by overtraining syndrome (OTS) were compared to a two control groups, of healthy athletes (ATL) and healthy non-physically active controls (NPAC). Since none of the parameters were directly dependent on exercise or performance, differences between these two groups were unexpected. From the fact that several parameters were shown to be different between ATL and NPAC, we realized that the use of the reference ranges for general population to analyze results in athletes may potentially under- and over-diagnose a wide range of conditions. Our objective is therefore to determine whether athletes should be biochemically evaluated through specific adapted ranges, and propose preliminary adaptations in these ranges. **Methods**: A systematic review on the literature on endocrine and metabolic adaptations to exercise was performed, as well as a thorough analysis of the seven arms of the Endocrine and Metabolic Responses on Overtraining Syndrome (EROS) study. **Results:**Multiple reference ranges were shown to be inaccurate for athletes. Among the parameters that should be adapted for athletes, and their respective adaptedranges include: 1. Cortisol response to an insulin stimulation test (ITT) (> 20.5 µg/dL); 2. GH response to an ITT (> 12 µg/L); 3. Prolactin response to an ITT (> 22 ng/mL); 4. Salivary cortisol at 8AM (> 450 ng/dL); 5. Total testosterone (> 450 ng/dL); 6. Estradiol (25-45 pg/mL) - and testosterone-to-estradiol ratio maintained > 13.7; 7. Total nocturnal urinary catecholamines (> 220 µg/12h); 8. Resting lactate (< 1.0 nMol/L); 9. Measured-to-predicted basal metabolic rate (BMR) (> 105%); 10. Fat oxidation (in relation to total BMR) (> 50%); and 11. Hydration status (body water > 62% of total body weight). **Conclusion**: Analysis of biochemical parameters in athleted should be interpreted with cautious, particularly hormonal and metabolic parameters, once many parameters likely undergo adaptive changes when under physical activity. Preliminary adaptations for the ranges have been proposed.

Adrenal

ADRENAL PHYSIOLOGY AND DISEASE

Chronic Cortisol Works Through the Transcription Factor KLF9 to Deregulate Immune Response and Metabolism

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Chronically elevated levels of glucocorticoids (GC) are associated with a number of disease states and negative side effects, including metabolic syndrome. Epidemiological studies show that elevated GC during a brief but vulnerable developmental window can have life-long and potentially multi-generational impacts on health. To elucidate underlying pathogenic mechanisms, our lab has used chronic treatment with a physiological dosage of cortisol (CORT) in developing zebrafish, Danio rerio, a model organism that has emerged as a useful tool for investigating GC signaling. In this paradigm, we have found evidence that high CORT during development alters a set point for the HPA axis and leads to continuous induction of aberrant GC production and transport, accompanied by altered immune gene regulation and decreased ability to maintain blood glucose homeostasis. To identify molecular and genetic pathways perturbed by chronic CORT treatment, we used CRISPR to generate mutant lines lacking the glucocorticoid receptor (GR) or the transcription factor Klf9, which we have found to be an important target/regulator of GC signaling. We performed RNA sequencing in these mutant lines and compared the transcriptomes of wild type (WT) and mutant animals treated with either chronic CORT or vehicle control (VEH). A broad overview of the data shows similarities between CORT treated wild-type fish and VEH treated GR mutants suggestive of GC resistance in the CORT treated WT animals. In Klf9 mutants, a number of genes involved in immune processes that were upregulated by chronic CORT in WT animals were not similarly upregulated, suggesting that Klf9 is an important feed-forward mediator of immune gene regulation by GC. Additionally, CORT increased expression of a number of metabolic genes in Klf9 mutants that were not similarly upregulated in WT, suggesting that Klf9 plays a regulatory role in the response of cellular metabolism to GC. To further investigate Klf9's role in governing cellular metabolism, metabolic rate assays were performed on live animals. The results show that Klf9 mutants have lower total respiration, and that chronic CORT increases non-mitochondrial respiration in both WT and Klf9 mutants. Mitochondrial respiratory capacity was unaffected across conditions. This, coupled with gene expression data, suggests that measured metabolic differences are due to shifts in substrate usage and differential reliance on non-mitochondrial metabolic pathways such as glycolsis and peroxisomal beta-oxidation. Additional studies are required, but the regulation of glycolysis by Klf9 could contribute to this gene's known tumor-suppresive role, and regulation of peroxisomal metabolism—key in immune cells—could partially explain the role of Klf9 in mediating these cells' responsiveness to CORT.

Tumor Biology

TUMOR BIOLOGY: DIAGNOSTICS, THERAPIES, ENDOCRINE NEOPLASIAS, AND HORMONE DEPENDENT TUMORS

Interleukin-8 - a Possible Target for Melanoma Treatment? In-Vitro Studies Based on Human Melanoma Cell Models

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Previous clinical studies showed that menstruating females were better protected in melanoma than postmenopausal women and men of any age. In addition, epidemiological studies showed an increased male mortality in melanoma. But these studies did not correlate with steroid status in females. Our in-vitro study showed female sex hormone progesterone significantly inhibited human melanoma cell growth. Further in-vitro study showed that progesterone action was mediated by a specific suppression