

Fig – the ideal biomedical model of obesity related traits?

INTRODUCTION

Obesity and related diseases such as atherosclerosis and diabetes in man are the primary cause of disease-associated mortality in industrialized countries. The current knowledge of the complex nature of obesity related traits has been achieved by different strategies of research. First, numerous epidemiological and clinical studies have identified disorders of lipoprotein metabolism as a major risk factor for atherosclerosis and consequently cardiovascular diseases (CAD). Moreover mice, rats and pigs have been used as models to estimate the number, location and effect of genes controlling these traits. Cloning of causative genes and elucidation of the molecular mechanisms underlying these traits has largely been achieved by *in vitro* studies and the use of several animal models including rats, mice, hamsters, guinea-pigs, rabbits, cats, dogs and pigs. One of the major limitations using these animal models is related to cholesterol and lipoprotein metabolism as these metabolic pathways significantly vary in animals compared to humans.

Energy homeostasis is predominantly regulated through transcriptional control and requires specific signals to be transduced to the cell nucleus where defined sets of genes are targeted. Virtually all transcription factors participate in metabolic regulation, however a few of them have a clear predominant role. Among these are members of the nuclear receptor family such as the peroxisome proliferator activated receptor (PPAR) and the liver X receptor (LXR) that both act as “sensor” receptors (reviewed by Desvergne et al., *In Press*). These metabolic sensors bind a broad range of molecules which are implicated in metabolic pathways, such as fatty acids, eicosanoids and oxysterols. Upon activation by dietary signals and/or metabolites generated by the organism, these receptors modulate the expression of their target genes and thus are responsible for metabolic adaptations at the cellular, organ and whole organism level. As could be suspected from sensors of fatty acids and their derivatives, PPARs regulate most of the main branches of intermediary metabolism of lipid, protein and carbohydrate (reviewed by Desvergne et al., 1999). The chemical nature of the specific fatty acid influences its potential for activating PPARs (Göttlicher et al., 1992, Schmidt et al., 1992, Issemann et al., 1993, Krey et al., 1993) and thereby its secondary metabolic effect. Among the natural existing fatty acids are commercially available isoforms of conjugated linoleic acid (CLA) which are PPAR-activators and further have potent positive effects on metabolism (Moya-Camarena et al., 1999). In mice this includes among other things a reduction of body fat mass and increased lean body mass, along with its hypolipidemic effect (reviewed by Moya-Camarena and Belury, 1999). The functional role of PPARs has largely emerged through their potential as drug targets for the insulin sensitizing

thiazolidinediones (TZD) (Lehman et al., 1995) and hypolipidemic fibrate like compounds in metabolic disorders such as diabetes and CAD in man, respectively.

Elucidation of the adverse metabolic effects of these bioactive fatty acids and drugs, as well as the underlying molecular mechanisms, requires a more human-like model for both the healthy and disease situations in man. The most widely used models are mice and rats that clearly suffer from the lack of similarity to human lipid- and lipoprotein metabolism and additionally are resistant to normal atherosclerosis development. In comparison, the pig should be a more appropriate model since pigs possess a human-like cardiovascular system that develops experimental CAD (Douglas et al., 1972, Lee et al., 1986). Additionally, the pig is suitable for studying lipoprotein metabolism associated with hyperlipidemia as pigs carry cholesterol in both LDL and HDL lipoprotein particles (Jokinen et al., 1985, Mahley et al., 1975).

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