

ADRENAL FUNCTION

Paradigm shift for ACTH suppression

“
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Glucocorticoid-replacement therapy with cortisol is the current recommended treatment for congenital adrenal hyperplasia (CAH). However, doses sufficient to suppress levels of adrenocorticotrophic hormone (ACTH) and excess androgens are associated with adverse metabolic effects such as obesity.

Now, new research published in *Science Translational Medicine* shows that another glucocorticoid, corticosterone, might be just as effective as cortisol but less likely to promote

metabolic dysfunction in peripheral tissues such as adipose tissue. As patients with CAH are at increased risk of cardiometabolic disease, which is exacerbated by glucocorticoid-replacement therapy, corticosterone might be a metabolically favourable alternative to cortisol for ACTH suppression in patients with adrenal insufficiency.

Using a transcriptomic approach, Brian Walker and colleagues at the University of Edinburgh showed that *ABCC1* (encoding the corticosterone transporter *ABCC1*) but not *ABCB1* (encoding the cortisol transporter *ABCB1*) was highly expressed in subcutaneous adipose tissue of healthy men. Functionality of this differential gene expression (that is, preferential export of corticosterone from adipocytes) was confirmed by the finding of lower intracellular levels of corticosterone in corticosterone-treated adipocytes than corresponding cortisol levels in cortisol-treated adipocytes. Moreover, expression of *ABCC1* mRNA was upregulated and concentrations of corticosterone were consistently low in samples of adipose tissue from individuals with obesity.

The findings are consistent with *ABCC1* making adipose tissue more sensitive to the effects of cortisol than to those of corticosterone.

The investigators tested their hypothesis that corticosterone could suppress ACTH levels as effectively as cortisol but without adverse metabolic effects in patients with Addison disease. Similar levels of suppression of ACTH were achieved with cortisol and corticosterone, but glucocorticoid-responsive gene transcription (a marker of metabolic dysfunction) was lower in subcutaneous adipose tissue with corticosterone than with cortisol. Going forward, the investigators are hoping to develop an oral formulation of corticosterone that can be used in clinical trials assessing the efficacy of this alternative glucocorticoid in patients with CAH and other forms of adrenal insufficiency.

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ORIGINAL ARTICLE Nixon, M. *et al.* *ABCC1* confers tissue-specific sensitivity to cortisol versus corticosterone: a rationale for safer glucocorticoid replacement therapy. *Sci. Transl. Med.* **8**, 352ra109 (2016)