The following abstracts from The Endocrine Society Journals have been selected by the editors as being particularly relevant to readers interested in translational science.

**Antibodies to Thyroid Peroxidase Arise Spontaneously with Age in NOD.H-2h4 Mice and Appear after Thyroglobulin Antibodies**

Chun-Rong Chen, Sepehr Hamidi, Helen Braley-Mullen, Yuji Nagayama, Catherine Bresee, Holly A. Aliesky, Basel Rapoport, and Sandra M. McLachlan


**ABSTRACT**

Hashimoto's thyroiditis, a common autoimmune disease, is associated with autoantibodies to thyroglobulin (Tg) and thyroid peroxidase (TPO). TPO, unlike abundant and easily purified Tg, is rarely investigated as an autoantigen in animals. We asked whether antibodies (Abs) develop to both TPO and Tg in thyroiditis in mice that is induced (C57BL/6 and DBA/1 strains) or arises spontaneously (NOD.H-2h4). Screening for TPOAbs was performed by flow cytometry using mouse TPO-expressing eukaryotic cells. Sera were also tested for binding to purified mouse Tg and human TPO. The antibody data were compared with the extent of thyroiditis. Immunization with mouse TPO adenovirus broke self-tolerance to this protein in C57BL/6 mice, but thyroiditis was minimal and TgAbs were absent. In DBA/1 mice with extensive granulomatous thyroiditis induced by Tg immunization, TPOAbs were virtually absent despite high levels of TgAbs. In contrast, antibodies to mouse TPO, with minimal cross-reactivity with human TPO, arose spontaneously in older (7–12 months) NOD.H-2h4 mice. Unexpectedly, TgAbs preceded TPOAbs, a time course paralleled in relatives of probands with juvenile Hashimoto's thyroiditis. These findings demonstrate a novel aspect of murine and human thyroid autoimmunity, namely breaking B cell self-tolerance occurs first for Tg and subsequently for TPO.

**Inflammation and Obesity Pathogenesis: The Hypothalamus Heats Up**

Joshua P. Thaler and Michael W. Schwartz

*(Endocrinology, published June 23, 2010, 10.1210/en.2010-0336)*

**ABSTRACT**

Obesity induced by high-fat (HF) feeding is associated with low-grade inflammation in peripheral tissues that predisposes to insulin resistance. Recent evidence suggests the occurrence of a similar process in the hypothalamus, which favors weight gain through impairment of leptin and insulin signaling. In addition to its implications for obesity pathogenesis, this hypothesis suggests that centrally targeted antiinflammatory therapies may prove effective in prevention and treatment of this disorder. This article highlights molecular and cellular mechanisms by which hypothalamic inflammation predisposes to diet-induced obesity.

**Large Litter Rearing Enhances Leptin Sensitivity and Protects Selectively Bred Diet-induced Obese Rats from Becoming Obese**

Christa M. Patterson, Sebastien G. Bouret, Sunny Park, Boman G. Irani, Ambrose A. Dunn-Meynell, and Barry E. Levin

*(Endocrinology, 10.1210/en.2010-0401)*

**ABSTRACT**

Because rearing rats in large litters (LLs) protects them from becoming obese, we postulated that LL rearing would protect rats selectively bred to develop diet-induced obesity (DIO) from becoming obese by overcoming their inborn central leptin resistance. Male and female DIO rats were raised in normal litters (10 pups/dam) or LLs (16 pups/dam) and assessed for anatomical, biochemical, and functional aspects of leptin sensitivity at various ages when fed low-fat chow or a 31% fat high-energy (HE) diet. LL rearing reduced plasma leptin levels by postnatal d 2 (P) 2 and body weight gain by P8. At P16, LL DIO neonates had increased arcuate nucleus (ARC) binding of leptin to its extracellular receptors and at P28 an associated increase of their agouti-related peptide and a-MSH axonal projections to the paraventricular nucleus. Reduced body weight persisted and was associated with increased ARC leptin receptor binding and sensitivity to the anorectic effects of leptin, reduced adiposity, and enhanced insulin
sensitivity in LL DIO rats fed chow until 10 wk of age. The enhanced ARC leptin receptor binding and reduced adiposity of LL DIO rats persisted after an additional 5 wk on the HE diet. Female LL DIO rats had similar reductions in weight gain on both chow and HE diet vs. normal litter DIO rats. We postulate that LL rearing enhances DIO leptin sensitivity by lowering plasma leptin levels and thereby increasing leptin receptor availability and that this both enhances the ARC-paraventricular nucleus pathway development and protects them from becoming obese.

Adrenomedullin Relaxes Rat Uterine Artery: Mechanisms and Influence of Pregnancy and Estradiol
Gracious R. Ross, Uma Yallampalli, Pandu R. R. Gangula, Luckey Reed, K. Sathishkumar, Hajjun Gao, Madhu Chauhan, and Chandra Yallampalli
(Endocrinology, published July 14, 2010, 10.1210/en.2010-0096)

ABSTRACT
Uterine arteries play a major role in regulating uteroplacental blood flow. Failure to maintain blood flow to the uteroplacental compartment during pregnancy often results in intrauterine growth retardation. Immunohistochemical staining of adrenomedullin (AM), an endogenous vasoactive peptide, in uterine artery was intense in pregnant compared to nonpregnant rats, but it is not known whether AM directly relaxes uterine artery or not. In this study, we elucidated the mechanisms of uterine artery relaxation by AM and its regulation by pregnancy and female sex steroids. AM was able to relax uterine artery, and this relaxation was influenced positively by pregnancy and estradiol as evidenced by the increased pD2 and Emax values of AM. Both pregnancy and estradiol treatment to ovariectomized rats amplified RAMP3 expression in uterine arteries while progesterone had no effect. AM-induced uterine artery relaxation is predominantly endothelium-dependent. The AM receptor antagonist CGRP8-37 is more potent than AM22-52 in inhibiting the AM relaxation, indicating the involvement of AM2 receptor subtype. Moreover, AM uses the classical nitric oxide-cGMP pathway along with KCa channels to mediate the vasodilatory effect in uterine artery. In conclusion, sensitivity of uterine artery to AM-induced relaxation is increased with pregnancy or estradiol treatment by increasing RAMP3 expression, suggesting an important role for AM in regulating the uterine hemodynamics, probably maintaining uterine blood flow during pregnancy and in pre- and postmenopausal cardiovascular adaptation differences.

Real-Time Monitoring of Somatostatin Receptor-cAMP Signaling in Live Pituitary
Stefan Jacobs, Davide Calebiro, Viacheslav O. Nikolaev, Martin J. Lohse, and Stefan Schulz
(Endocrinology, published July 7, 2010, 10.1210/en.2010-0341)

ABSTRACT
Fluorescence resonance energy transfer using genetically encoded biosensors has proven to be a powerful technique to monitor the spatiotemporal dynamics of cAMP signals stimulated by Gs-coupled receptors in living cells. In contrast, real-time imaging of Gi-mediated cAMP signals under native conditions remains challenging. Here, we describe the use of transgenic mice ubiquitously expressing the highly sensitive cAMP sensor exchange protein directly activated by cAMP 1-camps for cAMP imaging in living pituitary slices and primary pituitary cells. This technique can be widely used to assess the contribution of various pituitary receptors, including individual Gi protein-coupled somatostatin receptors, to the regulation of cAMP levels under physiologically relevant settings.

Mice Lacking the Neuropeptide α-Calcitonin Gene-Related Peptide Are Protected Against Diet-Induced Obesity
(Endocrinology, published July 7, 2010, 10.1210/en.2010-0284)

ABSTRACT
α-Calcitonin gene-related peptide (αCGRP) is a neuropeptide that is expressed in motor and sensory neurons. It is a powerful vasodilator and has been implicated in diverse metabolic roles. However, its precise physiological function remains unclear. In this