PharmaVOICE

THERAPEUTIC DIGEST

# ENDOCRINOLOGY

## ADVANCES IN THERAPEUTICS

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Written by Kristina Erfe Pines

# Advances in Endocrinology Therapeutics

Endocrinology is a dynamic and rapidly developing specialty. New hormones and applications are being discovered all the time with potential for use in a wide arena. In the last century, the therapeutic use of insulin for example, is arguably the most significant hormonal discovery; The oral contraceptive pill had widespread social ramifications; And the development of synthetic steroid hormones has allowed widespread benefits (as well as deleterious effects) for many and varied patient groups. These are but a few examples. Endocrine research has an influence in every biomedical sphere and it is often difficult to keep pace with new discoveries.

## OBESITY

The greatest challenge to healthcare in virtually every country across the globe is obesity. The scale of the obesity epidemic threatens to outstrip resources in even the richest societies[1]. The burden of morbidity arising from obesity and its corollary of type 2 diabetes, cardiovascular disease, and cancer present many challenges that are not restricted to those providing healthcare but reaching across society. Big questions of how we feed ourselves and how we live our lives need to be addressed, but some of the most fundamental questions center on how the body regulates energy balance: essentially an endocrine question[2]. Obesity is the direct result of a chronic imbalance between energy intake and energy expenditure with the excess energy stored in adipose tissue. Adipose tissue was traditionally considered a relatively inert tissue comprising cells that just functioned as stores of excess energy in the form of lipids. This changes during the 1990's when it was discovered that adipocytes were an important source of key hormones such as leptin and adiponectin with important roles in regulating both energy intake and expenditure[3]. Interest in adipose tissue was enhanced further a decade ago when imaging techniques using labeled glucose revealed that humans possess brown adipose tissue (BAT)[4]. Whereas, white adipocytes contain large stores of fats, in contrast brown adipocytes contain large numbers of mitochondria in which uncoupling protein 1 (UCP1) enables energy to be dissipated as heat rather than being stored. Until then it was considered that brown adipocytes were an important site of thermogenesis and hence energy expenditure in rodents but were considered absent from humans. This raised the potential of a new strategy to address human obesity by targeting BAT to enhance energy expenditure. A recent comprehensive study reviews the challenges that have been encountered in the subsequent decade of research in BAT in humans[5]. They address key questions such as the true extent of BAT in humans; Whether the original imaging techniques underestimated the total mass of BAT and to what extent "beiging" of white adipocytes, with the induction of UCP1, can occur in humans. These are critical questions that could establish whether beige and brown adipocytes in humans could be an effective target to bring about changes in energy expenditure that are of therapeutic benefit.

In addition to the advances in our understanding of energy expenditure there have been major progress in our knowledge of the endocrine controls of energy intake via hormones that control hunger and satiety and hence determine food intake[6]. Life within modern societies is increasingly stressful and whether this impacts on the controls of appetite and satiety resulting in over-eating is an interesting question. The effects of stress on the gut-brain signaling pathways and the neuropeptides involved are reviewed in a recent study by Stengel and Taché[7]. They've found that stress influences the expression or circulating levels of several gastrointestinal peptides involved in the regulation of metabolic status under conditions of hunger or satiety.

DR. ELIF ORAL

Our study suggests that having bariatric surgery before developing diabetes may result in greater weight loss.

The management of obesity remains a huge health challenge. Numerous dietary and lifestyle changes have been proposed and all have achieved modest weight loss that is invariably soon regained. The pharmaceutical industry has invested considerably in developing medications to treat the huge potential market with a long trail of failures with many concerns regarding adverse effects and long-term safety. While nutritionists, physicians, and pharmacologists have floundered in the quest to control the obesity epidemic, surgeons have developed a number of bariatric procedures that result in effective and sustained weight loss. "Our study suggests that having bariatric surgery before developing diabetes may result in greater weight loss from the surgery," says Dr. Elif Oral at the 2020 Endocrine Society annual meeting[8]. Dr. Oral is the lead endocrinology researcher at University of Michigan. "And together with data that is available from other studies, bariatric surgery may potentially prevent or delay diabetes from developing," Dr. Oral continues. One of the surprising observed effects of bariatric surgery has been the remarkable correction of the metabolic disturbances often resulting in complete remission of type 2 diabetes. That this effect is often apparent within days of surgery and before any appreciable weight loss has challenged many of the dogmas of the links between obesity and its associated metabolic disturbances. Studies have reviewed the potential new insights into metabolic endocrinology that these observations may provide[9]. They describe how such anatomical distinctions can provide insights into the various hormonal pathways and in particular the interactions between regions of the gut and the pancreas. They also touch on other interesting, less well-appreciated effects, such as how the surgery and endocrine changes can alter the perception of sweet-taste and hence alter calorie intake. The most studied surgical intervention

is Roux-enY gastric bypass and a review of these studies with an emphasis on what these studies have revealed regarding the gut endocrine system[10]. They highlight the many new questions raised in relation to the role of satiety hormones, incretins, and bile acids. The concepts of bile acids have been transformed from being regarded as just soaps that aid in the uptake of dietary fats to being a previously unappreciated complex endocrine system.

While the obesity epidemic has added to the focus on type 2 diabetes it has also become clear that there has been a 3% annual increase in the incidence of type 1 diabetes and a recent study[11] provide an overview of the development of strategies to prevent this and avoid the need for lifelong treatment. In order to prevent type I diabetes, it is important to understand the natural history of the development of the autoimmunity that results in pancreatic beta cell destruction and the onset of type 1 diabetes. The challenges of studying populations prior to the disease onset and how this is being addressed around the world are described. These studies have informed the various trials for primary prevention in subjects at risk and secondary prevention in those already exhibiting evidence of autoimmunity. To date these studies have had limited success and new and future strategies are discussed.

## STRESS

PROF. DR. HENRIK OSTER

Body clock function may be an underestimated factor in assessing the impact of chronic stress.

In a fine exposition of how studying one component can help inform on how interconnected the endocrine system has become, a recent study looks at how new observations of adrenal chromaffin cells have contributed to our understanding of how we coordinate response to stress[12]. The adrenal medulla has conventionally been considered the source of epinephrine to coordinate the cardiovascular, neuronal, and metabolic responses to stress. In this overview they describe recent observations of sympathetic nervous system regulation of chromaffin cell function and its secretion of not just epinephrine but also a rich cocktail of novel bioactive peptides. “We have shown that stress responses depend on the time of day, are affected by the internal body clock and can interact to negatively affect food intake and body weight to predispose to metabolic disorders,” says Professor Oster of University of Lübeck in Germany at the Society of Endocrinology 2019 conference in Brighton[13]. “These data suggest that body clock function may be an underestimated factor in assessing the impact of chronic stress on general health and well-being.” This new evidence is synthesized into a

broader understanding of how metabolic, cardiovascular, and inflammatory responses are integrated. They also highlight interesting new questions that have arisen from this work; such as whether the sensory nervous system and immune/inflammatory systems are looped-in together via the adrenal medullary stress response and what are the broader endocrine functions of the many bioactive peptides secreted from the chromaffin cells.

## REPRODUCTION

Population control and reproductive health remain major health issues globally. The important role of androgens both in ovarian follicle selection to ensure mono-follicular ovulation in women and in the normal cyclical secretion of estrodiol is reviewed by Franks and Hardy[14]. They focus on recent advances regarding the role of androgens in the development of polycystic ovary syndrome (PCOS), which remains the most common endocrine disorder in women of reproductive age.

One of the recent advances in techniques for maintaining fertility in women has been ovarian tissue cryopreservation (OTC) and transplantation. Originally developed to assist prepubertal girls and young women faced with reductions in the ovarian reserve due to pathologies, such as malignancies, or due to aggressive therapies that damage the ovary, Kristensen and Andersen discuss the many issues and challenges with extending this technique to more broader applications[15]. Using this technique to restore fertility to women with anovulatory PCOS is discussed. The many issues surrounding the more controversial application of the technique to enable healthy women to postpone childbearing into their more advanced years is also addressed.

During pregnancy a woman's endocrine system kicks into overdrive with most hormones adapting to enable the mother to meet the additional metabolic demands.

During pregnancy a woman's endocrine system kicks into overdrive with most hormones adapting to enable the mother to meet the additional metabolic demands and to provide an optimal environment in which the fetus can develop. Among all of these hormonal changes, vitamin D plays an under-appreciated role both in ensuring adequate calcium availability for fetal bone development and in enhancing maternal tolerance to the presence of paternal and fetal alloantigens. Recent advances in the understanding of the part played by vitamin D-binding protein (VDBP) in facilitating these roles is reviewed[16]. The ongoing questions regarding the role of VDBP in important clinical issues such as preeclampsia, preterm birth, and gestational diabetes are discussed.

## CANCER

Neuropeptide G protein-coupled receptors (GPCRs) are over-expressed in many different cancers; not just the relatively rare neuroendocrine tumors but also in some common cancers such as small cell lung cancers. There is a potential targeting of specific GPCRs for the development of novel cancer therapies. The development of agents that target receptors for bombesin, neurotensin, vasoactive intestinal peptide, and somatostatin are described in relation to the detection and treatment of both endocrine and non-endocrine cancers.

There have been recent advances in genetics, biochemical characterization, and imaging of pheochromocytomas (PCCs) and paragangliomas (PGLs). These are challenging cancers to treat and although most can be cured by surgery on rare occasions they metastasize and for these there are currently no approved treatments. The potential of systemic therapies, that have largely been developed to treat other cancers have different strategies that have been designed to target each of the accepted "hallmarks" are discussed in relation to their application to treating PCCs and PGLs. These include different strategies to inhibit angiogenesis, cell proliferation, invasion, and metastasis, to enhance the induction of cell death and the recently developed immunotherapies.

## AGING

As more and more people survive into advanced ages the problems of the elderly become an increasing burden on clinical services.

As more and more people survive into advanced ages the problems of the elderly become an increasing burden on clinical services. The prevalence of thyroid nodules in people over the age of 60 years is extremely high (50–70%) and although most of these are benign (85–95%) it is important to distinguish the few that can become malignant and require surgery. The limitations of current genetic markers, their cost-effectiveness and the next generation of tests currently being evaluated are discussed.

Another common ailment associated with aging is osteopenia, which leads to the high prevalence of fractures seen in the elderly population. The challenges of identifying individuals at risk of fractures and the uses and limitations of current therapies for osteopenia are discussed by Ramchand and Seeman[17]. The relative merits of antiresorptive and anabolic therapies are discussed as are the alternative strategies of combining these therapies or using them sequentially.

## Conclusion

The increasing speed of technological advances provides endocrinologists with ever more powerful tools for investigation, diagnosis and treatment. As the pressures of modern lifestyles involve major changes in how we live and eat and demographics markedly increase the elderly population the challenges endocrinologists face in the clinic are constantly evolving. This summaryof recent advances illustrates the variety of these challenges across the different specialties within endocrinology and the dynamic nature of modern endocrinology.

## NOTES

[1] Tremmel M, et al. "Economic burden of obesity: a systematic literature review. International Journal of Environmental Research and Public Health. 2017

[2] Samaras K, et al. "With obesity becoming the new normal, what should we do?" Frontiers in Endocrinology. 2019.

[3] Kershaw E, Flier J. "Adipose tissue as an endocrine organ." Journal of Clinical Endocrinology and Metabolism. 2004.

[4] Virtahen K, et al. "Functional brown adipose tissue in health adults." New England Journal of Medicine. 2009.

[5] Carpentier A, et al. "Brown adipose tissue energy metabolism in humans." Frontiers in Endocrinology. 2018.

[6] Ahima R, Antwi D. "Brain regulation of appetite and satiety. Endocrinology and Metabolism Clinics of North America. 2008.

[7] Stengel A, Taché Y. "Gut-brain neuroendocrine signaling under stress conditions of stress — focus on food intake-regulatory mediators." Frontiers of Endocrinology. 2018.

[8] "Bariatric surgery before diabetes develops leads to greater weight loss." Endocrine Society. March 30, 2020.

[9] Laferrère B, Pattou F. "Weight-independent mechanisms of glucose control after roux-en-y gastric bypass." Frontiers in Endocrinology. 2018.

[10] Laferrère B, Pattou F. "Weight-independent mechanisms of glucose control after roux-en-y gastric bypass." Frontiers in Endocrinology. 2018.

[11] Jacobsen L, et al. "Understanding pre-type 1 diabetes: the key to prevention." Frontiers in Endocrinology. 2018.

[12] Eiden L, Jiang S. "What's new in endocrinology: the chromaffin cell." December 4 2018.

[13] "Stress with disrupted body clock increases risk of metabolic disease." Endocrinology. November 13 2019.

[14] Franks S, Hardy K. "Androgen action in the ovary. Frontiers in Endocrinology. August 10 2018.

[15] Kristensen S, Andersen C. "Cryopreservation of ovarian tissue: opportunities beyond fertility preservation and a positive view into the future." Frontiers in Endocrinology. June 28 2018.

[16] Karras S, et al. "Deconvoluting the biological roles of vitamin d- binding protein during pregnancy: a both clinical and theoretical challenge." Frontiers in Endocrinology. May 23 2018.

[17] Ramchand S, Seeman E. "Advances and unmet needs in the therapeutics of bone fragility." Frontiers in Endocrinology. September 6 2018.

## RESOURCES

Ahima R, Antwi D. “Brain regulation of appetite and satiety. Endocrinology and Metabolism Clinics of North America. 2008.

“Bariatric surgery before diabetes develops leads to greater weight loss.” Endocrine Society. March 30, 2020.

Carpentier A, et al. “Brown adipose tissue energy metabolism in humans.” Frontiers in Endocrinology. 2018.

Eiden L, Jiang S. “What’s new in endocrinology: the chromaffin cell.” December 4 2018.

Franks S, Hardy K. “Androgen action in the ovary. Frontiers in Endocrinology. August 10 2018.

Karras S, et al. “Deconvoluting the biological roles of vitamin d- binding protein during pregnancy: a both clinical and theoretical challenge.” Frontiers in Endocrinology. May 23 2018.

Kershaw E, Flier J. “Adipose tissue as an endocrine organ.” Journal of Clinical Endocrinology and Metabolism. 2004.

Kristensen S, Andersen C. “Cryopreservation of ovarian tissue: opportunities beyond fertility preservation and a positive view into the future.” Frontiers in Endocrinology. June 28 2018.e chromaffin cell.” December 4 2018.

Laferrère B, Pattou F. “Weight-independent mechanisms of glucose control after roux-en-y gastric bypass.” Frontiers in Endocrinology. 2018.

Ramchand S, Seeman E. “Advances and unmet needs in the therapeutics of bone fragility.” Frontiers in Endocrinology. September 6 2018.

Samaras K, et al. “With obesity becoming the new normal, what should we do?” Frontiers in Endocrinology. 2019.

Stengel A, Taché Y. “Gut-brain neuroendocrine signaling under stress conditions of stress — focus on food intake-regulatory mediators.” Frontiers of Endocrinology. 2018.

“Stress with disrupted body clock increases risk of metabolic disease.” Endocrinology. November 13 2019.

Tremmel M, et al. “Economic burden of obesity: a systematic literature review. International Journal of Environmental Research and Public Health. 2017

Virtahen K, et al. “Functional brown adipose tissue in health adults.” New England Journal of Medicine. 2009.

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