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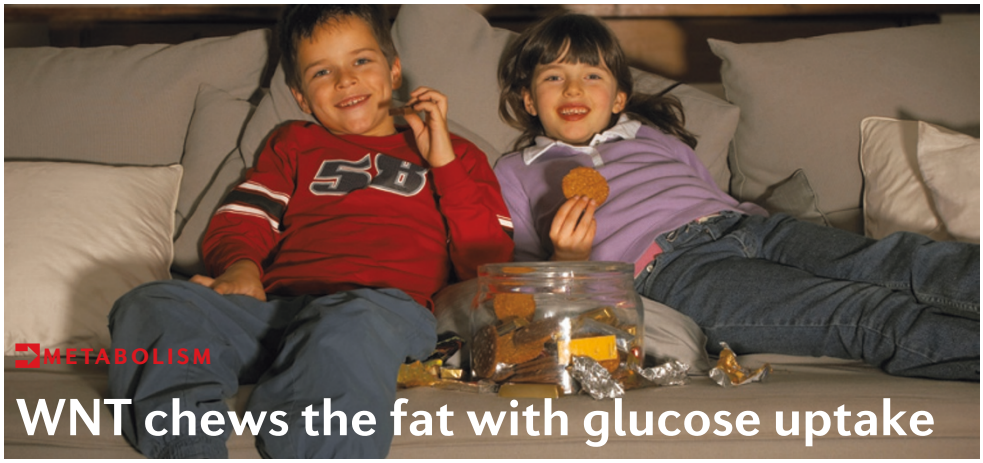

BANANASTOCK

METABOLISM

WNT chews the fat with glucose uptake

Adipose tissue regulates whole body metabolism through the secretion of factors that act at both proximal and distal sites. A recent study published in *Cell Metabolism* identified a link between the activation of β-catenin in adipose progenitor cells and glucose uptake in muscles.

Canonical WNT signalling, which results in the stabilization of the transcription factor β-catenin, regulates several developmental processes. WNT ligands have been previously shown to inhibit differentiation of adipose tissue. To identify the cell type in which WNT ligands act to mediate this inhibitory effect, Zeve *et al.* generated transgenic mice that express a constitutively active form of β-catenin specifically in differentiated adipocytes (A-BCA mice) or in peroxisome proliferator-activated receptor-γ (PPARγ)-expressing adipose progenitor cells (P-BCA mice).

Constitutive activation of β-catenin in mature adipocytes had no effect on adipose tissue integrity and whole body metabolism. By contrast, β-catenin activation in adipose progenitor cells resulted in adipose tissue degeneration (lipodystrophy), as defined by low fat content, almost undetectable adipokine (adiponektin and leptin) levels, near-complete loss of visceral fat depots and unconventional morphology of subcutaneous fat depots. Notably, subcutaneous depots in P-BCA mice lacked adipocytes but contained collagen fibres and fibroblast-like cells. Moreover, fate-tracing experiments revealed that active β-catenin promoted the differentiation of adipose progenitor cells into a fibroblastic cell lineage rather than an adipocytic cell lineage.

But what are the metabolic effects of β-catenin-driven fat tissue degeneration? As expected, loss of adipose tissue correlated with increased triglyceride levels in the blood. However, unlike adipose tissue-deficient lipodystrophic mice (such as mice lacking PPARγ expression), P-BCA mice did not show any increase in blood glucose and insulin levels after feeding. In addition, P-BCA mice displayed low glucose levels (hypoglycaemia) in response to fasting. Thus, loss of fat as a consequence of constitutive activation of β-catenin in adipose progenitor cells is associated with an unexpected increase in glucose uptake.

Next, injection of radioactively labelled 2-deoxyglucose revealed that skeletal and cardiac muscles were the main sites of glucose absorption in P-BCA mice. Interestingly, increased glucose uptake in these mice was not due to increased insulin levels or insulin sensitivity. Instead, the authors observed increased AMP-activated protein kinase (AMPK) activation and increased membrane localization of glucose transporters in muscles of P-BCA mice, both before and after feeding. Furthermore, AMPK inhibition was sufficient to reverse hypoglycaemia in fasting mice as well as to increase blood glucose levels in fed mice, suggesting that insulin-independent glucose uptake in muscles of P-BCA mice requires AMPK activity.

Finally, Zeve *et al.* investigated the link between constitutive activation of canonical WNT signalling in adipose progenitor cells and AMPK-dependent glucose uptake in muscle. As they failed to detect cells that differentiated from PPARγ-expressing progenitors and WNT-induced gene expression in muscle, they hypothesized that increased muscle glucose uptake in P-BCA mice was induced by a soluble muscle-extrinsic factor. Indeed, incubation of isolated wild-type muscle in serum from P-BCA mice or in supernatant from β-catenin-expressing adipose progenitor cell cultures was sufficient to increase AMPK activation and glucose uptake.

Thus, activation of canonical WNT signalling in adipose progenitor cells and the resulting adipose tissue degeneration seem to regulate distal glucose uptake in muscles through an undefined fat–muscle endocrine axis. Further elucidation of the components of this pathway might provide new insights into the regulation of glucose homeostasis.

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ORIGINAL RESEARCH PAPER Zeve, D. *et al.* WNT signaling activation in adipose progenitors promotes insulin-independent muscle glucose uptake. *Cell Metab.* **15**, 492–504 (2012)