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## High T Gives $\beta$ Cells a Boost

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Androgen deficiency in men is associated with metabolic syndrome and diabetes, which has been attributed to actions of androgens upon insulin target tissues. In this issue of *Cell Metabolism*, Navarro et al. (2016) report a role for androgens and their receptor in the regulation of insulin secretion in  $\beta$  cells.

It has been long recognized that fundamental aspects of energy metabolism are regulated differently in males and females. Circulating gonadal hormones, namely androgens and estrogens, control these sex differences. Clinical evidence points to androgen deficiency in men as a major risk factor for the development of metabolic syndrome and type 2 diabetes (Zitzmann, 2009). For example, prostate cancer patients treated with anti-androgens were found to have a higher incidence of type 2 diabetes (Keating et al., 2012). An abundant literature has shown that androgen deficiency in men causes insulin resistance and visceral obesity. Androgens exert their action by binding to the androgen receptor (AR), which upon ligand binding can translocate to the nucleus to regulate gene transcription. Consistent with the clinical observations in androgen-deficient men, AR-deficient male mice are obese and insulin resistant (Lin et al., 2005). Mechanistically, this AR-dependent phenotype has been shown to reflect functional roles for the AR in skeletal muscle, where it promotes oxidative metabolism, and the hypothalamus,

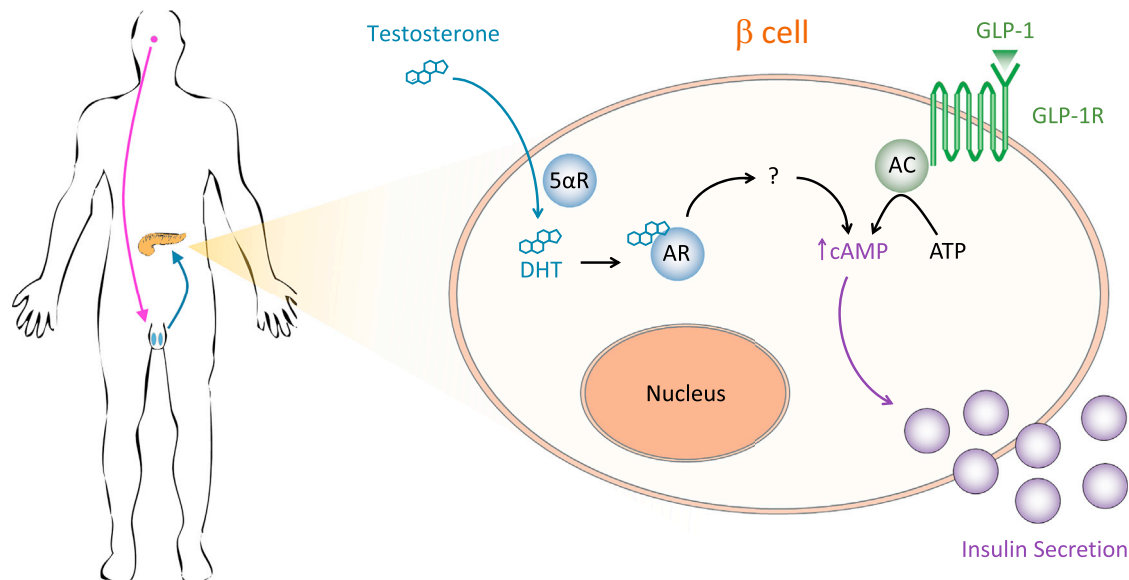
where AR-mediated signals suppress food intake. In this issue of *Cell Metabolism*, Navarro et al. (2016) report an additional role for androgens and their receptor in regulating the secretion of insulin in pancreatic  $\beta$  cells (Figure 1).

There is clinical evidence to suggest that androgen deficiency could impair  $\beta$  cell function. For example, impaired  $\beta$  cell function has been reported among prostate cancer patients on androgen deprivation therapy, and testosterone deficiency in men was shown to associate with prediabetes independent of obesity and metabolic syndrome (Ho et al., 2013; Inaba et al., 2005). Previous work in rodents has indicated that testosterone can protect  $\beta$  cells from apoptotic damage as well as stimulate insulin production and secretion (Morimoto et al., 2001, 2005). Yet, whether androgens directly act on  $\beta$  cells and are necessary to maintain normal  $\beta$  cell function in vivo has remained unclear.

The study by Navarro et al. (2016) now provides evidence that AR signaling in  $\beta$  cells potentiates insulin secretion in males. Using two different genetic approaches to inactivate the

AR selectively in  $\beta$  cells (*Rip-Cre*-mediated deletion in embryonic  $\beta$  cells and inducible *Mip-CreER*-mediated deletion after puberty), they observed decreased plasma insulin levels in male, but not female, mice in both the fasted state and after stimulation with glucose. Despite significantly reduced insulin levels in mice lacking the AR in  $\beta$  cells ( $\beta$ AR-deficient mice), plasma glucose levels were surprisingly normal under fasting and fed conditions, and glucose tolerance was only mildly reduced in mice fed regular chow. However, when exposed to a western diet,  $\beta$ AR-deficient mice developed hyperglycemia.

To gain a better understanding of how androgens affect  $\beta$  cell function, Navarro et al. (2016) isolated islets from the pancreas of  $\beta$ AR-deficient and control mice and studied insulin secretion dynamics in response to glucose. As expected based on the phenotype of  $\beta$ AR-deficient mice and in line with previous in vitro studies (Morimoto et al., 2001), treatment of islets with dihydrotestosterone (DHT) increased insulin secretion at low and high glucose in control, but not  $\beta$ AR-deficient, islets. The same



**Figure 1. The Testes-Pancreatic  $\beta$  Cell Signaling Axis**

Left: pulsatile gonadotropin-releasing hormone secretion by hypothalamic neurons constitutes the initial step in the hypothalamic–pituitary–gonadal axis and in males leads to increased testosterone production by the testes. Right: mechanism of testosterone potentiation of insulin secretion proposed by the study of Navarro et al. (2016). Testosterone is converted to its active form, dihydrotestosterone (DHT), by the enzyme 5 $\alpha$ -reductase (5 $\alpha$ R). Subsequent activation of the androgen receptor (AR) by DHT promotes cAMP accumulation through an unknown extranuclear mechanism. AR-mediated cAMP production acts jointly with other cAMP-generating pathways, particularly that of the gut hormone GLP-1. AC, adenylyl cyclase; GLP-1R, GLP-1 receptor.

effect was seen at high glucose in male human islets treated with DHT, suggesting that androgens enhance insulin secretion also in man. Surprisingly, AR deletion not only abolished DHT-mediated stimulation of insulin secretion, but also caused a reduction in insulin secretion without exogenous DHT in islets of mice fed a Western diet. While the mechanistic basis for this insulin secretion defect remains unclear, the finding suggests ligand-independent roles for the AR in metabolic adaptation of  $\beta$  cells.

The classic mechanism of action for sex hormone receptors is their nuclear function as ligand-activated transcription factors. Contrary to this paradigm, Navarro et al. (2016) observed predominantly cytoplasmic localization of the AR in  $\beta$  cells after exposure to DHT. The same group (Liu and Mauvais-Jarvis, 2009) has recently described a similar atypical cytoplasmic localization of the estrogen receptor in  $\beta$  cells. To determine whether cytosolic or nuclear AR mediates AR effects on insulin secretion, the authors synthesized an androgen dendrimer conjugate that selectively activates extranuclear AR. The conjugate exerted a stimulatory effect on islet insulin secretion under high glucose comparable to DHT, suggesting an extranuclear mechanism

for androgen-mediated regulation of insulin secretion.

Glucose-stimulated insulin secretion (GSIS) is triggered by glucose metabolism, which leads to an increase in the ATP/ADP ratio, followed by closure of ATP-sensitive K<sup>+</sup> channels, membrane depolarization, Ca<sup>2+</sup> influx, and insulin exocytosis. The response to this triggering pathway of insulin secretion can be potentiated by the gut hormone glucagon-like peptide-1 (GLP-1), which is released in response to food intake and stimulates GSIS via a cAMP-dependent mechanism (Figure 1). To determine where in this cascade androgens function, Navarro et al. (2016) treated islets with DHT in conjunction with various activators and inhibitors of GSIS. Combined, the results revealed no obvious role for androgens in the triggering pathway, but rather suggest a role in cAMP production and potentiation of the GLP-1 response in  $\beta$  cells. While DHT and GLP-1 clearly exerted synergistic effects upon GSIS, it is less clear whether potentiation of the GLP-1 response is indeed the main mechanism by which androgens act. For instance, the profound decrease in fasting insulin levels observed in  $\beta$ AR-deficient mice is not consistent with a GLP-1-dependent mechanism,

which is most relevant in response to meals. Moreover, DHT failed to potentiate insulin secretion after KCl-mediated membrane depolarization, as expected if DHT solely functioned by increasing cAMP. Thus, further studies are needed to fully define the mechanisms by which androgens regulate  $\beta$  cell function.

In sum, Navarro et al. (2016) convincingly show that androgens act directly on  $\beta$  cells and regulate insulin secretion in males. The extensive data on human islets strongly suggest that this mechanism is conserved in man and help explain clinical observations of impaired  $\beta$  cell function in men with androgen deficiency. It is important to consider that testosterone release is pulsatile in vivo. A fascinating question is how  $\beta$  cells integrate fluctuating testosterone levels with nutritional cues and how androgen secretion relates to fasting/feeding cycles or metabolic state. Perhaps each testosterone pulse has an enduring effect to sensitize  $\beta$  cells by raising the level of cAMP. Alternatively, the effect could be limited to periods when androgen pulses coincide with meals. Together with recently discovered roles for the circadian clock in regulating rhythmicity of insulin secretion (Perelis et al., 2015), diurnal fluctuations in

testosterone secretion could constitute another layer of regulation that affects  $\beta$  cell function. The study by Navarro et al. (2016) sets the stage for further exploration of the role of androgens in  $\beta$  cells and the pathogenesis of type 2 diabetes.

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## Starving Intestinal Inflammation with the Amino Acid Sensor GCN2

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Metabolic stressors are emerging as important controls over immune system function. In a recent paper, Ravindran et al. (2016) uncovered a novel mechanism by which an amino acid sensing pathway controls inflammation in the gut.

Emerging evidence suggests that immune system function is heavily influenced by signals of cellular stress, including those of nutrient availability. The integrated stress response (ISR) is a coordinated cellular program that allows cells to respond to such microenvironmental stressors, including endoplasmic reticulum (ER) stress and nutrient deprivation. In the case of low amino acid levels, the ISR is initiated by a kinase known as general control nonderepressible 2 (GCN2). GCN2 phosphorylates the translational initiator eukaryotic initiation factor 2 $\alpha$  (eIF2 $\alpha$ ), which leads to translational arrest and restoration of amino acid homeostasis. As the intestine is faced with dynamic changes to nutrient bioavailability, the crosstalk between nutrient

metabolism and the gut immune system could potentially shape the immune responses in the gut. These responses may be particularly relevant during conditions of gut inflammation, such as in inflammatory bowel disease (IBD). In a recent article in *Nature*, Ravindran et al. (2016) used several genetically engineered mouse models to delineate the link between amino acid starvation-sensing mechanisms and gut inflammation in the dextran sodium sulfate (DSS) model of colitis.

The authors first showed that total body GCN2 deficiency results in worsened intestinal inflammation, enhanced Th17 immune responses, and extensive mucosal damage with DSS. To determine the relative contribution of epithelial and anti-gen-presenting cells (APCs), colitis was

induced in mice lacking GCN2 specifically in intestinal epithelial cells (IECs) and CD11c<sup>+</sup> APCs. In both of these models, mice developed more severe weight loss and gut inflammation, suggesting that both IECs and APCs mediate the protective effects of GCN2 during colitis.

Ravindran et al. further investigated the chain of events by which GCN2 prevents gut inflammation. GCN2-mediated phosphorylation of eIF2 $\alpha$  was found to be one event, as mice with IECs and APCs lacking phosphorylated eIF2 $\alpha$  showed worsened colitis. In addition to eIF2 $\alpha$  phosphorylation, defective autophagy was found to mediate the effects of GCN2 deficiency on gut inflammation. Autophagy is a conserved process whereby cellular components are