Editorial Review

Regulation of adipose cell number in man

Johannes B. PRINS and Stephen O’RAHILLY
Departments of Medicine and Clinical Biochemistry, University of Cambridge, Addenbrooke’s Hospital, Cambridge, U.K.

1. Adipose tissue mass is dependent on both the average volume and the number of its constituent adipocytes. Significant alteration in body mass involves alteration in both adipocyte volume and number.
2. Increases in adipocyte number occur via replication and differentiation of preadipocytes, a process which occurs throughout life. Decreases in adipocyte number occur via preadipocyte and adipocyte apoptosis, and possibly adipocyte dedifferentiation.
3. Overall regulation of adipose mass involves endocrine, paracrine and possibly autocrine systems. Hypothalamic centres appear to control appetite, metabolic rate and activity levels in a co-ordinated manner. Within the hypothalamus, known weight regulatory molecules include glucagon-like peptide-1, neuropeptide Y and leptin. Leptin is a major afferent signal from adipose tissue to the hypothalamus, providing information on overall adipose tissue mass. However, the precise means by which the hypothalamic signals to adipose tissue is less well understood.
4. In adipose tissue, known molecular regulators of adipose cell number include insulin, ligands for the peroxisome proliferator activated receptor-\(\gamma\), retinoids, corticosteroids and tumour necrosis factor-\(\alpha\). The net effect of these and other regulators is to effect a concerted alteration in adipocyte volume and number. This review largely focuses on the control of fat cell acquisition and loss and the influence of these processes on adipose tissue mass and regional distribution.

INTRODUCTION

Obesity is common, and is a major cause of, or contributor to, morbidity and mortality in Western societies. To a lesser extent, subnormal amounts of adipose tissue, as in anorexia nervosa, also have significant associated morbidity and mortality. There is considerable evidence that the incidence of both disorders is increasing, and therefore it is obvious that effective treatments or interventions for both disorders would alleviate much suffering, and may also reduce healthcare costs significantly. It is for this reason that adipose tissue research has undergone a resurgence in recent years – a resurgence buoyed by some major advances in our understanding of the pathophysiology of this complex tissue. It is now recognized to be a biologically active and dynamic tissue, with major endocrine and possibly immunological roles as well as its ‘traditional’ function as an energy storage depot.

Adipose tissue has a characteristic and unique feature in its enormous potential for volume (and hence mass) change. For example, the major tissue alteration that occurs in an individual whose weight increases from 70 to 150 kg is the quadrupling of fat mass – the skeletal and muscle mass remaining relatively (compared with the change in fat mass) unchanged. Should this individual then, by reducing energy intake but maintaining nutrition, slowly return to his ‘ideal’ weight, the reverse would occur with marked loss of adipose tissue and relative sparing of skeletal and muscle mass. How can adipose tissue accommodate these changes, what are their short- and long-term effects, and how are these processes regulated? Recent progress in our understanding of factors regulating adipose mass has provided some insight into these questions, and the aim of this review is to examine the contribution of changes in adipose cell number to the regulation of adipose tissue mass.

EVIDENCE FOR OVERALL REGULATION OF ADIPOSE MASS

Over the long term, adipose tissue mass reflects the net balance between energy expenditure – determined largely by basal metabolic rate (BMR) and exercise – and energy intake (quantity and type...
of food eaten). Depending on activity levels, 55–75% of human energy requirements are related to BMR [1]. That energy expenditure is amenable to change (aside from the effects of exercise) is evidenced by, for example, studies of individuals with thyroid disease, inflammatory diseases or pyrexia. However, even in view of the plasticity of BMR and (often dramatic) alterations in energy intake and exercise-related expenditure, most adults remain relatively constant in weight throughout their lives. This weight constancy suggests the possibility that BMR, appetite and energy expenditure are in some way linked, a notion supported in recent years by the realization that hypothalamic regions appear to control all three factors.

Evidence that body weight (and hence possibly BMR, appetite and levels of energy expenditure) may be genetically controlled comes from epidemiological, twin and adoption studies. These indicate that adult weight and fat distribution are genetically determined to a significant extent with a smaller environmental influence over adult weight or body mass index [2] and up to 85% of population variance in central abdominal fat attributable to genetic influences [3].

A question that has challenged researchers for decades pertains to the means whereby the hypothalamic centres controlling BMR, appetite and energy expenditure (and hence adipose mass) ‘know’ how fat the individual is at any time. The now classical parabiosis experiments of the 1960s (reviewed in [4]) suggested the existence of an endocrine feedback loop, and the recent identification of leptin [5] and its receptors [6, 7] have given dramatic support to this concept and led to improved understanding of the system. Further studies of the leptin hormonal axis indicate that it may be a significant regulator of BMR and that it appears to regulate appetite and activity levels [8–11] and to influence the gonadal, thyroid and adrenal axes [12, 13]. Furthermore, the immense power of the leptin system is demonstrated by the parabiosis experiments in which animals exposed to (what we now realize to be) high and unregulated levels of leptin starved to death.

Given that the total mass of adipose tissue appears to be centrally controlled [14] to a large degree, a key question is how the message to increase or decrease adipose mass is signalled.

MECHANISMS OF REGULATION OF ADIPOSE MASS

‘Central’ regulation of adipose mass

The leptin system is receiving enormous research attention currently, but the actual central signalling pathways involved in transducing the leptin signal await delineation. It is clear that other signalling molecules are involved, not least glucagon-like peptide-1, 5-hydroxytryptamine and neuropeptide Y, and an increased understanding of the interrelationships between these and other neurotransmitters may provide avenues for intervention. That this approach is at least feasible is shown by the efficacy of leptin administration (to rodents) in the induction of weight loss, and the effect of centrally acting drugs (e.g. dexfenfluramine, barbiturates) to assist in weight loss. Because BMR, appetite and activity levels appear to be centrally controlled, manipulation of the ‘central’ weight regulatory system offers an attractive avenue for pharmacological intervention.

Relationships between higher centres and adipose tissue

While hunger and satiety can be seen to induce weight gain or loss by a direct alteration in energy balance, the way in which a central (presumed hypothalamic) ‘decision’ to alter metabolic rate is mediated is not well understood (Fig. 1). How are heart rate and body temperature centrally regulated? How are cells and tissues signalled to alter energy use and what are the mediators? Obvious candidates include thyroid hormones and catecholamines. The role of the small amounts of brown adipose tissue and adipose \( \beta_3 \) adrenergic receptors present in adults [15] is largely unknown as trials of \( \beta_3 \) adrenoceptor agonists (aimed at stimulating brown adipose tissue and hence BMR) have proved disappointing with respect to weight loss [16]. Again, an understanding of the central to peripheral communication system may provide opportunities for intervention, with perhaps the added attraction of limiting other central nervous system (side) effects.

Local regulatory mechanisms in adipose tissue

Adipocyte size and number appear to be regulated in a co-ordinated manner. In weight gain, adipocyte volume and number increase. Similarly, when adipose loss occurs, adipocyte volume and number appear to reduce in concert. This suggests that local (paracrine) systems may be in part responsible for the regulation of adipose mass. The signalling pathways involved are as yet unknown, and an understanding of them, and possibly depot-related differences in them, may lead to interventions which could modify adipose mass via a local effect.

ADIPOSE TISSUE MASS REFLECTS ADIPOCYTE SIZE AND NUMBER

At any point in time, adipose tissue mass reflects the number and average volume of the component adipose cells [17]. Cell number and volume in turn reflect the balance of processes that decrease or increase each parameter (Fig. 2). Thus, because lipogenesis and lipolysis occur continuously in all adipocytes, with cytoplasmic lipid being in a state of
Regulation of human adiposity

flux, cell volume reflects the net outcome of these processes. Similarly, adipose cell number reflects the balance of cell acquisition and cell loss.

Lipogenesis and lipolysis are well-characterized processes affecting adipose cells, and can be relatively easily assessed *in vitro*. There is a substantial literature on these processes, and their controls and regulation *in vivo* and *in vitro* [18, 19]. In general terms, insulin and acylation stimulating protein [20] are the major lipogenic influences and catecholamines, thyroid hormones and growth hormone the major lipolytic influences. However, changes in cell volume are insufficient to fully account for variations in adipose mass either within or between individuals [17, 21]. Indeed, adipocyte volume and number appear to be in some way co-regulated. This is demonstrated by studies demonstrating that in a setting of weight gain, there is an initial increase in adipocyte volume until a 'critical' point is reached, and thereafter recruitment of new cells occurs [22]. This review will concentrate on the regulation of adipose cell number, and the mechanisms by which it may be increased or decreased.

**EVIDENCE THAT ADIPOSE CELL NUMBER IS VARIABLE**

While many studies have compared adipocyte volume and number between individuals, few studies have examined these parameters prospectively in the...
setting of weight change. Adipocyte size is greater in obese than lean individuals, but this size change does not account for the overall difference in adipose mass observed [23]. Hence, the only explanation is that obese individuals have a greater number of fat cells, and this was confirmed by Hirsch in 1971 [17]. Given that all obese individuals had at some stage less adipose tissue, these observations suggest that fat cell acquisition can occur in adult life. The identification of adipocyte stem cells (preadipocytes) [24] and the recognition of the adipocyte replication/differentiation program [25, 26] provided a mechanism by which adipose cells could be acquired at any stage of life (Fig. 3). The ability to repeat this replication/differentiation program in vitro, and the demonstration that preadipocytes injected subcutaneously in nude mice develop into mature fat pads [27], has provided convincing and well-accepted evidence that adipocyte cell acquisition occurs by this mechanism in vivo.

However, while the notion of adipocyte acquisition has gained widespread acceptance, it has also been generally accepted that this acquisition is permanent [28]. This is despite the knowledge that the vast majority of mammalian tissues are dynamic, and, as outlined above, the observation that in most individuals fat mass is relatively stable over time. This suggests that if adipose cell acquisition does occur in vivo, then a process of cell deletion must also be occurring to maintain cell number. Furthermore, based on our understanding of other tissues, this process is likely to be apoptosis.

Evidence for adipose cell loss does indeed exist. Firstly, a study by Geloen et al. [29] demonstrated that loss of adipocytes (based on quantification of adipose DNA and histology) occurs in rats rendered catabolic by streptozotocin-induced diabetes. Secondly, a number of studies of weight loss in humans by Sjöström et al. [30] and Miller et al. [31] have demonstrated that significant weight loss involves reduction in adipocyte number as well as adipocyte volume. Finally, we have demonstrated that adipocyte apoptosis occurs in vivo [32] in some circumstances.

**PROCESSES REGULATING ADIPOCYTE NUMBER**

**Adipose cell acquisition**

The process of adipocyte acquisition is analogous to that of haemopoetic cells and involves the clonal expansion and subsequent differentiation of preadipocytes. Thus, adipocytes represent terminally differentiated cells. Preadipocytes, first recognized in 1971 by Ng et al. [24], are located in the stromal-vascular fraction of adipose tissue, and can be isolated by collagenase digestion and centrifugation. The preadipocytes from the cellular pellet can then be cultured, and techniques for passaging and differentiation of these cells in vitro have been developed [25, 33–35]. Using these techniques we have successfully isolated and cultured preadipocytes from individuals up to 78 years of age, indicating that a pool of adipocyte precursors is present in humans throughout life. Utilizing these in vitro methods, much has been learnt about factors that influence preadipocyte replication and differentiation. It should be noted, however, that the vast majority of these studies used established cell lines of murine origin (e.g. 3T3-L1 and Ob 17) which differ substantially from human preadipocytes [36], not least in being aneuploid and capable of very high passage numbers [37]. The replication/differentiation schema based on these cell lines suggests that the replication of preadipocytes occurs before significant differentiation [38, 39]. However, in human preadipocyte studies, partially differentiated cells (as evidenced by substantial cytoplasmic lipid accumulation) are still capable of division as assessed histologically and by flow cytometry. In general, it appears that growth
factors favour preadipocyte replication (and not
differentiation) [40], while steroid hormones [41]
and insulin [42] favour differentiation. The orphan
nuclear receptor, peroxisome proliferator activated
receptor-γ (PPAR-γ), appears to be important in
adipose cell determination and differentiation [43,
44], and we have recently demonstrated that ligands
for the receptor promote human preadipocyte
differentiation (M. Adams, J. B. Prins, J. Holder, L.
Sanders, C. T. Montague, M. Lazar, S. Smith, S.
O'Rahilly and V. K. K. Chatterjee, unpublished
work).

There have also been some reports of replication
of mature adipocytes in vitro [45, 46]. While there is
ongoing debate [47], it seems unlikely that this
occurs in vivo as the cells are terminally differen-
tiated. Evidence for adipocyte replication in vitro
is therefore likely to be due either to replication of
preadipocytes ‘contaminating’ the adipocyte
preparations, or to initial dedifferentiation (see
below) and subsequent division of the adipocytes.

Thus it is clear that adipose cell acquisition may
occur via the process of preadipocyte replication/
differentiation, and it is likely that it may do so at
any stage of life.

Adipose cell loss

Two distinct mechanisms of adipocyte loss have
been described – dedifferentiation and apoptosis.

Adipocyte dedifferentiation [45, 48] is the in vitro
process in which terminally differentiated cells
revert morphologically and biochemically to less
differentiated cell types – in this case preadipocytes.
The process was first described by Van and co-
workers [25, 49] who noted morphological rever-
sion of differentiated cells in culture, with loss of
cytoplasmic lipid and acquisition of the fibroblast-
like morphology. Later studies have demonstrated
that, in addition to morphological changes, dediffer-
entiated adipocytes display the gene expression
patterns of preadipocytes [48, 50], not adipocytes.
Further studies by the Petruschke and Hauner [51]
have demonstrated that tumour necrosis factor
(TNF) induces dedifferentiation in human adipo-
cyes. Currently, it is not known if adipocyte
dedifferentiation occurs in vivo.

We have previously demonstrated that human
adipocyte apoptosis may be induced in vitro [52],
and that it occurs in vivo, at least in a proportion of
patients with malignancy [32]. These studies indicate
that human adipocytes are able to undergo
apoptosis, and therefore suggest the likelihood that
the adipose cell mass is dynamic. This proposal is
further strengthened by our observations (J. B.
Prins, N. I. Walker, C. Winterford and D. P.
Cameron, unpublished work) that human preadipo-
cyes may also be induced to undergo apoptosis in
vitro, indicating that stem cell commitment to the
adipocyte lineage is not irreversible.

Thus, study of adipose mass from the perspective
of cell number must include, at the very least, the
study of factors influencing preadipocyte replication,
preadipocyte differentiation, adipocyte apoptosis, and possibly adipocyte dedifferentiation.

At present, experimental models of preadipocyte
differentiation are ‘well established and much
utilized, and consequently there is a considerable
literature available (albeit relatively little regarding
human cells). In contrast, adipose cell apoptosis in
particular is understudied.

KNOWN AND POTENTIAL MOLECULAR
REGULATORS OF ADIPOCYTE NUMBER

Insulin

Insulin is the classical anabolic hormone [53], and
as such might be expected to stimulate the acquisi-
tion of fat cells. In support of this concept is the
weight (including adipose tissue) loss associated with
insulinopaenia that occurs in disease – insulin-
dependent diabetes mellitus – or experimental situa-
tions – e.g. streptozotocin-treated rodents. In both
situations, restoration of circulating insulin levels
restores fat mass [54]. Histological studies in experi-
mental insulinopaenia demonstrate that there is loss
of adipose cells, not just of cytoplasmic lipid [29].
This loss of cells is likely to occur by apoptosis, a
postulate consistent with the known anti-apoptotic
role of insulin in other settings. Furthermore, insulin
excess appears to promote adipose tissue gain. This
appears to occur disproportionately in the visceral
depot and is seen in patients with the syndrome of
hyperinsulinaemia, hypertension and hyperlipi-
daemia (Syndrome X) [55], patients with insulinoma
[56], and patients with non-insulin-dependent
diabetes treated with high-dose insulin. That the
adipose deposition is visceral in all these groups
indicates that the distribution pattern cannot be
explained by portal-systemic differences in insulin
concentrations, and therefore is likely to reflect site-
related differences in the (pre)adipocyte response to
insulin.

Insulin suppresses neuropeptide Y action at the
level of the hypothalamus [57], indicating a
mechanism whereby it may act as a ‘central’
regulator of adipose stores. Insulin upregulates
leptin mRNA production by 3T3-Ll adipocytes [58,
59] and in rodents [60]. However, human studies
published to date indicate that insulin does not
acutely regulate plasma leptin levels [61, 62].

In vitro studies support the adipogenic effect of
insulin. Cultured preadipocyte replication and
differentiation are stimulated by insulin [42], and
indeed, insulin is an obligate hormone for human
preadipocyte differentiation [63].

Thus, insulin is able to exert an adipogenic influ-
ence by a number of mechanisms: stimulation of
preadipocyte replication, stimulation of preadipocyte
differentiation, and possibly suppression of adipo-
cyte apoptosis. Furthermore, it may also have a central anti-adipogenic effect through regulation of leptin and neuropeptide Y.

**PPAR-γ and its ligands**

PPAR-γ is a member of the nuclear receptor superfamily [64–66], and is highly expressed in adipose tissue. Recent evidence suggests that the natural ligand for the receptor is an arachidonic acid metabolite, prostaglandin J₂ [67, 68]. Of equal interest is the fact that members of a new class of insulin-sensitizing drugs – thiazolidinediones – are also ligands for PPAR-γ [69]. It appears that the PPAR-γ (and presumably available ligand) is necessary for preadipocyte differentiation to occur. Indeed, expression of the receptor into non-preadipocyte cells commits them to the adipocyte lineage [44], suggesting that PPAR-γ expression is of crucial importance in the preadipocyte–adipocyte differentiation pathway [43, 70]. In vitro studies have demonstrated that exposure of murine preadipocytes to ligands for PPAR-γ – either prostaglandin J₂ or thiazolidinediones – dramatically enhances the differentiation process [71]. This would indicate a possible in vivo mechanism by which preadipocyte acquisition (and hence adipocyte number) could be controlled. That the natural ligand appears to be a prostaglandin raises the possibility that dietary alterations may – by modifying prostaglandin concentration and type – affect adipocyte cell number by a relatively direct means. The relationship between the adipogenic and insulin-sensitizing effects of thiazolidinediones is as yet unknown, but is under active investigation. These studies should provide further insights into the complex interplay between adipose tissue and insulin sensitivity.

**Retinoids**

Retinoids are natural and synthetic analogues of vitamin A (retinol). The compounds have complex effects on the replication, differentiation and apoptosis of numerous cell types including preadipocyte cell lines. In high concentration retinoids enhance replication of preadipocytes in vitro [72]. Retinoids also have effects on preadipocyte differentiation – stimulatory in low concentration [73] and inhibitory in high concentration [72]. The mechanism of action of retinoids in modulating preadipocyte differentiation appears to be via retinoic acid receptors (RXR and RAR), and it is likely that the PPAR-γ receptor may be a co-regulator [70, 74]. The effect of retinoids on adipose cell apoptosis is unknown.

These findings again raise the possibility that dietary content may have direct effects on regulation of adipocyte cell number and hence adipose tissue mass.

**Corticosteroids**

Although the effect of corticosteroids on protein is clearly catabolic, the effect on adipose tissue is not as well defined but tends to be anabolic. This is best characterized in patients with supraphysiological levels of corticosteroids, either endogenous (Cushing's syndrome) or exogenous (iatrogenic through steroid therapy). These individuals have overall weight gain despite muscle loss. Although a proportion of the gained weight is due to fluid retention, there is also adipose tissue gain. Again, this predominantly affects the visceral depot and there may at times be loss of subcutaneous adiposity. These changes are often obvious clinically (and indeed represent some of the classical clinical features of Cushing's) and are also demonstrable radiologically [75]. The opposite clinical scenario is present in Addison's disease (corticosteroid deficiency) in which adipose tissue loss is a feature, as is the case after reduction of supraphysiological corticosteroid levels. Furthermore, epidemiological studies suggest a positive correlation between physiological range corticosteroid levels and (particularly visceral) obesity [76–78]. These studies suggest that corticosteroids may have a fundamental role in regulation of energy and hence adipose balance. This role is complex, with effects at the level of adipose tissue such as regulation of lipoprotein lipase activity [79] and induction of insulin resistance [80] and GLUT4 gene expression [81], as well as central effects via ob [82] and glucagon-like peptide-1 [83].

Again, in vitro studies tend to support the adipogenic effect of corticosteroids with the demonstration that the hormones promote human preadipocyte differentiation [41]. In contrast to the effect of insulin however, preadipocyte replication is not enhanced by corticosteroids. The effect of the hormones on adipocyte apoptosis is not known.

**TNF-α**

There is increasing evidence that TNF-α has a major metabolic role in adipose tissue [84]. TNF is produced by human preadipocytes and adipocytes and this production is higher in obesity, with up to 3-fold increases in TNF-α mRNA, protein [85] and circulating levels [86]. There is evidence that this role may include the regulation of adipocyte function and possibly number.

With respect to adipocyte function, TNF-α induces insulin resistance by at least two mechanisms – downregulation of insulin receptor tyrosine kinase activity [87] and through induction of an abnormality in insulin receptor substrate-1 which inhibits phosphorylation of components of the insulin signalling cascade [88]. The net effect of the induction of insulin resistance in adipocytes is likely to be lipolysis, given that insulin has a primarily anti-lipolytic function in these cells. Furthermore,
TNF-α induces lipolysis in adipocytes by direct effects on lipoprotein lipase activity (downregulation) and hormone-sensitive lipase activity (upregulation) [89]. Thus, adipose mass is likely to decrease, or at least be less likely to increase, depending on nutrient balance. Whether the ‘insulin resistance’ induced by TNF-α is purely to insulin’s metabolic effects or at least be less likely to increase, or at least be less likely to increase, depending on nutrient balance. Whether the ‘insulin resistance’ induced by TNF-α is purely to insulin’s metabolic effects is unknown, as the effect of TNF-α on the mitogenic and anti-apoptotic effects on insulin has not been studied.

With respect to cell number, TNF-α also has multiple actions. It suppresses human preadipocyte differentiation, and causes delipidation and dedifferentiation of adipocytes [51], effects that are blocked by thiazolidinediones [90]. We have also shown that it induces human adipocyte and preadipocyte apoptosis in vitro (J. B. Prins, C. V. Niesler, C. M. Winterford, N. A. Bright, K. Siddle, S. O’Rahilly, N. I. Walker and D. P. Cameron, unpublished work). Thus the net effect of TNF-α on adipose tissue is one of reduction of adipose mass, through reduction in both cell number and volume. It is for these reasons that TNF-α has been proposed to be the ‘link’ between insulin resistance (and Type II diabetes) and obesity. It also raises the possibility that the increase in adipocyte TNF-α production in obesity may be a protective mechanism, in some way limiting the potential of the individual to gain weight. This concept has the attraction of ensuring that adipose accumulation to a degree that would impair mobility would not occur. However, like many physiological ‘protective’ mechanisms it also has disadvantages – in the setting of long-term overnutrition, fat mass may be preserved at the expense of hyperlipidaemia with consequent exacerbation of cardiac (and other) risk.

Central regulatory molecules – leptin, glucagon-like peptide-1, neuropeptide Y, 5-hydroxytryptamine

Leptin is a peptide hormone produced by adipocytes, and it appears to act primarily on hypothalamic receptors. It has the effect of reducing food intake and increasing metabolic rate, and causes significant adipose tissue loss when administered parenterally to ob/ob mice (which lack intact leptin) and normal rodents. The hypothalamic signalling pathway of the leptin system has not yet been characterized, but it appears that neuropeptide Y is involved [14, 91], leptin inducing its downregulation. The observation that hypothalamically lesioned rodents (surgery or gold thioglucose) have extremely high leptin levels [92, 93] and become and remain obese is evidence that leptin does not have a direct catabolic effect on adipocytes. This is supported by the recent characterization of the leptin receptor subtypes [6, 7, 94, 95] and the demonstration that the only subtype identified to date that is capable of signalling is not present in significant amounts in adipose tissue. Thus it appears that while leptin has an important role in regulation of adipose tissue mass, this is not achieved by a direct effect on adipocyte number. Glucagon-like peptide-1 [96, 97], 5-hydroxytryptamine [98, 99] and neuropeptide Y [57, 91] also have effects on energy balance and adiposity, with their site of action being predominantly central. Intervention in the central signalling pathways of all three molecules induces weight change, but again, no direct effect on adipose cell number has been observed.

Elucidation of the mechanism by which the central signal originating from these molecules (alone or in combination) is translated to mediate change in adipose cell number or volume will provide an important advance in our understanding of adipose tissue regulation, and uncover a further potential site for intervention.

ROLE OF DIFFERENTIAL REGULATION OF ADIPOSE CELL NUMBER IN DETERMINATION OF ADIPOSE TISSUE DISTRIBUTION

Excess intra-abdominal adiposity is more strongly associated with morbidity and mortality from cardiovascular disease and non-insulin-dependent diabetes than is the degree of obesity per se. Factors regulating adipose tissue distribution are largely unknown but in addition to genetic influences, there is evidence for roles of steroid hormones, insulin, growth hormone, catecholamines, exercise and environmental factors. In general terms, patterns of adipose tissue distribution may be the result of depot-specific intrinsic differences in adipose cells, depot-specific differences in factors influencing adipose cell number and/or volume, or unequal contributions to the adipose–hypothalamic ‘feedback loop’ from different adipose tissue depots.

Evidence exists supporting all three possibilities – in each case providing a possible means by which adipose cell number could be differentially regulated in clinically important depots. Firstly, glucocorticoid receptor number is greater in omental than subcutaneous adipocytes [100]. This allows differential corticosteroid-induced regulation of adipose cell volume and number. Secondly, the higher insulin concentration in the portal vasculature may contribute to differential effects of insulin on adipose tissue mass in visceral and subcutaneous depots. Thirdly, we have recently demonstrated that subcutaneous and omental adipocytes express different amounts of leptin mRNA [101]. Hence the two adipose depots could differentially contribute to circulating leptin levels and hence to central regulation of overall adiposity. A greater understanding of regional regulation of adipose cell number may lead to interventions aimed at modifying adipose distribution rather than overall adiposity – an intervention likely to promote substantial reduction in morbidity and mortality.
CONCLUSION

In this review we have attempted to outline the current understanding of factors regulating adipose mass, with particular emphasis on the regulation of adipose cell number. We have also indicated a number of areas in which further research may lead to the development of fundamentally different intervention strategies aimed at modifying adipose mass or distribution.

While the simplest, most and most elegant treatment for disorders of adipose mass is still the modification of diet and exercise patterns, this intervention is either impossible, impractical or not achievable for a great many individuals. It is hoped that recent major advances in our understanding of adipose tissue regulation will be expanded upon, and that the current resurgence in research interest will lead to the development of alternative and effective interventions.

REFERENCES


57. Sahu 


