The metabolic syndrome is a disease with ever-increasing prevalence and extensive cost to the health systems of the Western world. Until a decade ago, the etiology of this disease, dominated by obesity, diabetes mellitus type 2, hyperlipidemia, hypertension and subsequent morbidity such as arteriosclerosis, coronary heart disease and chronic renal failure, has by and large been attributed to overeating and a lack of physical exercise. In the last decade, however, exciting new findings have greatly increased our knowledge about factors contributing to the pathogenesis of obesity and its sequelae. One such finding is the association between low birth weight and obesity, diabetes mellitus and coronary heart disease first advocated by Barker leading to the so-called Barker hypothesis (1, 2). This initially criticized hypothesis has been widely accepted and confirmed for a number of different populations. However, the pathophysiological link between low birth weight and the metabolic syndrome still needs to be elucidated.

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The role of 11β-hydroxysteroid dehydrogenase activity in the metabolic syndrome: lessons learned from the animal model

The metabolic syndrome is a disease with ever-increasing prevalence and extensive cost to the health systems of the Western world. Until a decade ago, the etiology of this disease, dominated by obesity, diabetes mellitus type 2, hyperlipidemia, hypertension and subsequent morbidity such as arteriosclerosis, coronary heart disease and chronic renal failure, has by and large been attributed to overeating and a lack of physical exercise. In the last decade, however, exciting new findings have greatly increased our knowledge about factors contributing to the pathogenesis of obesity and its sequelae. One such finding is the association between low birth weight and obesity, diabetes mellitus and coronary heart disease first advocated by Barker leading to the so-called Barker hypothesis (1, 2). This initially criticized hypothesis has been widely accepted and confirmed for a number of different populations. However, the pathophysiological link between low birth weight and the metabolic syndrome still needs to be elucidated.

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controls. Intraportal glucose tolerance and insulin tolerance tests revealed pathological profiles.

Certain restrictions, however, must be taken into account with regard to the transgenic model of visceral obesity described by Masuzaki et al. (8). As usual in the field of energy balance and body weight, rodent data cannot be transferred directly to the human, although hyperphagia in the transgenic mice, despite hyperleptinemia, much resembles conditions in the human. Secondly, the data depicted have been established only in male mice, completely neglecting female animals. Although visceral obesity is more prevalent in male humans, it is also present in women. It would be interesting to evaluate whether female animals behave like their male littermates in characterizing gender-specific effects. Another aspect is that blood pressure measurements are lacking in the report. Since hypertension is an essential feature of the metabolic syndrome and cortisol binds as avidly to the mineralocorticoid receptor as aldosterone (11) (Fig. 1), data on blood pressure regulation are needed to characterize the metabolic syndrome in the animals. Finally, the precise pathophysiological sequence of events following local hypercortisolism in transgenic animals remains to be shown. Despite descriptive evidence that glucocorticoid receptor α isoform and lipoprotein lipase mRNA expression in mesenteric adipose tissue may be involved, and expression of adipose genes that are known or suspected of influencing systemic metabolic pathways (adipocyte complement-related protein 30 (Acrp30)-AdipoQ, Resistin, Angiotensinogen, uncoupling protein 1 (UCP-1)) are altered in this animal model, functional and pharmacological studies may help to prove the relevance of these pathways and elucidate the exact mechanism.

Taken together, the transgenic 11β-HSD1 mice allows for a link between human Cushing’s syndrome in which hypercortisolism is mandatory and merely local (i.e. tissue-confined) hypercortisolism. Although cortisol concentrations are not elevated in the serum of obese humans (12), adipose tissue from obese humans has increased 11β-HSD1 activity (13). Thus, the enzyme may serve as a tissue-specific amplifier of glucocorticoid action (14). The concept of tissue-specific alteration of glucocorticoid activity is not new and is well known for the placental 11β-HSD2 isoenzyme. By converting maternal cortisol to cortisone, the human placenta protects the fetus from cortisol excess which promotes intrauterine growth retardation and prenatal programming of hypertension (15, 16).

In summary, we learn from the exciting study on 11β-HSD1 transgenic mice that tissue-specific glucocorticoid-dependent adipocyte pathways have a major impact on systemic metabolism and may provide a possible new target for the treatment of visceral obesity and the metabolic syndrome in humans.

References


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