



Of mice and men: Considerations on adipose tissue physiology in animal models of obesity and human studies[☆]

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ABSTRACT

The ever-increasing burden of obesity demands a better pathophysiological understanding, especially regarding adipose tissue pathophysiology. Animal models of obesity are of great importance in investigating potential mechanisms and implications of obesity. Many issues should be considered while interpreting the preclinical results as anatomical and pathophysiological differences exist among species. Importantly, the natural history of obesity development differs considerably. An important example of conflicting results among preclinical models and human physiological studies is that of adipose tissue oxygenation, where rodent models almost unanimously have shown the presence of hypoxia in the adipose tissue of obese animals while human studies have yielded conflicting results to date. Other issues which require further clarification before generalizing preclinical data in humans include adipose tissue browning, endocrine function and fibrosis. The aim of this mini-review is to synopsise similarities and differences between rodent models and humans, which should be taken into consideration in obesity studies.

Obesity has increased substantially in the last few decades, becoming an important worldwide public health problem that impacts on the risk and prognosis of several disease states, including cardiovascular disease, metabolic syndrome, Type 2 diabetes mellitus (T2DM), COVID-19 and cancer [1–10]. Obesity is a complex, multifactorial chronic disease, defined by a body mass index (BMI) of 30 kg/m² or above, and is characterised by an excessive increase of white adipose tissue (AT) mass [11]. The pathophysiological background of obesity and its complications are not only determined by the AT mass, but are also influenced by AT dysfunction, body fat distribution, and disease stage [11–15]. Rodent models are the most used animal models at the preclinical level to investigate human obesity [16–20]. However, confirmation of important similarities and differences between rodent models and humans are necessary and should be taken into consideration in obesity studies (see Fig. 1).

Dissimilar to humans who have two main subcutaneous depots located in the abdominal and gluteofemoral region, rodent adipose tissue has two main subcutaneous pads located anteriorly and posteriorly [16]. Visceral adipose tissue in humans surrounds mainly intra-abdominal organs while in rodents it surrounds primarily the perigonadal region, epididymal in males and periovarian in females [16, 21]. Adipocytes in these depots display genetic and metabolic heterogeneity and are intrinsically different within and amongst species [16, 22,23].

An important aspect of AT physiology concerns the so-called “browning” of WAT. Brown AT (BAT) constitutes a distinct functional AT component exhibiting a high degree of vascularization and density of mitochondria, which partake in futile respiratory cycles promoting thermogenesis [24]. Evidence from rodent models has suggested that WAT browning may exert protective effects against weight gain and

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related dysmetabolism, rendering this pathway also an attractive candidate for the prevention and treatment of human obesity [25,26]. Despite accumulating evidence from preclinical models, there is a long way ahead before their clinical application in humans, whereby the relevance of BAT in obesity and metabolism is still unsatisfactory understood. The finding of opposite trends between mice and humans with respect to the expression of browning genes in the subcutaneous and visceral WAT depot further highlight the imperativeness of this task [24].

Another issue relevant to inter-species differences concerns the function of AT as an endocrine organ. The discovery of leptin, the first adipokine in 1994, was followed by the identification of a remarkable variety of AT-derived hormones, some with well-characterized and conserved across species functions (i.e. adiponectin) [7,27–32], and others less so [33–38]. Although several important similarities between rodents and humans exist, the common cellular origin [39], systemic metabolic actions [40–43] or interactions with other hormonal systems [44] is not a given. As the role of several adipokines is becoming increasingly clear, this is particularly important before generalising mechanistic findings from rodent obesity models in humans.

Outside of the strict frame of pathophysiological mechanisms, the pathogenesis of human obesity is shaped through complex interactions between biological, environmental, and behavioural factors which are unique to our species. A striking paradigm is the gradual development and indolent progression of obesity in most humans over several years, which comes in stark contrast with the rapid and massive gain in adipose tissue mass observed in rodent models, either genotype- or diet-related [45–49]. Diet-induced obesity (DIO) animal models reproduce with greater reliability human obesity in comparison with genetic models, usually utilizing high-fat diets (HFD) with elevated concentrations of saturated fatty acids [23,50]. The most frequently used animal models through diet are mice, with isogenic or inbred strains, such as C57BL/6, C57BL/6J, AKR/J, and A/J [23]. Further considerations that should be taken into account is that rats and mice respond differently to diet; and strain, sex and age, affect the responses to diet, with younger animals and males being more sensitive to obesity-related comorbidities [23].

Besides, another unique feature of human obesity which cannot be readily replicated in animal models, is the modification of caloric intake and, to a lesser degree, energy expenditure through environmental, behavioural and body image-related factors. An overly simplified example of this notion concerns the question on why humans become obese and strive for unhealthy, highly caloric diets and overall lifestyles, even though being aware of the unavoidable consequences. Obviously,

this feature is usually not dependent upon the quantity or quality of available dietary resources, as is the case in most animal models [51]. To further complicate the matters, data from animal models with respect to the relative contribution of isolated hormonal appetite and satiety signals cannot be directly applied in human research and clinical practice. For example, even though leptin-deficient rodents have been frequently used in various studies to investigate obesity, leptin or leptin receptor mutations are rare in humans and the drivers for the behavioural traits of the vast majority of cases of human obesity are complex and yet to be elucidated [51–53].

Many animals have been examined and provided valuable mechanistic insights in adipose tissue physiopathology in obesity, partly characterised by chronic low-grade inflammation [54,55]. It has been postulated that the chronic low-grade inflammation present in adipose tissue in individuals or animals with obesity is triggered partly by hypoxia, caused by the decreased capillary density, and blunted adipose tissue blood flow [55–57]. The presence of hypoxia in obese adipose tissue was originally shown in murine models of obesity [14,58]. Direct measurements of pO₂ using needle-type O₂ electrodes showed that WAT oxygenation is lower in *ob/ob*, *KK^{ay}* and *DIO* mice as compared to lean controls [14,45–48,59]. In line with these findings, gene expression of several hypoxia-related genes, including hypoxia-inducible factor-1 alpha (HIF-1 α), was also increased. Moreover, using pimonidazole hydrochloride, which stains hypoxic areas, it has been demonstrated that hypoxic areas were more prevalent in the WAT of obese rodents [14,45–48,59]. However, the presence of hypoxia in adipose tissue in human obesity was shown to be present at least in participants with severe obesity and co-exists with type 2 diabetes, being challenged by recent studies in humans [55,60–63]. This example if further replicated and confirmed in further research studies, may show a potential interspecies difference which it could be partly attributed to the acutely induced obesity in these models. AT fibrosis constitutes another partly hypoxia-related event observed in rodents and humans with consequences regarding AT-function and systemic metabolism [64]. Since this phenomenon seems to also exert an impact on bariatric surgery-related outcomes, it is of capital importance for the generalizability of findings from animal studies to humans to be further clarified.

In conclusion, animal models of obesity are valuable means of examining various mechanisms of obesity and related comorbidities in preclinical status. However, caution should be given with respect to the potential limitations and applicability to humans, especially regarding the issue of hypoxia and other potentially important aspects of rodent AT physiology, whose role in human obesity remains elusive.

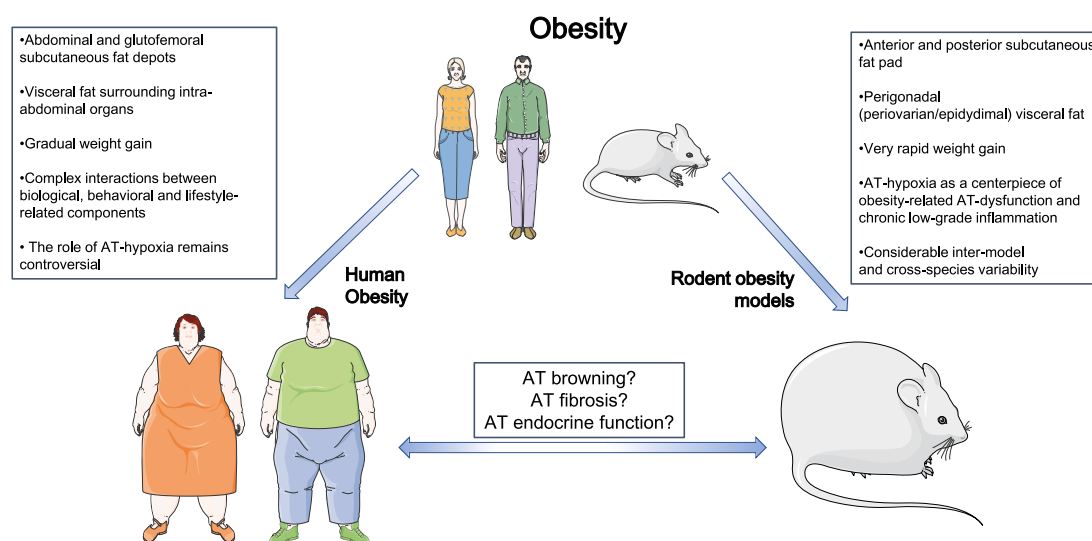


Fig. 1. Features of adipose tissue and its role in obesity which differ between rodent models and humans.

Declaration of competing interest

None.

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