

SLEEPING SICKNESS AND OTHER INFLAMMATORY CONDITIONS

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African trypanosomiasis (Sleeping sickness, SS;) is an anthroponozoonosis transmitted by the tsetse fly. Infection with *Trypanosoma brucei* in humans is associated with symptoms suggestive of endocrine dysfunction. Recent evidence suggests that experimental infection in animals with *Trypanosoma brucei* species causes polyglandular endocrine failure by local inflammation of the pituitary, thyroid, adrenal, and gonadal glands. In a cross-sectional study we demonstrated significant neuroendocrine abnormalities in Ugandan patients with SS. There was a high prevalence of adrenal insufficiency (27%), hypothyroidism (50%) and hypogonadism (85%). Pituitary function tests suggested an unusual combined central (hypothalamic/pituitary) and peripheral defect in hormone secretion. Specific therapy resulted in a rapid recovery of adrenal/thyroid function, whereas hypogonadism persisted for years in a substantial portion of patients. The presence of hypopituitarism correlated with high cytokine concentrations (TNF-alpha, IL-6) which together with direct parasitic infiltration of the endocrine glands are responsible for SS-associated endocrine dysfunction. In studies by other groups serine oligopeptidases of trypanosomatids are emerging as important virulence factors in trypanosome infections. For example, the oligopeptidase B (OpdB) from *Trypanosoma evansi*, a pathogen of significant veterinary importance, is released into the plasma of infected hosts where it retained catalytic activity and blocked endocrine effects of atrial natriuretic factor (ANF). In vitro, OpdB cleaved the peptide hormone ANF thereby abrogating smooth muscle relaxant and prohypotensive properties of ANF. The in vivo ANF half-life was reduced 5-fold in *T. evansi*-infected rats. These data suggest a role of oligopeptidases in hormone dysregulation in trypanosomiasis.

LOW GRADE INFLAMMATION IN CHRONIC INFECTIOUS DISEASES: THE PARADIGM OF PERIODONTAL INFECTIONS

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Increasing evidence implicates periodontitis, a chronic inflammatory disease of the tooth-supporting structures, as a potential risk factor for increased morbidity or mortality for several systemic conditions including cardiovascular disease (stroke, heart attacks and atherosclerosis), pregnancy complications (spontaneous preterm birth, SPB) and diabetes. The impact of periodontal infection on systemic diseases has been termed "Periodontal Medicine" and represents a new field of investigation. Cross-sectional, case-control and cohort studies indicate that periodontitis may confer two- and up to seven-fold elevations in the risk for cardiovascular disease and premature birth, respectively. Pilot intervention trials indicate that periodontal therapy may improve surrogate cardiovascular outcomes, such as endothelial function and may reduce by four to five-fold the incidence of prematurity. Recent findings emphasize that an enhanced systemic inflammatory response is a likely component of pathogenesis in these systemic complications. Clinical studies show that periodontitis patients have elevated markers of systemic inflammation, such as C-reactive protein (CRP), interleukin 6 (IL-6), haptoglobin and fibrinogen. This elevation appears to be evident even in patients with acute myocardial infarction (AMI), since AMI patients with periodontal disease have higher CRP levels than AMI patients without periodontal disease. Furthermore, recent intervention trials show that periodontal therapy may reduce systemic inflammatory markers, such as CRP and IL-6, supporting the

notion that periodontal disease is an independent contributor of systemic inflammation. This chronic, low-grade, systemic inflammatory response associated with periodontal disease is likely triggered by a blood-borne exposure to oral bacteria and bacterial products. Indeed, evidence of periodontal pathogens in plaque lesions of carotid arteries in biopsy specimens obtained from atherosclerotic patients has been provided by both immunohistology and PCR. Similarly, studies on fetal cord blood from SPB babies indicate a strong in utero IgM antibody response specific to several oral periodontal pathogens. This provides direct evidence that the fetus can be exposed to maternal oral pathogens in utero, which in turn may induce an inflammatory response at the fetal-placental unit leading to prematurity. Further study of the periodontal disease - systemic disease connection can provide insight into the mechanisms by which distant chronic infections can impact systemic health.

THYMUS SELF-ANTIGENS AS A WAY FOR RESTORING SELF-TOLERANCE IN TYPE 1 DIABETES

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A repertoire of neuroendocrine-related genes is transcribed in the parenchyma of the thymus in different species. This repertoire is organized in an "economical" way so that one dominant self-antigen per each neuroendocrine family is expressed in the thymus network for presentation to differentiating T cells: oxytocin for the neurohypophysial peptides, neurokinin A for tachykinins, neurotensin for neuromedins, and insulin-like growth factor 2 (IGF-2) for the insulin family. Central immune self-tolerance to neuroendocrine principles results from the intrathymic presentation of these self-antigens. Furthermore, there is now accumulating evidence that the development of the diabetogenic autoimmune response (in Type 1 diabetes) first proceeds from a thymus dysfunction in the establishment of central self-tolerance rather than from a breakdown in peripheral immune self-tolerance. Based on the homology between dominant thymic self-antigens and peripheral autoantigens, on the one hand, and the difference between the immune responses elicited by the presentation of these antigens (respectively, tolerance vs. immunity), a novel strategy is proposed for the development of a "negative" self-vaccine designed to (re)install immune self-tolerance to pancreatic islet β cells and to prevent Type 1 diabetes. [Supported by the National Fund of Scientific Research (NFSR, Brussels), the European Association for the Study of Diabetes (EASD, Düsseldorf), and by the European Union FP6 Integrated Project Euro-Thymaide (contract LSHB-CT-2003-503410.)]

THE TOLL-LIKE RECEPTOR SYSTEM IN THE IMMUNE-ADRENAL CROSSTALK

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Sepsis and septic shock remain major health concerns worldwide and rapid activation of adrenal steroid release is a key event in the organism's first line of defence during this form of severe illness.

Toll-like receptors (TLRs) are critical in the early immune response upon bacterial infec-

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