Adipose tissue changes in obesity

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Abstract

This review gives a broad description of some of the changes in adipose tissue seen in obesity. There are multiple changes in adipose tissue in obesity: histological, neural and vascular, relating to lipid and carbohydrate metabolism and to adipose tissue’s endocrine functions. Some may originate from a simple physical expansion of cell size and number. It is unclear which are the most important either in terms of intermediary metabolism or of contributing to the co-morbidities of obesity. Important questions for the future include the reversibility of obesity-related changes and indeed whether the changes differ between depots and species. Recent studies examining physiological regulation within adipose tissue demonstrate it to be relatively unresponsive to changes in everyday life.

Introduction

Although currently defined by the WHO (World Health Organization) in terms of excess weight for a given height [1], obesity is best considered as being an increase in adiposity. Of necessity, this involves an increase in adipose tissue mass. This review will outline some of the changes in adipose tissue that occur in obesity, with special reference to the changes in behaviour of the tissue as well as to the expanded adipose tissue mass. Given that there are important differences in the way that species respond to net energy surpluses, not least in the behaviour of adipose tissue [2,3], this review will concentrate on human data when possible.

There are multiple changes in adipose tissue in obesity. Some of the headings under which the changes can be considered are listed in Table 1. This review will not consider changes in non-adipose tissue, although these are potentially of considerable importance; for example, insulin resistance seen in adiposity may be especially closely linked to hepatic steatosis rather than to other features of obesity [4,5].

Regarding the multiple changes in adiposity outlined in Table 1, it may be worthwhile considering which are (i) ‘basal state’, rather than changes in physiological regulation, (ii) whether the changes are reversible with weight loss, and (iii) to what extent the changes are universal across different adipose depots and different models of obesity.

Basal state versus changes in physiological regulation

Although often characterized as a relatively inert organ used for long-term storage, adipose tissue is more than that in that it also shows active changes in response to each meal, to short periods of exercise and to even overnight fasts [6,7]. Perhaps because it is easier to study the static condition, most work examining adipose tissue has concentrated on the adynamic basal state changes in adipose tissue in obesity. However, recent work had demonstrated clear differences in the way that adipose tissue responds to feeding/fasting in obesity, and these changes in physiological regulation are potentially at least as important as the basal state abnormalities. Not least because some of these changes are more recently recognized, this review will pay especial attention to them.

Macroscopic changes in adipose tissue

In obesity, most adipose depots visibly expand. In humans, there is a tendency for waist/hip ratios to increase with obesity [8]. MRI (magnetic resonance imaging) scan studies show this to be due to a relative expansion of liver and splanchnic adipose tissue. However, we currently have an incomplete understanding of the factors that determine adipose tissue distribution. The factors that are known to affect adipose distribution include steroid hormones (both sex steroids and glucocorticoids) [9], but these do not account for all the changes seen. Other confounding factors are that exercise seems to ‘shrink’ visceral fat faster than gluteal fat [10] and that recent weight gain (as opposed to stable adiposity) is especially prone to enlarge visceral depots.

Histological changes in adipose tissue

The reader can do no better than consult the works of Cinti [11–14] for this area. Consistently, obesity is associated with (i) increase in numbers of adipocytes, (ii) increase in size of adipocytes, (iii) infiltration of adipose depots by mononuclear cells [15], (iv) relative rarefaction of blood vessels, and (v) relative rarefaction of neural structures.

Increases in adipocyte turnover rate, differentiation and apoptosis are described in relation to weight gain, to various drugs (e.g. thiazolidinediones) and other conditions (e.g. HIV lipodystrophy). There seems to be less information about rates of adipocyte turnover in weight-stable obesity.

Functional changes in adipose tissue innervation

As mentioned above, the cross-sectional area of neural structures per unit weight of adipose tissue is reduced in...
Summary of changes in adipose tissue in obesity

Changes in non-adipose tissue
- Increased fat content in liver
- Increased fat content in skeletal muscle
- Increased infiltration of organs with adipocytes

Macroscopic changes in adipose tissue
- Increase in size of many or all adipose depots
- Changes in relative size of different adipose tissue depots

Histological changes
- Changes in adipocyte number
- Changes in adipocyte size
- Changes in adipocyte differentiation and apoptosis
- Changes in non-adipocyte cell content
- Changes in neural network
- Changes in vasculature in adipose tissue

Functional changes in adipose tissue blood supply
- Blood flow
- Capillary permeability
- Changes in blood flow in response to food

Functional changes in adipose tissue innervation
- Changes in sensory innervation of adipose tissue
- Changes in effector innervation of adipose tissue
- Changes in adrenoceptor number and type

Changes in adipose tissue in relation to energy storage
- Uptake of glucose
- Uptake of fatty acids

Changes in adipose tissue in relation to energy release
- Changes in 'basal' rates of lipolysis
- Changes in responses of lipolysis in relation to food
- Changes in response of lipolysis in relation to exercise

Changes in adipose tissue autocrine/paracrine function
- Changes in secretion of paracrine factors

Changes in adipose tissue endocrine function
- Changes in secretion of endocrine factors

Table 1 | Summary of changes in adipose tissue in obesity

<table>
<thead>
<tr>
<th>Category of change</th>
<th>Specific change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in non-adipose tissue</td>
<td>Increased fat content in liver, increased fat content in skeletal muscle, increased infiltration of organs with adipocytes</td>
</tr>
<tr>
<td>Macroscopic changes in adipose tissue</td>
<td>Increase in size of many or all adipose depots, changes in relative size of different adipose tissue depots</td>
</tr>
<tr>
<td>Histological changes</td>
<td>Changes in adipocyte number, changes in adipocyte size, changes in adipocyte differentiation and apoptosis, changes in non-adipocyte cell content, changes in neural network, changes in vasculature in adipose tissue</td>
</tr>
<tr>
<td>Functional changes in adipose tissue blood supply</td>
<td>Blood flow, capillary permeability, changes in blood flow in response to food</td>
</tr>
<tr>
<td>Functional changes in adipose tissue innervation</td>
<td>Changes in sensory innervation of adipose tissue, changes in effector innervation of adipose tissue, changes in adrenoceptor number and type</td>
</tr>
<tr>
<td>Changes in adipose tissue in relation to energy storage</td>
<td>Uptake of glucose, uptake of fatty acids</td>
</tr>
<tr>
<td>Changes in adipose tissue in relation to energy release</td>
<td>Changes in 'basal' rates of lipolysis, changes in responses of lipolysis in relation to food, changes in response of lipolysis in relation to exercise</td>
</tr>
</tbody>
</table>

Changes in adipose tissue energy storage

Energy storage in adipose tissue takes place in the post-prandial period rather than in 'basal' post-absorptive states and has been relatively little studied. The limited amount of data available suggests that glucose uptake into adipose tissue is not markedly different in a group of obese humans (who were significantly hyperinsulinaemic and hyperglycaemic) compared with a lean group [28].

Comparisons of fatty acid uptake (from circulating triacylglycerol-rich lipoproteins under the influence of lipoprotein lipase, LPL) in lean and obese demonstrate abnormalities both in terms of LPL mass and activity [29] and net fatty acid flux [30].

Changes in adipose tissue energy release

Consideration of this issue requires consideration of what might be termed the 'denominator problem'. In general, in human obesity (i) whole body studies show lipolysis to be increased in absolute terms, (ii) whole body studies show lipolysis to be increased per 100 g of lean body mass, (iii) whole body studies show lipolysis to be reduced per 'basal' of obese subjects [18,19]. Furthermore, there appears to be a defect in the response to food where lean subjects show an increase in spillover, while obese subjects do not [19]. These defects appear to be specific to adipose tissue in that they are not seen in forearm skeletal muscle.

There are multiple changes in adrenoceptors in obesity [20,21]. These appear to differ between depots [22,23]. It is difficult to establish whether these receptors are responding to locally released noradrenaline or to circulating catecholamines. Pharmacological studies imply that they are capable of responding to both, but the physiological situation is unclear in both lean and obese subjects.

**Functional changes in adipose tissue vasculature**

As mentioned above, the cross-sectional area of blood vessels per unit weight of adipose tissue is reduced in obesity. Post-absorptive ('basal') blood flow per unit weight of tissue is reduced in obesity [24,25].

Capillary diffusion capacity for glycerol (measured as the capillary permeability × surface area product 'ps') is reduced in obesity [26]. Given that glycerol is passively transported, this is likely to be true for all other solutes that are passively transported across the capillary without a specific transport mechanism.

In contrast with the response of lean subjects, adipose tissue blood flow does not increase in response to food in obese subjects [25]. The normal increase in blood flow is blocked by local infusion of propranolol [27], suggesting that this defect may be linked to the defect in noradrenaline release previously mentioned.

Changes in adipose tissue energy release

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obesity. Sensory nerves in adipose tissue can be demonstrated by various sophisticated methods. Specific lesions of these nerves appear to cause atrophy of the adipose depots [16]. Unfortunately, little is known about how the function of sensory nerves in adipose tissue changes with obesity.

In rodent brown adipose tissue, effector nerves appear to stimulate lipolysis and thermogenesis. In white adipose tissue of human adults (and other species), the main effect of sympathetic nerves appears to be to stimulate blood flow, although it may also regulate pulsatile behaviour of the tissue [17]. Noradrenaline spillover (a surrogate marker for release from local nerve terminals) is reduced in the post-absorptive
100 g of fat tissue, and (iv) local studies show lipolysis to be reduced per 100 g of fat tissue. See [31] for information.

Lipolysis is also relatively unresponsive to food [30,32] and failure to increase lipolysis is a common feature of lack of physical fitness (most obese subjects being relatively unfit) [33].

Changes in secretion of paracrine and endocrine factors

There are multiple factors secreted by adipose tissue. For comprehensive lists, the reader is referred to previous reviews [34–37] and to Professor Trayhurn’s companion review in this issue [38].

However, demonstration that a protein is released by adipose tissue raises further interesting questions, including (i) Does the adipokine secretion vary with obesity? (ii) Is the adipokine truly secreted (it must reach circulation)? (iii) Is it secreted from human adult white adipose tissue? (iv) Is adipose secretion quantitatively important (with significant amounts of adipokine secreted)?

For most of the proteins mentioned in the aforementioned reviews, the secretion of protein is either increased per unit weight of adipose tissue (e.g. leptin) or at least similar per unit weight of tissue (e.g. angiotensin). In either case, the expanded whole-body fat mass in obesity would increase protein release by the whole-body adipose tissue mass. The notable exception is adiponectin, which declines both in whole-body terms and in release per unit mass of adipose tissue in obesity.

Table 2 lists some of the most interesting proteins secreted by adipose tissue in vitro and indicates whether studies have sought to determine whether the protein is truly secreted in vivo in amounts that produce a detectable arteriovenous difference. The third column of Table 2 indicates the results of such studies. The absence of a detectable arteriovenous difference does not exclude physiologically important systemic release in the case of proteins with a long plasma half-life. However, other interpretations of proteins that have no detectable arteriovenous difference are that these proteins are paracrine, rather than endocrine, factors or that regional heterogeneity may necessitate that release by other depots be evaluated.

Even if proteins are secreted by adipose tissue, it should not be assumed that such secretion is quantitatively important to the whole body. Adipose tissue can act as an apparently ‘feeble’ endocrine organ (for example, sex and glucocorticoid steroid conversion occurs in adipose tissue), but this is only a minor contribution to whole-body steroid production [39].

Regional heterogeneity

This has been inadequately explored; however, regional heterogeneity has been demonstrated by almost all studies that have sought it whether by histology, mRNA expression, enzymatic activity, microdialysis or arteriovenous difference methods [40]. The mechanisms determining heterogeneity between different adipose tissue depots are poorly understood.

Consequences of regional heterogeneity include both uncertainty as to the amount of secretion of lipids or proteins by the whole-body adipose organ and whether changes in obesity seen in one depot can be extrapolated to others.

Abnormalities of physiological regulation

The above-mentioned difficulties of the denominator problem, endocrine compared with paracrine secretion of proteins and regional heterogeneity complicate the interpretation of basal state findings. However, not all of these problems occur with the interpretation of studies examining the physiological regulation of adipose tissue. As has already been mentioned, in obesity, adipose tissue appears to show much reduced responses to physiological regulators, such as exercise or fasting/feeding. In response to these physiological changes,

Table 2 | Some proteins secreted by adipose tissue

<table>
<thead>
<tr>
<th>Protein</th>
<th>Release sought by in vivo studies?</th>
<th>Release detected by in vivo studies?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzymes</td>
<td></td>
<td></td>
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<tr>
<td>LPL</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Adipsin (ASP)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Growth factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGF</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>IGF-1</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cytokines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>IL-6</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>TNF</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cytokine soluble receptors</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Angiotsin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Adipophilin</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Resistin</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>PAI-1</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Metallothionein</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>FIAF</td>
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<td>No</td>
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<tr>
<td>Lipoprotein-related factors</td>
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<td></td>
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<tr>
<td>Apo E</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>FABP</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Intracellular regulatory proteins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADD1/SREBP1c</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>C/EBPα</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>PPARγ2</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
the adipose tissue of obese subjects does not show changes in blood flow [25], noradrenaline spillover [19], LPL or HSL (hormone-sensitive lipase) [30] activity.

### Universality and reversibility of changes in adipose tissue with obesity

As intimated above, it is very unclear whether obesity-related changes seen in individual adipose depots occur in other depots in the same individual, much less in different species.

The question of reversibility is a big and clinically important issue which has only recently begun to be addressed [41]. It is apparent that most of the abnormalities of adipose tissue and number. It is unclear which are most important either in

### Conclusions

There are multiple changes in adipose tissue in obesity. Some may originate from simple physical expansion of cell size and number. It is unclear which are most important either in terms of intermediary metabolism or of contributing to the co-morbidities of obesity. Important questions for the future include the reversibility of obesity-related changes and indeed whether the changes differ between depots and species. Recent studies examining physiological regulation within adipose tissue demonstrate it to be relatively unresponsive to changes in everyday life.

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### References


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