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Selective Inhibitors of 11β-Hydroxysteroid Dehydrogenase Type 1 for Patients With Metabolic Syndrome

Is the Target Liver, Fat, or Both?

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An exciting era is upon us in terms of new therapies for patients with diabetes, obesity, and metabolic syndrome. One such advance is the ability to selectively manipulate tissue levels of glucocorticoids through targeted inhibition of cortisol metabolic pathways. Perhaps the best paradigm for metabolic syndrome comes from patients with Cushing's syndrome, with their characteristic central obesity, glucose intolerance, hypertension, and premature cardiovascular mortality. Although circulating cortisol concentrations are invariably normal in patients with obesity and metabolic syndrome (1), in vitro, in vivo, and clinical studies over the last decade have collectively shown the importance of local generation of cortisol, via 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in liver and fat, in mediating many facets of the metabolic syndrome (2). Major pharmaceutical companies are now engaged; over 50 patents have been issued detailing compounds and strategies for selective 11β-HSD1 inhibition. Preclinical animal studies have shown proof of concept, with improved glucose tolerance and weight reduction reported in many diabetic and obese mouse models treated with 11β-HSD1 inhibitors (3–6). Phase I and II clinical data reported at the American Diabetes Association's Scientific Sessions in June 2008 were equally encouraging (7).

11β-HSD1 is a bidirectional enzyme that interconverts hormonally inactive cortisone to cortisol. Unlike cortisol, cortisone is not synthesized within the adrenal gland; its circulating pool of ~80 nmol/l is largely dependent on dehydrogenase activity (cortisol to cortisone) from the related isozyme 11β-HSD2, expressed in kidney and gut. Nevertheless, the reductase activity of 11β-HSD1 can regenerate cortisol in tissues with high enzyme expression, predominantly liver and fat.

The autocrine consequences of this are clear: in the liver, facilitating hepatic glucose output through stimulated gluconeogenesis, and in adipose tissue, stimulating adipogenesis and lipolysis with release of free fatty acids. But what is the overall contribution, if any, of this generation of cortisol from liver and fat to circulating concentrations? Importantly, what might be the additional effect of 11β-HSD1 in omental fat delivering excess cortisol to the liver via the portal vein?

In this issue of *Diabetes*, Stimson et al. (8) and Basu et al. (9) have used stable cortisol isotopes in detailed clinical integrative physiological studies to evaluate the relative contribution of liver versus fat in generating cortisol via the 11β-HSD flux. Deuterated D4 cortisol is infused, which, when converted by 11β-HSD2, yields D3 cortisone. The subsequent appearance of D3 cortisol exclusively reflects 11β-HSD1 reductase activity. Selective catheterization of hepatic vein, portal vein, and abdominal vascular beds confirms that the liver is a major cortisol producer; the absolute values differ markedly from study to study, and some results seen are incompatible with normal daily cortisol secretion rates. For example, Basu et al. report a hepatic cortisol production rate of 23 μg/min, which equates to 33 mg/day, and Stimson et al. report ~18 mg/day; both are greatly in excess of the established daily cortisol production rate of ~10 mg/day (10). Stimson et al. also show that subcutaneous fat can generate cortisol, and this may explain in part the increased cortisol secretion rates documented in obesity. Both studies, however, are quite clear in showing no apparent release of cortisol from the viscera: all of the increased cortisol production in the splanchnic circulation reflects hepatic and not visceral production. The data confirm earlier canine studies performed in the laboratory of R.A. Rizza (11) but seem to contradict earlier studies by Walker and colleagues (12) that suggested that up to two-thirds of splanchnic cortisol production might originate from the viscera.

There are some additional caveats. Such invasive studies are not possible on healthy volunteers. Patients studied had either severe obesity and were undergoing bariatric surgery or had severe liver disease and were undergoing portal venous shunting; both scenarios have been shown to significantly alter cortisol secretion and metabolism. Furthermore, the catheterization procedures do not specifically sample omental fat but reflect drainage into the whole portal vein that may cause some dilution from other visceral tissues. Of particular relevance might be the gut, which expresses abundant amounts of 11β-HSD2 that may contribute to increased portal vein cortisone concentrations. These issues aside, it seems unlikely that visceral fat contributes a significant delivery of cortisol to the liver.

Do these findings alter our desire to inhibit 11β-HSD1 in liver and fat in patients with metabolic syndrome? Proba-

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bly not. Undoubtedly, the major immediate effect of 11β-HSD1 inhibition in patients with diabetes will relate to reduced glucocorticoid-mediated hepatic glucose output. However, the longer-term beneficial effects of blocking the autocrine actions of cortisol in omental adipose tissue should not be dismissed. This may not impact on exposure of the liver to portal vein steroids, but the reduction in adipogenesis will improve body composition and potentially improve other cardiovascular risk factors such as dyslipidemia and hypertension.

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