

Metabolic balancing acts of vitamin A in type-2 diabetes and obesity

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Abstract

Using mice that lack retinaldehyde dehydrogenase 1 gene (Raldh1^{-/-} mice), Kierfer *et al* demonstrated that retinoids (metabolites of Vitamin A) play an important role in the regulation of cellular metabolisms and energetics. The Aldh1a1^{-/-} mice were leaner and less prone to accumulate subcutaneous and visceral fat, and to acquire insulin resistance on high fat diet. Their lower fasting glucose levels concomitant with reduced hepatic expression of glucose 6-phosphatase and phosphoenol pyruvate carboxy kinase genes indicated that Aldh1a1^{-/-} mice were defective in gluconeogenesis. These mice also had lower plasma levels of triglycerides, very low-density lipoprotein and low-density lipoprotein-triacylglycerol, while their skeletal muscles elicited higher expression of carnitine palmitoyl transferase, medium chain acyl-A dehydrogenase, peroxisome proliferation activated receptor (PPAR α and PPAR δ). Thus, the improved lipid and lipoprotein profiles of Raldh1a1^{-/-} mice resulted from a combination of reduced lipogenesis and enhanced fatty acid oxidation by retinoids. The mechanistic details of how retinoids integrate fasting glucose, hepatic gluconeogenesis and adaptive thermogenesis independent of body mass deserve further study.

INVITED COMMENTARY ON HOT ARTICLES

According to the estimates of the World Health Organization (WHO), nearly one billion people worldwide are overweight and about one third of these individuals may be considered clinically obese (WHO Global Infobase: data on overweight and obesity, mean body mass index, healthy diets and physical inactivity; <http://www.who.int/mediacentre/>). Many organizations including the WHO have called for global action to devise effective strategies for the prevention and treatment of obesity and its medical complications (WHO Global Alliance for the prevention of obesity and related chronic diseases; <http://www.preventionalliance.net/>). Recent epidemiological, clinical and experimental studies indicate that the worldwide outbreak of obesity and type-2 diabetes (T2D) is multi-factorial in nature, with a strong socio-economic dimension. While changes in nutrition and life style - i.e., the availability of calories-dense food and lack of physical exercise, are the root causes of obesity and T2D their pathogenesis involves additional mechanisms. For example, in a recent Field of Vision column, I discussed a role of maternal under-nutrition and how a fetus grow-

ing under such conditions has a higher predilection for developing obesity and metabolic syndrome in later life.

The hormonal and neural mechanisms involved in energy utilization and storage in the body of mammals, including humans, have revealed insulin and its counter-regulatory hormone, glucagon, to be the key regulators of nutrient metabolism and cellular energetics. Insulin regulates the uptake and metabolism of carbohydrates, lipids and proteins in the liver, adipose and skeletal muscle. The pathogenesis of T2D associated with obesity involves abnormal insulin secretion as a consequence of β -cell failure and the development of insulin resistance as reflected in the need for abnormally high levels of insulin to maintain normal blood glucose^[1,2]. At the molecular level, insulin resistance presents as sub-optimal insulin signaling that has widespread consequences for the metabolism of nutrients and disposal of excess calories. As a result, the delineation of insulin signaling pathways and their defective relay in insulin resistant tissues have been analyzed extensively over the years. These studies have uncovered two key aspects of insulin signaling that bears directly on the mechanisms of obesity, T2D and metabolic syndrome. First, although overall weight gain results from an excessive intake and reduced dissipation of calories in insulin sensitive tissues, particularly in the skeletal muscle, the size and location of the adipose tissue (visceral *vs* subcutaneous) contribute significantly to cellular energetics and thus to the pathogenesis of obesity. Secondly, although the mechanisms of metabolism and storage of excess nutrients are undoubtedly dependent on insulin its actions are greatly modulated by a number of pro-inflammatory cytokines, autocooids and nuclear hormones some of which are produced by adipose tissue.

Vitamin A and its metabolites, retinoids, have emerged as key participants in the mechanisms of regulation of cellular metabolisms and energetics. It was discovered more than three thousand years ago that consumption of certain foods could reverse night blindness. The identification of vitamin A as the nutritional component responsible for the salutary effect of diet on vision was reported in 1913; since then, many natural and man-made retinoids have been shown to regulate a variety of physiological processes^[3,4]. Thus, in addition to their classical role in vision, retinoids have been shown to regulate cellular differentiation, immunity and embryogenesis. More recent observations have also implicated retinoids in the pathogenesis of cancer, obesity and metabolic syndrome^[5]. The uptake of vitamin A, its intracellular and extracellular biotransformation into various metabolites, and elimination is a highly regulated process. The dietary vitamin A (retinol) is first oxidized to retinaldehyde (Rald) by a family of alcohol dehydrogenases and retinol dehydrogenases. Retinaldehyde is subsequently oxidized to retinoic acid (RA) by retinaldehyde dehydrogenase; the conversion of Rald into RA is a rate-limiting reaction in its biogenesis^[6].

The molecular actions of retinoids are exerted *via*

their interactions with a family of nuclear hormone receptors that include retinoic acid receptor (RAR) and retinoid X receptor (RXR); in addition to forming RXR:RXR homodimers, RXR heterodimerizes with RAR (RAR:RXR) and also partners with peroxisome proliferator activated receptors (PPAR:RXR)^[6]. The ligand-bound retinoid receptors are recruited to the *cis*-regulatory elements in the promoters of their target genes to regulate their transcription; a number of genes regulated by retinoids are involved in glucose homeostasis, fatty acid oxidation and adipogenesis^[5]. The unique cell specific activities of retinol-binding protein and enzymes that metabolize vitamin A into retinoids, combined with heterogeneous distribution of their receptors in different cell types are thought to determine the tissue-specific actions of retinoids^[3]. It has been reported earlier that mice lacking a functional retinaldehyde dehydrogenase 1 gene (Raldh1^{-/-} mice) had reduced levels of RA and increased levels of Retinaldehyde in their livers^[7]. Raldh1 knockout mice also had leaner body mass and were less prone to accumulate subcutaneous and visceral fat, and acquire insulin resistance on high fat diet^[8]. There was some evidence to suggest that Retinaldehyde could bind to retinol-binding proteins and putatively signaled *via* RXR and PPAR- γ receptors *in vivo* and these actions were involved in the ability of Rald to protect Raldh1^{-/-} mice against diet-induced obesity and diabetes. Consistent with these data, Ziouzenkova *et al*^[8], reported that exogenous administration of Rald in ob/ob mice also repressed adiposity whereas a similar treatment with vitamin A or all trans retinoic acid (ATRA) had no effect. These observations strongly implicated the biogenesis of Rald as a critical regulatory node in metabolic homeostasis in Raldh1^{-/-} mice on high fat diet. However, the question of whether endogenous retinoids, specifically Rald, regulated glucose metabolism in non-obese Rald knockout mice remained unanswered.

In the July 2012 issue of *Endocrinology*, Kiefer *et al*^[9] report that a closer examination of Aldh1a1^{-/-} mice revealed that the pathways of gluconeogenesis and lipid metabolism were strikingly altered in these animals even on normal chow diet and without overt obesity. The analysis of glucose homeostasis showed that although random fed blood glucose levels were normal in Aldh1a1^{-/-} mice, they had lower fasting glucose levels. To explore the underlying mechanism, the authors carried out pyruvate tolerance test and hyperinsulinemic-euglycemic clamp studies and discovered that glucose production in Aldh1a1^{-/-} mice was reduced, both under basal and clamped conditions. In contrast, rates of glucose infusion and insulin secretion were similar in WT and Aldh1a1^{-/-} mice and so were the rates of glucose uptake in the adipose and skeletal tissues. Based on these experiments, the authors surmised that Aldh1a1^{-/-} mice were defective in hepatic gluconeogenesis. Consistent with this conclusion, the authors found that the hepatic expression of glucose 6-phosphatase (G6Pase) and phosphoenol pyruvate carboxy kinase (PEPCK) was

decreased in *Aldh1a1*^{-/-} vs WT mice while levels of glycogen synthase and glycogen phosphorylase in the two groups were similar.

To further explore the mechanistic basis of defective glucose production in *Aldh1a1*^{-/-} mice, the authors investigated the potential involvement of two well-known regulators of gluconeogenesis, the transcription factor forkhead O1 (FoxO1) and the signaling kinase adenosine mono phosphate kinase (AMPK). Following a bolus of insulin administered intraperitoneally, *Aldh1a1*^{-/-} mice elicited enhanced phosphorylation of FoxO1 and AMPK in their livers that concomitantly elicited reduced expression of *G6Pase* and *PEPCK* genes. As mentioned above, since *Aldh1a1*^{-/-} mice have increased hepatic levels of Rald^[8], Kiefer *et al*^[9] hypothesize that altered retinoid signaling in the liver was involved in gluconeogenesis. A comparison of retinoid receptor signaling in the hepatocytes from WT and *Aldh1a1*^{-/-} mice elucidated that altered retinoid signaling in the livers of Rald in *Aldh1a1*^{-/-} mice was indeed responsible for the observed metabolic phenotype. The authors discovered that hepatocytes from WT mice induced expression of *G6Pase* and *PEPCK* in response to Rald and ATRA. In contrast, hepatocytes from *Aldh1a1*^{-/-} mice responded only to Rald. As expected, co-treatment of liver cells with an RXR antagonist, HX531, neutralized their responses to Rald as well as ATRA thus demonstrating a differential involvement of retinoid receptor signaling in WT and *Aldh1a1* knockout mice with consequential differences in their gluconeogenesis responses. This conclusion was further bolstered by the observation that the constitutive expression of cytochrome P450 26a1 (*Cyp 26a1*) gene, a major downstream target of RA^[10], was reduced by 10-fold in the livers of *Aldh1a1*^{-/-} mice.

To address the question of whether *Aldh1a1*^{-/-} mice elicited altered fasting-induced pro-gluconeogenesis signals such as cAMP and glucagon, Kiefer *et al*^[9] compared induction of *PEPCK* and *G6Pase* expression in response to forskolin or insulin in WT and *Aldh1a1*^{-/-} hepatocytes and found that the latter were significantly less responsive to both signals. These data are consistent with the authors' conclusion that control of biotransformation of vitamin A into Rald and its subsequent conversion into RA *via* *Aldh1a1* is a putatively important regulatory node in the regulation of hepatic gluconeogenesis.

These authors also noted that *Aldh1a1*^{-/-} mice, in addition to eliciting altered gluconeogenesis, had a significantly different profile of lipids and lipoproteins, independent of body mass and adiposity. It was found that after a 6 h-fast, *Aldh1a1*^{-/-} mice compared with WT animals had lower plasma levels of triglycerides, very low-density lipoprotein and low-density lipoprotein-triacylglycerol. Additionally, serum high-density lipoprotein-cholesterol concentration in *Aldh1a1*^{-/-} mice was high while other cholesterol fractions remained unchanged, resulting in increased total cholesterol. In the presence of lipolysis inhibitor tyloxapol, production of triglycerides

was much greater in WT mice compared to their *Aldh1a1*^{-/-} counterparts. To further delve into the potential mechanisms of altered lipogenesis, Kiefer *et al*^[9], examined the expression of carbohydrate response element binding protein (ChREBP) and sterol response element binding protein-1c (SREBP-1c), two major transcriptional regulators of genes that control *de novo* lipid synthesis. They observed that while expression of ChREBP was considerably reduced in the livers of *Aldh1a1*^{-/-} mice the steady state levels of SREBP-1c remained unchanged in these animals. Such a differential expression of ChREBP and SREBP-1c was unexpected since it is known that enhanced activation of AMPK by phosphorylation leads to reduced expression of both ChREBP and SREBP-1c.

Finally, Kiefer *et al*^[9] undertook metabolic cage studies to demonstrate that the ambient rate of oxygen consumption (VO₂) was higher in *Aldh1a1*^{-/-} mice that also elicited reduced respiratory quotient (VCO₂/VO₂). Interestingly, there were no changes in the rates of lipid oxidation in the liver as corroborated by similar hepatic expression levels of acyl Co-A oxidase 1, carnitine palmitoyltransferase 1 (CPT1) and PPAR coactivator 1 α (PGC-1 α) in WT and *Aldh1a1*^{-/-} mice. In contrast, skeletal muscle of *Aldh1a1*^{-/-} mice elicited higher expression of CPT1, medium chain acyl A dehydrogenase, PPAR α and PPAR δ . These data are consistent with the authors' conclusion that the improved lipid and lipoprotein profiles of *Aldh1a1*^{-/-} mice reflected a combined contribution of reduced lipogenesis and enhanced fatty acid oxidation.

The data presented in the current report come on the heels of another study reported by the same laboratory^[11] showing that genetic ablation of *Aldh1a1* resulted in lean body mass, reduced adiposity and increased ambient body temperature in the knockout animals. The *Aldh1a1* gene is highly expressed in the WAT of rodents and humans. However, whether retinoids are involved in the regulation of adipose tissue differentiation was not fully appreciated until the report of Kiefer *et al*^[11]. Using a number of complementary strategies, these authors revealed that a functional ablation of *Aldh1a1* in WAT induced a BAT like phenotype in these cells. The WAT of *Aldh1a1*^{-/-} mice expressed high levels of uncoupling protein 1, an observation consistent with the observed changes in adaptive thermogenesis in these animals. It is reasonable to surmise that in mice lacking *Aldh1a1*, Rald signaling *via* activation of its putative retinoid receptors lead to induction of BAT-like program of gene expression. Experimental ablation of *Aldh1a1* in WAT of obese mice by antisense oligonucleotides induced a *BAT-like* gene expression program mediated *via* recruitment of PGC-1. Taken together, these findings establish that retinoids integrate fasting glucose, hepatic gluconeogenesis and adaptive thermogenesis independent of body mass. The accumulated evidence strongly supports a role of Rald as a signaling retinoid with a potential to control adipocyte differentiation and as a regulator of metabolic homeostasis of lipids and lipoproteins.

While the studies of Kiefer *et al*^[11], significantly ad-

vance our understanding of a role of retinoids in the mechanisms of energy homeostasis they also raise a number of questions that remain unanswered. For example, while it is clear that Rald alters the phenotypic differentiation of WAT it is not known whether such a change in WAT phenotype also changes its ability to elicit pro-inflammatory cytokines (e.g., tumor necrosis factor- α or interleukin-6) that are known to modify T2D-associated pathology. Furthermore, we need to explore the potential changes in the expression of retinaldehyde transporters in Rald $^{-/-}$ mice since RBP-4 is known to significantly affect insulin sensitivity and T2D^[12,13]. Finally, the molecular mechanisms of the differential regulation of ChREBP and SREBP-1c by Rald and other retinoids need to be investigated in greater detail. Striking differences in the regulation of nutrient metabolism and mitochondrial oxidation in adipose tissue, liver and skeletal muscle deserve to be elucidated in greater detail in order to precisely define a role of Rald in the overall energy homeostasis.

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