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21st century endocrinology

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ABSTRACT – Recent developments in the field of diabetes and endocrinology have led to greater understanding of the body's complex hormonal axes. This article reviews the latest significant treatments which have the potential to impact greatly on a wide variety of disease states in the not too distant future.

KEY WORDS: diabetes mellitus, endocrinology, ghrelin, growth hormone, HIV, incretin, kisspeptin, thymus

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. In this review, the latest and at this time most important endocrine developments that have the potential to affect the next 100 years are discussed.

The gut

The gastrointestinal tract is a major target for hormonal action. More is being learnt not only about the signalling between the gut and the brain but also between adipose fat stores, nervous tissue and other endocrine glands. It is now clear that signals from the gut are crucial for the control of appetite and the regulation of energy balance, glucose homeostasis and more.

Ghrelin, discovered relatively recently, has emerged as the first circulating hunger hormone. It is produced by cells lining the fundus of the stomach and epsilon cells of the pancreas. Ghrelin levels increase before, and decrease after, meals.[1] It is considered the counterpart of the hormone leptin, produced by adipose tissue, which induces satiation when present at higher levels. It is also produced in the hypothalamic arcuate nucleus where it stimulates the secretion of growth hormone from the anterior pituitary gland. Ghrelin activates the mesolimbic cholinergic-dopaminergic reward link, a circuit that communicates the hedonic and reinforcing aspects of natural rewards, such as food, as well as of addictive drugs, such as alcohol.[2]

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The development of type 2 diabetes is closely associated with how the gut handles food – our understanding of the pathophysiology of diabetes has brought about new treatments. The stable analogue of glucagon-like peptide-1 has rapidly advanced to become one of the most promising treatment options for type 2 diabetes, this works via the incretin effect in which the gut directly affects insulin release and the central nervous system (CNS) control of glucose metabolism and fat stores.[3]

Changes in the signalling patterns of these and other gut hormones best explain the remarkable capacity of gastric bypass surgery to lower food intake and excess body weight. In some bariatric procedures, the level of ghrelin is reduced in patients, thus causing satiation before it would normally occur.[4] Given the enormous societal implications of the obesity epidemic, these are no small feats. Recently, Scripps research scientists have developed an anti-obesity 'vaccine', which is directed against ghrelin.[5] The vaccine uses the immune system, specifically antibodies, to bind to selected targets, directing the body's own immune response against them. This prevents ghrelin from reaching the CNS, thus producing a desired reduction in weight gain. Success in this field would be the Holy Grail in the fight against the obesity epidemic.

The placenta

Researchers at the University of Reading studying females suffering from recurrent miscarriages and pre-eclampsia have discovered that the placenta secretes peptide hormones. There is a small protein called neurokinin B (NKB) which is raised significantly in mothers when pre-eclampsia develops. It contains the molecule phosphocoline, which is used by nematode worms, to escape host immune systems.[6] This would explain why the placenta and foetus – which have a different genotype from the mother – avoid rejection and can exert influence over her metabolism for their own benefit. It is hoped that this mechanism of host evasion will have applications beyond the placenta, especially with regards to autoimmune diseases. Rheumatoid arthritis and systemic lupus erythematosus (SLE), for example, improve during pregnancy. By devising a system whereby you could make certain cells invisible to the immune system through attachment or manipulation of NKB and phosphocoline would potentially lead to cures for several conditions.

Kisspeptin

The most exciting discovery so far this century in the field of reproductive biology is that of kisspeptin and its receptor

GPR54. Kisspeptin is the product of the Kiss1 gene which was originally identified as a human metastasis suppressor gene which has the ability to suppress melanoma and breast cancer metastasis.[7] It has, however, become clear that kisspeptin-GPR54 signaling has an important role in initiating the cascade of biochemical changes that lead to puberty and turn children into hormonally challenged adolescents.[8]

Humans with mutations or absence of GPR54 and subsequent hypogonadotrophic hypogonadism do not undergo puberty, their gonads are small, their sex hormone and gonadotrophin levels are low and they are sterile. In several animal models, a single injection of kisspeptin stimulates a massive increase in the secretion of gonadotrophins, as strong as that observed by administering gonadotrophin releasing hormone (GnRH) itself. Repeated injections in immature rats can advance the age of puberty. In Japan, scientists have developed antibodies directed against kisspeptin in the brain of female rats and this stops their reproductive cycles.[9] By inhibiting kisspeptin, even once puberty has occurred, reproductive function can be blocked, therefore demonstrating it is essential for not only puberty to occur but also for reproductive function to continue.

The discovery of the role of kisspeptin and its receptor opens exciting new possibilities in the treatment of a variety of conditions including delayed or precocious puberty, infertility and also for the treatment of sex hormone-dependent cancers, such as breast and prostate cancer, which are nurtured by oestrogen and testosterone respectively.[10]

New uses for old hormones

Growth hormone (GH) has a variety of functions in the body, the most noticeable of which is the increase of height throughout childhood, and there are several diseases which can be treated through the therapeutic use of GH, such as inflammatory bowel disease.[11,12] It is used by bodybuilders and for athletic enhancement as well as for increasing milk production in cattle.

Growth hormone is also an underappreciated but important regulator of T-cell development.[13] Researchers in California have performed several studies looking at the effects of GH in patients with HIV.[14,15] Infection with the HIV virus is frequently characterised by T-cell loss and an increased risk of death due to immune system failure. Using regular injections of recombinant human GH can 'kick-start' the thymus and consequently increase the size of the gland and double T-cell production. Thymic function is felt to be a pivotal factor in determining T-cell recovery, thus facilitating immune restoration. The results are promising and what is now required are longitudinal data to explore subsequent infection and mortality rates. Also, because participants in the studies were originally recruited to look at the effects of GH on HIV-1 lipodystrophy, a condition known to be associated with GH deficiency, it is possible that the response to GH was based upon underlying endocrinological derangement secondary to HIV.[16]

Cardiovascular endocrinology

The heart is an endocrine organ. Stimuli that affect the cardiovascular system work through hormone receptors. Many of these hormone signalling systems are so interwoven and interconnected that in many cases the components are hard to separate.[17] Endocrine signals that influence the cardiovascular system can be divided largely into two types according to whether they are mediated by nuclear receptors (including cholesterol and fatty acid metabolites, steroids and thyroid hormones) or cell surface receptors that work by initiating second messenger signalling cascades (including peptide hormones, cytokines and neurotransmitters). In reality, however, the actions of both types of endocrine signal overlap extensively (Table 1).

Nuclear receptors also regulate inflammatory responses, which are emerging as a key contributor in the incidence of cardiovascular disease.[17,18] Rapid advancements in pharmacology of the nuclear receptor family suggest that it will be possible to devise new treatments for cardiovascular disease based on modulation of the actions of many nuclear receptors (Table 2).

The classic steroid receptors also influence cardiovascular disease. Aldosterone is a well known cardiovascular risk hormone whose actions are mediated through the mineralocorticoid receptor (MR). New interest in this hormone has arisen for two major reasons.[19] Firstly, aldosterone has deleterious effects on the heart (and on the kidneys and vasculature) to cause cardiac fibrosis that are independent of blood pressure elevating activities. Second, primary hyperaldosteronism is a much more common cause of hypertension than was previously realised, accounting for as much as 5–10% of cases of so-called essential hypertension.[20,21] Glucocorticoid receptors (GRs) have extensive effects in the metabolic syndrome but are also classic anti-inflammatory hormones.[22] The increasing realisation of the importance of inflammatory response in cardiovascular disease points toward possible roles for dissociated glucocorticoids in medical therapy.[23]

Table 1. Signals mediated by nuclear receptors.

Effects on cardiovascular system	Receptors
Reverse cholesterol transport	PPAR, LXR
Lipoprotein levels	PPARs, LXRs, FXRs, SHP, TRs, ER, AR, VDR
Atherosclerotic plaque formation	PPARs, LXR, ROR, RXR, VDR, ER, AR
Cardiac fibrosis	MR
Blood pressure	MR, GR, ER
Obesity/metabolic syndrome	PPARs, TR, GR, RARs, RXR
Vascular tone	ER, AR, MR
Arrhythmia	TR
Cardiac myopathy	PPARs, TR

AR = androgen receptors; ER = oestrogen receptors; GR = glucocorticoid receptors; MR = mineralocorticoid receptors; PPAR = peroxosimal proliferator-activated receptors; TR = thyroid receptors.

Other steroid receptors play key roles in cardiovascular disease. Receptors for androgens (ARs) mediate actions of testosterone and dihydrotestosterone and have extensive effects on the cardiovascular system – in relation to vascular biology, coronary artery disease, hypertension, cardiac hypertrophy, cerebrovascular disease, peripheral arterial disease, and other aspects of cardiovascular biology.[24] It has long been established that there are significant differences in the development of cardiovascular disease between men and women. Up until recently, it was thought that oestrogen replacement in postmenopausal women would prevent cardiovascular complications, but prospective trials have not supported this notion.[25] Moreover, the previous dominance of the oestrogen protection hypothesis overlooked evidence that there is no break-point in female cardiovascular risk at the expected age of menopause, a key prediction of this hypothesis. Nevertheless, the cardiovascular effects of this class of hormones cannot be denied, and in the future a regimen may be developed in which there may be potential beneficial effects of oestrogens.

Diabetes developments

Significant developments in the understanding of the pathophysiology of type 1 and type 2 diabetes have led to new treatments. The incretin mimetic class of drugs, for example, work on the basis of enhancing enteroendocrine signalling and produce widespread effects on metabolism as listed in Table 3.

DPP-IV inhibitors and GLP-1 agonists have been on the market in the UK since early 2007 and their impact on type 2 diabetes has not yet been fully assessed. With regards to patients already on insulin therapy, its delivery is not always straightforward. Compact, wearable insulin pumps which are programmable and allow continuous subcutaneous infusion of short-acting insulin are now becoming more widespread in their availability. They are most commonly used at the current time in those patients with difficult to control type 1 diabetes, especially when recurrent hypoglycaemia or troublesome diabetic ketoacidosis is a problem, and also in children. The ultimate goal for such systems is that of a 'closed-loop' artificial pancreas, whereby, changes in plasma glucose can be quickly titrated against the rate of insulin infusion. Much work is ongoing to develop suitable algorithms, especially in the field of fuzzy logic.[26]

Curative therapy for diabetes mellitus mainly implies replacement of functional insulin-producing pancreatic beta cells, with pancreas or islet-cell transplants. However, a shortage of donor organs spurs research into alternative means of generating beta cells from islet expansion, encapsulated islet xenografts, human islet cell-lines, and stem cells. Both embryonic and adult stem cells have been used to generate surrogate beta cells or otherwise restore beta-cell functioning.[27] One notable study from Brazil to report success used high-dose immunosuppression along with autologous haematopoietic stem cell transplantation in patients with newly diagnosed type 1 diabetes mellitus.[28] The results were encouraging and demonstrated that beta-cell function was increased in all but one of the patients and it induced prolonged insulin independence in the majority of the patients. However, the cohort was relatively small and there was no control group. Research so far has shown proof of principle in both patients with newly diagnosed and long-standing diabetes that some pancreatic function can be restored and time without insulin is one of the best markers of this. Work is ongoing in major centres such as Alberta, Canada, and Kings College, London, to refine and optimise the process.

Other important developments in the field include:

- better insulin analogues[29]
- the Diapep277 'vaccine' designed to suppress the autoimmune process in those at high risk of developing diabetes[30]
- implanatable nanosensors for continuous subcutaneous glucose monitoring[31]
- measuring metabolic variables through exhaled breath – a rather novel approach to the prevention, diagnosis and monitoring of diabetes[32]
- in terms of education the dose adjustment for normal eating (DAFNE) and SADIE courses designed to directly aid and empower individual patients with management of their chronic condition.[33]

Table 2. Signals mediated by cell surface receptors.

Effects on cardiovascular system	Receptors
Vasodilatory action, increase glomerular filtration rate, enhance sodium excretion	ANP, BNP
Reduces platelet reactivity in vascular endothelial cells, Protects against myocardial ischaemia	CNP
Increased cardiovascular mortality risk (acromegaly)	Growth hormone
Calcium ion levels regulation, deposit in atherosclerotic plaques	PTH
Regulation of vascular resistance	Insulin
Blood pressure effects of catecholamines	Alpha and beta adrenoceptors, DA

ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; DA = dopamine; PTH = parathyroid hormone.

Table 3. The effects of incretin hormones. Reproduced with permission from Medknow publications.[3]

Pancreatic effects	Extra-pancreatic effects
Increased glucose dependent insulin secretion	Reduced hepatic insulin extraction
	Reduced gastric acid secretion
Increased pro-insulin biosynthesis	Increased satiety
Increased beta-cell survival	Reduced body weight (chronic effect)
Decreased glucagon secretion	Reduced gastric emptying rate
	Increased myocardial glucose extraction
	? Increased lipogenesis

Conclusions

The endocrine system is a complex, beautiful, sensitive regulating mechanism for the growth, differentiation, metabolism and survival of the human organism. However it can go wrong and putting things right is not always easy. There is an explosion of research and development in the field which is not only relevant to endocrinologists but to all specialties and we hope that a flavour of this has been outlined above.

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