, including the role of cytokines and other mediators, are crucial in the pathophysiology of psychiatric disorders. Antidepressants, particularly SNRIs, have been shown to modulate these processes, and understanding these mechanisms is critical for the development of more effective treatments.

**References:**
- Vollenweider et al., 2004 [395] (others)
- Stronkhorst et al., 2008 [358]
- Stronkhorst et al., 2013 [338]
- Kranz et al., 2002 [142]
- Kranz et al., 2004 [347]
Dendritic cells are

- linking innate and adaptive immunity
- the most potent antigen-presenting cells
- migrating into draining lymph nodes and presenting antigens to B cells for humoral immune responses or a cellular response by inducing naïve T lymphocytes

Various vaccination trials using Dendritic cells:
- Medullary thyroid cancer
- parathyroid cancer
- neuroendocrine pancreatic cancer
- adrenal cancer

Muehleisen et al., Vitamin D in allergic disease. J Allergy Clin Immunol 2013
Enhanced immunological response by dendritic cells in male hypogonadism

Background The effect of male hypogonadism on the immune response is poorly understood, even though testosterone has both immunosuppressive and anti-inflammatory effects in men.

Design In this study, we compared the distribution and functional status of peripheral blood (PB) monocytes, dendritic cells (DCs) CD161+ (monocyte), CD33+ (myeloid) and CD33+ (plasmacytoid) and CD4+ CD25+ CD127- regulatory T cells from hypogonadal men and control subjects. Immunophenotypic studies were performed both on resting and in vitro stimulated cells.

Conclusions These findings show an enhanced immunological response of circulating (activated) CD161+ DCs to antigen stimulation, which was inversely related to testosterone and gonadotropin serum levels. Such findings suggest a modulation by the hypothalamic–hypophyseal–gonadal axis of the immune response and may have clinical implications for hypogonadal men, as regards susceptibility to autoimmune diseases and increased responses to antigenic stimuli.


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Proof-of-Concept, Randomized, Controlled Clinical Trial of Bacillus-Calmette-Guerin for Treatment of Long-Term Type 1 Diabetes

Denise L. Faustman1, Linlin Wang1, Yoshiki Okubo1, Douglas Berger2, Linlin Ban1, Guotong Man1, Hui Zheng1, David Schoenfeld2, Richard Pompei3, Joseph Avrukh3, David M. Nathan2

1 The Immunology Laboratory, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, United States of America; 2Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, United States of America; 3Division of Allergy and Immunology, Massachusetts General Hospital, Boston, Massachusetts, United States of America

Background: No targeted immunotherapies reverse type 1 diabetes in humans. However, in a rodent model of type 1 diabetes, Bacillus Calmette-Guerin (BCG) reverses disease by restoring insulin secretion. Specifically, it stimulates innate immunity by inducing the host to produce tumor necrosis factor (TNF), which, in turn, kills disease-causing autoantibodies and restores pancreatic beta-cell function through regeneration.

Methodology/Principal Findings: Translating these findings to humans, we administered BCG, a generic vaccine, in a proof-of-principle, double-blind, placebo-controlled trial of adults with long-term type 1 diabetes (mean 15.3 years) at one clinical center in North America. Six subjects were randomly assigned to BCG or placebo and compared to self, healthy paired controls (n=6) or reference subjects with (n=57) or without (n=16) type 1 diabetes, depending on the outcome measure. We monitored weekly blood samples for 20 weeks for insulin-autoreactive T cells, regulatory T cells (Tregs), glutamic acid decarboxylase (GAD) and other autoantibodies, and C-peptide, a marker of insulin secretion. BCG-treated patients and one placebo-treated patient, who, after enrollment, unexpectedly developed acute Epstein-Barr virus infection, a known TNF inducer, exhibited increased insulin secretion in dead insulin-autoreactive T cells and induction of Tregs. C-peptide levels (pg/mL) significantly rose transiently in two BCG-treated subjects (mean: 3.49 pmol/L [95% CI 2.95–3.30], 2.57 [95% CI 1.65–3.46]) and the EBV-infected subjects (3.16 [95% CI 2.54–3.69] vs. 1.65 [95% CI 1.35–2.3]) in reference diabetic subjects. BCG-treated subjects each had more than 50% of their C-peptide values above the 95th percentile of the reference subjects.

Conclusions/Significance: We conclude that BCG treatment or EBV infection transiently modified the autoreactivity that underlies type 1 diabetes by stimulating the host innate immune response. This suggests that BCG or other stimulators of host innate immunity may have a role in the treatment of long-term diabetes.
Never give up – be tough!

Growing Old Is Not For Sissies
Melatonin administered immediately before an intense exercise reverses oxidative stress, improves immunological defenses and lipid metabolism in football players.

6 mg of melatonin

Fig. 2. Evolution of the effect of acute exercise of high intensity and melatonin treatment on total antioxidant activity (TAS) in young male football players. Data are expressed as the mean ± S.E.M. of control and melatonin-treated group at baseline and at 15, 30 and 60 min after exercise. The control group showed a downward trend, in TAS values, statistically significant (*P<0.005 and **P<0.001) at 15 and 60 min respectively after high intensity exercise. However, the melatonin group maintained TAS values similar to baseline, 3 and 15 min after exercise and increased significantly, only after 60 min (**P<0.005) of exercise.

New perspectives in melatonin uses

**Immune system**
- Cytokine production
- T cell differentiation in spleen, thymus, lymph and bone marrow
- Phagocytes and antigen presentation
- Natural killer cell activity
- In autumn/winter: Mel secretion
- In lymphocytes TH2 IL-4 production
- In early phase: PLA2, LOX and Cytokines (IL-1, TNF-a)
- In chronic inflammation: PLA2, LOX and Cytokines

**Antioxidant properties**
- Scavenger of ROS and RNS
- GH synthesis
- mRNA of SOD, GSH and GSH enzymes
- Activity of SOD, GSH enzymes
- In Mitochondria
- Expression and activity of Complex I and IV of ETC
- ATP synthesis
- Membrane lipid peroxidation
- Mitochondrial GSH synthesis
- In DNA and nuclear DNA oxidation
- Mitochondrial permeability transition
- Cytochrome c release

**Nervous system**
- Induces sleep initiation
- Produces hypnosis
- Regulates circadian clock
- Suppresses neural firing
- NOS neuronal activity
- Neuronal Ca signaling
- Sedative and Neuroprotective effects
- Alzheimer disease (in Hippocampus)
- Parkinson disease (in Substantia Nigra and Striatum)
- mRNA of SOD2, GSH, CAT
- Normalizes mitochondrial oxidation status
- Mitochondrial NOX

**Gastrointestinal tract**
- Regulates intestinal motility
- Regulates intestinal ion transport
- Reverses intestinal Ca absorption inhibited by MEC
- Pancreatic digestive enzyme secretion
- Regulates endocrine pancreatic function
Are you ready for an injection or gel ???

Thanks !!!!