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REVIEW

Regulation of human subcutaneous adipose tissue blood flow

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Subcutaneous adipose tissue represents about 85% of all body fat. Its major metabolic role is the regulated storage and mobilization of lipid energy. It stores lipid in the form of triacylglycerol (TG), which is mobilized, as required for use by other tissues, in the form of non-esterified fatty acids (NEFA). Neither TG nor NEFA are soluble to any extent in water, and their transport to and out of the tissue requires specialized transport mechanisms and adequate blood flow. Subcutaneous adipose tissue blood flow (ATBF) is therefore tightly linked to the tissue's metabolic functioning. ATBF is relatively high (in the fasting state, similar to that of resting skeletal muscle, when expressed per 100 g tissue) and changes markedly in different physiological states. Those most studied are after ingestion of a meal, when there is normally a marked rise in ATBF, and exercise, when ATBF also increases. Pharmacological studies have helped to define the physiological regulation of ATBF. Adrenergic influences predominate in most situations, but nevertheless the regulation of ATBF is complex and depends on the interplay of many different systems. ATBF is downregulated in obesity (when expressed per 100 g tissue), and its responsiveness to meal intake is reduced. However, there is little evidence that this leads to adipose tissue hypoxia in human obesity, and we suggest that, like the downregulation of catecholamine-stimulated lipolysis seen in obesity, the reduction in ATBF represents an adaptation to the increased fat mass. Most information on ATBF has been obtained from studying the subcutaneous abdominal fat depot, but more limited information on lower-body fat depots suggests some similarities, but also some differences: in particular, marked alpha-adrenergic tone, which can reduce the femoral ATBF response to adrenergic stimuli.

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INTRODUCTION AND SEARCH STRATEGY

Subcutaneous adipose tissue accounts for about 85% of all body fat in people of a wide range of adiposity.[1] As we will discuss, its perfusion is tightly linked to its metabolic function. There have been many studies of adipose tissue, or adipocyte, metabolism, but fewer of the regulation of the blood flow through the tissue. Our aim here is to review what is known of the regulation of subcutaneous adipose tissue blood flow (ATBF).

There are also important adipose depots within the abdominal cavity (so-called visceral fat) and around other organs, for example, perirenal fat and epi- and peri-cardial fat. Regulation of the perfusion of visceral fat is potentially very interesting in view of the relationships between visceral fat and adverse metabolic profile. However, it is more difficult to study than that of subcutaneous fat. The only satisfactory method is the use of the positron emission tomography (PET). We mention below some studies using this technique. On the whole, however, much less is known about the perfusion of intra-abdominal fat depots and how it is regulated in contrast with the blood flow through subcutaneous tissue, and we will not attempt to review those areas here. Similarly, we will not cover the regulation of blood flow through brown adipose tissue. Brown adipose tissue is another specialized tissue with a function quite different from that of white adipose tissue, and the regulation of its blood flow is also entirely distinct. We have reviewed the regulation of subcutaneous ATBF previously,[2] and our aim here is to bring that up to date. Another recent review of ATBF regulation provides additional information.[3] Other recent reviews of various aspects of adipose tissue or of metabolic diseases provide some further information on ATBF regulation.[4–7]

We searched PubMed for ('Adipose tissue blood flow' AND subcutaneous /limits 'humans') and retrieved 132 articles. Some of these are covered in the previous reviews mentioned above. We scrutinised them for relevance to the theme of blood flow in relation to adipose tissue physiology that we wished to develop and included 85 references.

ADIPOSE TISSUE METABOLISM AND BLOOD FLOW

White adipose tissue comprises a variety of cell types. The major cell type in terms of volume is the white adipocyte, which is a specialized cell storing fat in the form of triacylglycerol (TG). The mature white adipocyte has a single lipid droplet that occupies the major proportion of the cell volume. In fact, the lipid content of the intact tissue is typically 85% by weight, and for individual adipocytes, it will be even higher. This marks it out as a unique tissue: in most other tissues, water is by far the greatest component by weight followed by protein (the brain is an exception, with 50–60% dry weight of lipid, mainly phospholipid).

Like most tissues, adipose tissue is supplied with arterial blood and returns venous blood into the venous pool. Adipose tissue capillaries are easily visualised microscopically, and a common view is that at least one capillary is in close contact with each adipocyte. Adipose tissue is innervated by sympathetic nerves, which can be clearly visualised making contact with blood vessels. There is not quite such clarity over whether the sympathetic nerves reach the adipocytes themselves, but as we will describe, there is no doubt that adipocyte function is influenced directly by catecholamines. We have reviewed these aspects previously.[2]

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There is current controversy over the question of parasympathetic innervation of adipose tissue and, if it exists, its function role.[8,9]

The primary metabolic role of white adipose tissue is the storage of excess energy in the form of TG, and the release of stored lipid when it is required by other tissues. Adipose tissue is also now recognised as an important endocrine organ and produces and secretes a number of peptides and other factors, including the hormone leptin. These are known collectively as adipokines. In this review we will concentrate upon blood flow in relation to the metabolic activities of white adipose tissue, but will make some remarks about blood flow and adipokine secretion later.

Fat is delivered to adipose tissue in the form of circulating TG in the lipoproteins. The TG-rich lipoproteins comprise chylomicrons, the largest of the lipoprotein particles, carrying dietary fat and derived from small intestinal enterocytes and very-low-density lipoproteins, carrying 'endogenous' TG and secreted by the liver. Other major lipoprotein fractions, low-density lipoprotein and high-density lipoprotein, are carriers of cholesterol more than TG and do not play major roles in adipose tissue metabolism. Chylomicron-TG is the preferred substrate for adipose tissue lipid storage,[10] and indeed the fatty acid composition of adipose tissue (i.e., the fatty acids that make up its TG) tends to mirror the composition of an individual's dietary fat intake,[11] showing that dietary fat is a major source of adipose tissue TG. However, there is also convincing evidence for production of some TG from non-lipid precursors (*de novo* lipogenesis) in human adipose tissue.[12,13] In addition, certain fatty acids are both elongated and desaturated in adipose tissue,[13,14] so that there are consistent differences in composition from dietary fat.[11]

Chylomicrons appear in the circulation over a period of around 2–8 h following a meal that contains fat. Peak chylomicronaemia is typically around 3 h after a meal, although it can be detected earlier (around 30–60 min after a meal). This is the period when adipocytes store fat.[10] The pathway involves hydrolysis of the circulating TG within adipose tissue capillaries by the enzyme lipoprotein lipase (LPL). LPL is synthesised within adipocytes, but transported to the capillaries, where it is bound to the luminal aspect of the capillary endothelium (reviewed in Camps *et al.*[15] and Wang *et al.*[16]). Passing lipoprotein particles bind transiently to the endothelium while LPL hydrolyses their TG, releasing fatty acids. These fatty acids diffuse, or may be actively transported (the pathway is not entirely clear), into the adipocytes, where they are esterified with glycerol 3-phosphate to make TG. Adipose tissue LPL is activated by insulin, and possibly other factors associated with meal intake, and the pathway of fatty acid esterification within the adipocyte is also activated by insulin, so providing a strong stimulus for storage of meal-derived fatty acids in adipose tissue.[17] As described later, meal intake provides a strong stimulus to ATBF, which seems physiologically adequate in terms of storage of dietary-derived fatty acids in the tissue. However, after an overnight fast, the upregulation of LPL in adipose tissue is slower than the appearance of the chylomicrons and the well-timed blood flow response, which leads to less efficient lipid storage in adipose tissue after the first meal of the day.[18]

During fasting or exercise, when there is a demand for fuel by other tissues, this stored TG is 'mobilized'. This occurs by the sequential hydrolysis of the three fatty acids of each TG molecule by a series of intracellular lipases (reviewed in Zechner *et al.*[19] and Lafontan *et al.*[20]). The resulting fatty acids (which are known as NEFA or free fatty acids) enter the circulation, where they are bound to albumin, and are thus distributed to other tissues.

The main point of this description of white adipose tissue metabolic function is to draw attention to two features. First, adipose tissue metabolism is highly regulated: within an hour or so of eating a meal, it switches from fat mobilization to fat storage, and vice versa, and even more quickly in the case of starting physical exercise. Secondly, the major metabolic exchanges between adipose tissue and the circulation are of the non-water-soluble compounds TG and NEFA. Unlike glucose or gases, these compounds cannot diffuse appreciably through interstitial spaces. This makes the perfusion of adipose tissue of particular importance for its metabolic function, and there are clear links between metabolism and perfusion,[21] which we shall draw out in the remainder of this review.

ATBF measured in the overnight-fasted state is typically close to 3 ml per min per 100 g tissue. As will be described below, that value changes markedly in different physiological states, for example, after ingestion of a meal or during exercise. It is similar to values measured in resting skeletal muscle. But it should also be borne in mind that (as noted above) most of the volume of adipose tissue is occupied by inert fat stores. Blood flow per volume of cytoplasm must be several-fold higher than in resting skeletal muscle, emphasising again the close relationship between perfusion and metabolic function in adipose tissue.

QUANTIFICATION OF ATBF

We have reviewed some methods for measuring ATBF recently[22] and that article provides more practical information. An earlier review also contains useful information.[23] A variety of methods is available in experimental animals, including simply severing the venous drainage of adipose tissue and measuring outflow, and the use of radioactively labelled microspheres, which lodge in the tissue capillaries. In humans, two methods have been used predominantly, with some other technologies emerging.

The most commonly-used method for measurement of ATBF in humans is to monitor the removal of ^{133}Xe which has been injected into the tissue.[24] Xenon is inert and highly fat-soluble. When injected into adipose tissue, it forms a small, local depot, and it is slowly removed as blood flows through the tissue. ^{133}Xe is a gamma-emitting radioactive isotope, which can readily be monitored externally. Therefore, ^{133}Xe may be injected into the tissue and its removal ('washout') measured with a small detector attached to the skin.[25] The removal is exponential and the slope of the semi-logarithmic plot reflects the rate of blood flow. This can be made quantitative by knowing the partition coefficient for xenon between adipose tissue and blood,[23] for which there are experimentally measured values in the literature.[26,27]

The ^{133}Xe-washout method is simple, quantitative and sensitive to small changes. Its drawback is the use of a radioactive isotope, although the radiation dose to the volunteer is very small indeed. It is very amenable to pharmacological investigation. Drugs (e.g., adrenergic blocking agents or agonists) may be given systemically (e.g. Samra *et al.*[21] and Simonsen *et al.*[28]), but a more specific method, known as microinfusion, has been developed,[22,29] whereby drugs can be introduced directly into the ^{133}Xe depot. This allows investigation of the pharmacology of ATBF without interference from systemic effects of the agent under study. It has been extensively used to elucidate the regulation of ATBF.[29–32]

The other method that has been extensively used in recent years in humans is to combine microdialysis with the washout of an inert marker. Microdialysis involves the placement of a catheter of semi-permeable membrane into the tissue so that substances can exchange between the fluid within the catheter and the interstitial fluid of the tissue. If the catheter is perfused with a solution containing ethanol, which is not metabolized in adipose tissue, some of the ethanol will leave the catheter, and the concentration in the fluid leaving will be lower than that entering. The 'ethanol ratio' is dependent upon blood flow: the greater the ATBF, the more ethanol is removed. Thus, the ethanol ratio is an inverse reflection of ATBF. This method was used in early experiments that showed that measurements of lipolysis by microdialysis (measuring interstitial glycerol as a marker of lipolysis) could be confounded by effects on blood flow.[33] It has been used widely since that time.[34–36]

The ethanol–microdialysis method is also easy to perform and avoids the use of a radioactive isotope. However, in most people's hands it is probably not as sensitive as the ^{133}Xe-washout method for measurement of relatively small changes in ATBF.[37] This has emerged clearly in the literature on ATBF during exercise, reviewed below.

Another method that is emerging is the use of PET. Measurements of organ blood flow are routinely made using the tracer $H_2^{15}O$. ^{15}O is a short-lived isotope with a half-life of $\sim$2 min. PET measurements of ATBF allow quantitation of different fat depots, including the intra-abdominal depots, simultaneously with measurements of adipose tissue metabolism.[38,39] Thus, this is potentially a very powerful technique. However, the radiation dose is large (limiting the number of studies that can be performed in any one individual), and specialized equipment, including a cyclotron to generate the isotopes, is needed.

Alternative methods that can be applied in humans include both laser Doppler (using laser light to monitor flow) and ultrasound. We are unaware of any direct comparison between laser Doppler and other ways of quantifying human ATBF. The laser Doppler signal is often superficial, and it can be difficult to limit the influence from skin blood flow. However, due to similarities in regulation upon a variety of physiological provocations between skin blood flow measured by laser Doppler and subcutaneous ^{133}Xe washout, it has been suggested that skin and subcutaneous tissue have similar regulation or that some parts of the most superficial subcutaneous tissue could be drained through the subdermis.[40] Ultrasound in the Doppler mode could in principle be used, but the signal from ATBF is weak. In order to enhance the Doppler signal, contrast-enhanced ultrasound has been used to estimate ATBF, and a recent paper compared this estimation with ^{133}Xe.[41] Briefly, after intravenous injection of the contrast agent (typically Sonovue), the tissue is perfused by the contrast-containing agent, which upon continuous ultrasound will be picked up as a markedly increased Doppler recording in B-mode. In essence this increase will correspond to increased capillary volume, which theoretically should equal an increase in blood flow. Using this technique it has been possible to demonstrate an expected increase in ATBF following oral glucose ingestion,[42] in good correspondence with simultaneous ^{133}Xe measurements. The potential limitation of this technique is that the signal-to-noise ratio is fairly low, that is, more subtle changes in blood flow would be difficult to detect. Also, it would be difficult to estimate an absolute flow, and the best use would be in dynamic studies within the same individual where a change from a baseline recording is required.

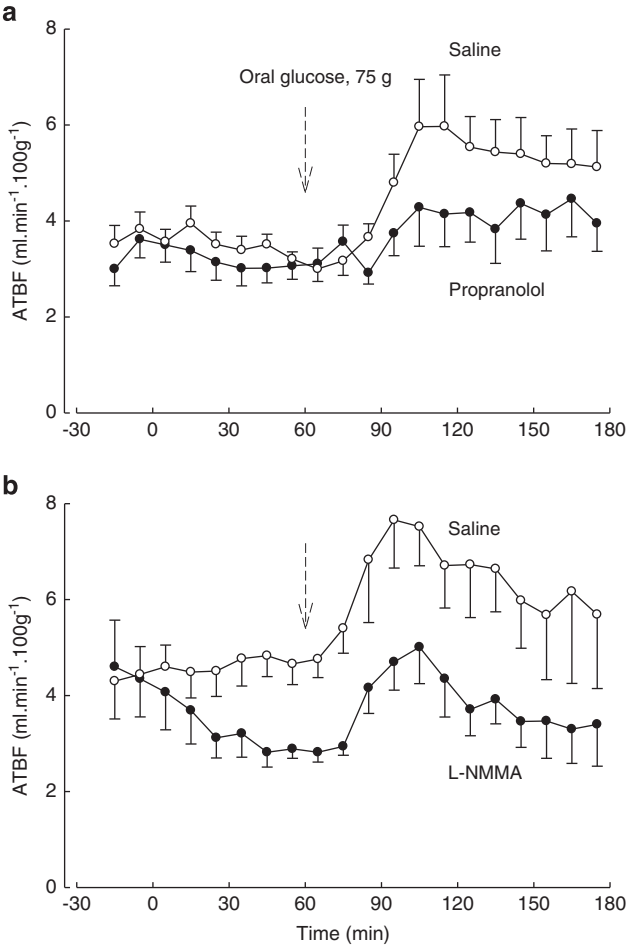

Figure 1. Regulation of subcutaneous abdominal ATBF in the fasting state and after glucose ingestion. Measurements were made by ^{133}Xe washout and manipulations by microinfusion, in healthy volunteers. In each case a control site was perfused with saline (open circles), and another site with active agent (solid circles). (**a**) Control side shows normal increase in ATBF in response to 75 g glucose given orally. This response is markedly blunted when propranolol (beta-adrenergic blocker) is micro-infused. (**b**) Microinfusion of N_G-monomethyl-L-arginine (L-NMMA), a blocker of NO synthesis, markedly reduces fasting ATBF but does not affect the magnitude of the response to oral glucose. Data from and figure based on.[30]

ATBF REGULATION IN VARIOUS PHYSIOLOGICAL STATES

In the overnight-fasted state, subcutaneous ATBF is steady and a typical value, as noted earlier, is around 3 ml per min per 100 g tissue. Pharmacological experiments using the technique of microinfusion have shown some aspects of the regulation of fasting subcutaneous ATBF. Introduction of L-NMMA (N_G-monomethyl-l-arginine), a blocker of NO synthesis, reduces fasting ATBF by 30–50%,[30,31] showing that the endothelial NO system plays an important role in maintaining normal ATBF (Figure 1). Adrenergic influences appear less important. Introduction of propranolol, a beta-adrenergic blocker, has no effect on fasting ATBF (Figure 1). In contrast, phentolamine, a non-selective alpha-adrenergic blocker, may increase ATBF,[30] suggesting that there is a small inhibitory tone from alpha adrenergic receptors; furthermore, local infusion of an α_1-adrenoceptor agonist, norfenefrine, reduces ATBF, implying a role for α_1 receptors.[43] However, the effect of phentolamine has not been found in other studies.[44] The renin-angiotensin system also plays a role. Local microinfusion of angiotensin-II reduces fasting ATBF by up to 50% at high concentrations; microinfusion of losartan, an angiotensin-receptor blocker, increases ATBF by about the same amount.[31] Therefore, there is normally a vasoconstrictive effect of circulating angiotensin-II. Microinfusion of an angiotensin-converting enzyme inhibitor, enalaprilate, had no effect, suggesting that the effect is due to systemic angiotensin-II rather than that generated within the tissue.[31] There are potential roles for the other regulatory systems, including the endothelin system and the atrial natriuretic peptide (ANP) and brain natriuretic peptide system. Systemic infusion of human ANP in healthy volunteers produced an increase in ATBF.[45] The role of the endothelin system in regulation of fasting ATBF has not been investigated, perhaps because of the limited scope for pharmacological intervention with this system in humans. Local infusion of bradykinin caused a marked increase in leg ATBF measured by PET,[39] showing the complexity of local and systemic regulation of ATBF.

Local administration of theophylline, an inhibitor of cyclic AMP (cAMP) breakdown, increases ATBF in lean and obese people.[46,47] Theophylline also increases lipolysis, suggesting perhaps a link between ATBF and lipolysis, for which there is evidence during exercise (discussed below).

It seems that subcutaneous ATBF increases whenever there is a need for increased delivery of lipid substrate or removal of the products of lipolysis (NEFA especially). There is a marked rise in ATBF, especially in lean people (discussed further below), in response to ingestion of a meal.[48,49] It is tempting to attribute this rise to a physiological need to deliver chylomicron-TG to the tissue, but there are difficulties with this hypothesis. First, the rise in ATBF is seen even after a pure glucose load, when there is no delivery of dietary fat into the circulation.[29,50] Secondly, the timing of the peak in ATBF (typically 30–60 min after glucose or meal ingestion) is much earlier than the peak chylomicronaemia (typically 2–5 h after ingestion of a fatty meal). Another possibility is that the physiological role of this increase in ATBF is to deliver a 'signal' to the tissue, for example, insulin or cortisol, both important in the up-regulation of adipose tissue LPL that is necessary for efficient storage of incoming TG.[16,51] Even though cortisol concentrations do not change acutely in response to feeding, an increase in ATBF will expose the tissue to increased cortisol delivery. In the case of insulin, the rise in ATBF is closely coincident with maximal insulin concentrations,[29] so the effect on insulin delivery will be very marked.

The mechanism of this postprandial increase in ATBF has been studied in some detail. It is largely blocked by the beta-adrenergic blocker propranolol, given either locally[30] (Figure 1) or systemically.[28] It is mimicked during systemic infusion of adrenaline (epinephrine),[21,52] although infused noradrenaline (norepinephrine) may have a vasoconstrictive effect.[52] There is a well-known sympatho-adrenal response to feeding,[53] which probably explains most of the ATBF responses. Studies of gene expression in human abdominal subcutaneous adipose tissue have shown that mRNA expression of the receptor type A for ANP (*NPRA*), and of endothelial NO synthase (*NOS3*), are both strongly positively related to postprandial ATBF, suggesting additional roles for these systems.[54]

Another obvious candidate for mediating the meal-induced rise in ATBF would be an intestinal hormone.[29] Glucagon-like peptide-1 does not appear to affect ATBF (albeit via measurements made with microdialysis/ethanol escape),[55] but recently there has been an interesting demonstration that glucose-dependent insulinotropic polypeptide may have such an effect.[56] Glucose-dependent insulinotropic polypeptide in addition, in the presence of elevated insulin and glucose concentrations, stimulated the pathway of TG deposition in adipose tissue, potentially making this hormone a key controller of postprandial fat deposition.[56]

In the fed state, there is a physiological need to deliver substrate (or, as noted above, perhaps to deliver a hormonal signal) to the adipose tissue. During exercise, the active muscles need a supply of fatty acids, which must be delivered from adipose tissue. This requires activation of both lipolysis (fat mobilization) and ATBF. Activation of lipolysis during exercise has been shown in many studies, often by isotopic measurement of the whole-body rate of production (into the circulation) of NEFA.[57] It can also be demonstrated by direct catheterization of the venous drainage from subcutaneous adipose tissue.[58,59] Early measurements of ATBF during prolonged, heavy exercise indeed showed an increase,[60] albeit perhaps not to the extent that might be expected for the increased delivery of NEFA. In some other studies, this rise in ATBF has not been found. However, this may be because measurements have been made using the technique of microdialysis with ethanol washout which, as noted above, is not as sensitive as the Xe-washout method. In an extensive review of measurements of ATBF during exercise, Thompson *et al.*[7] recently concluded that the consensus view is that there is, indeed, an increase in ATBF, but this may be missed if the measurement is made with microdialysis. This has been borne out by recent measurements using the technique of PET.[61] It should be noted that measurement of ATBF during exercise poses quite severe practical difficulties, and this may account for some of the discrepancies in the literature.

Both lipolysis and ATBF are therefore increased during exercise, and it is tempting to suggest coordinate control. Possible mechanisms would include sympatho-adrenal stimulation (circulating catecholamines or noradrenaline (norepinephrine) released locally from sympathetic nerves) or stimulation by ANP/ brain natriuretic peptide system. The exercise-induced increase in ATBF is almost entirely blocked by the beta-adrenergic blocker propranolol.[62] However, whilst this may seem to indicate a sympatho-adrenal mechanism, the ATBF response is also blocked by oral administration of nicotinic acid.[62] Nicotinic acid acts on adipocytes to reduce lipolysis and is not thought to have direct effects on ATBF. These observations have been taken to indicate that the exercise-induced increase in ATBF may be directly related to the stimulation of lipolysis.[62] As noted earlier, infusion of ANP increases ATBF,[45] and ANP is released in response to exercise,[63] in which condition it appears to be an important stimulator of adipose tissue lipolysis.[36,63] There is no clear evidence that ANP is involved in the acute exercise-induced ATBF increase, partly because of methodological difficulties (lack of ANP antagonists for use in humans). However, a 4-month exercise training programme increases ATBF and also the ATBF responses to both isoprenaline (isoproterenol) (beta-adrenergic agonist) and ANP.[64] Recently, it has been shown that ATBF is increased only in those fat depots in proximity to the working muscles of the thigh and not in depots close to non-working thigh muscles.[61] That somewhat conflicts with the many studies (summarised above) showing increased abdominal subcutaneous ATBF during exercise, but might reflect generally lower ATBF in leg compared with abdominal depots (see below). Mechanisms for this selective increase in ATBF might include selective sympathetic activation or perhaps simply local temperature effects.

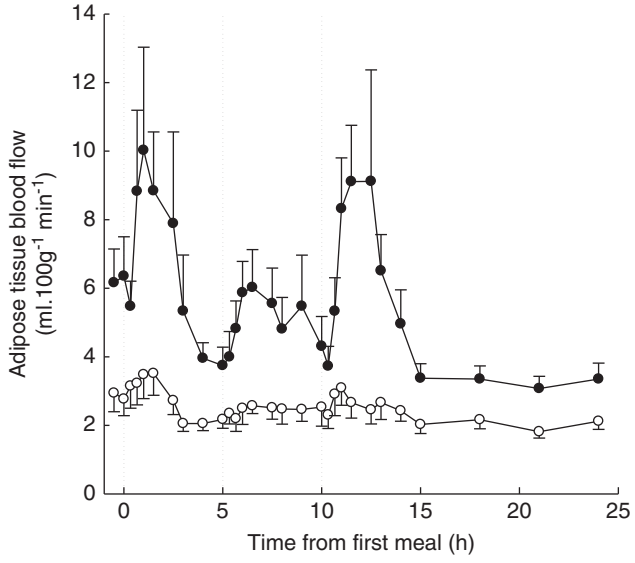

Figure 2. ATBF over a 24 h period in lean and obese individuals. Lean (solid circles) and obese (open circles) volunteers were studied over a 24 h period, during which they were fed three meals (marked by vertical dashed lines) matched to their predicted energy requirements. ATBF measurements are expressed per 100 g tissue, but it should be borne in mind that the obese people studied here had ~2.5 times as much adipose tissue as the lean. However, beyond the absolute reduction in ATBF per 100 g tissue, there is a loss of responsiveness to meals. Redrawn from McQuaid *et al.*[67] with permission from American Diabetes Association.

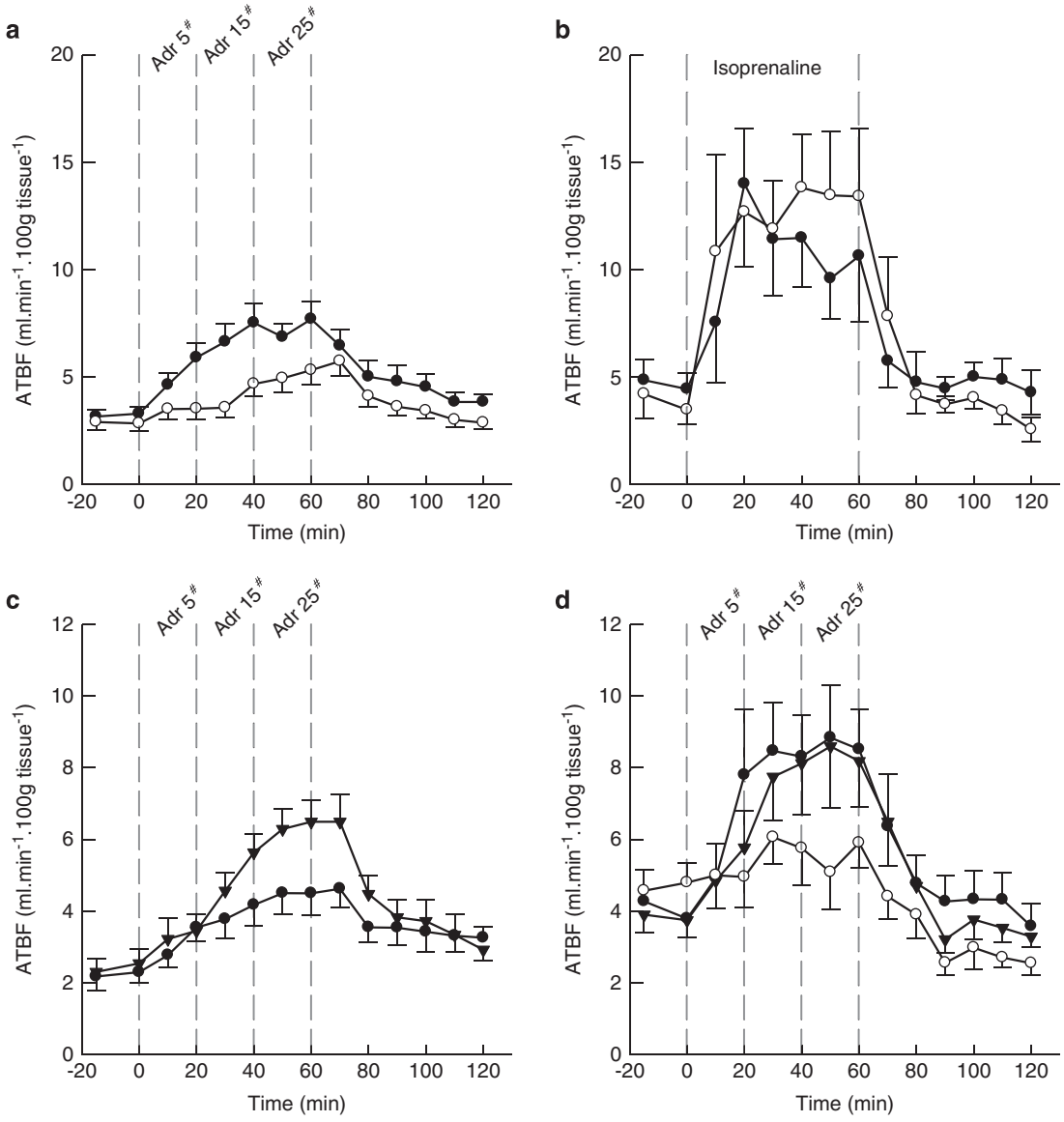

Figure 3. Regulation of abdominal and femoral adipose tissue blood flow by adrenergic stimulation *in vivo*. Studies were conducted in healthy volunteers, with simultaneous measurement of ATBF in abdominal and femoral depots using ^{133}Xe washout. (**a**) ATBF in abdominal subcutaneous (solid circles) and femoral tissue (open circles) during increasing systemic doses of adrenaline (epinephrine). Labels ('Adr 5*, etc.) refer to adrenaline dose in ng per min per kg fat free mass. (**b**) ATBF in abdominal subcutaneous (solid circles) and femoral tissue (open circles) during a constant systemic dose of isoprenaline (isoproterenol) (beta-adrenergic agonist). (**c**) Femoral ATBF in response to increasing doses of adrenaline (epinephrine) (solid circles) and simultaneous local inhibition by microinfusion of phentolamine (solid triangles). The local administration of the non-specific alpha-adrenergic blocker (phentolamine) augments the adrenaline-induced blood flow in the femoral region. (**d**) Abdominal ATBF in response to increasing doses of adrenaline (epinephrine) (solid circles) and simultaneous local inhibition by microinfusion of phentolamine (solid triangles). The local administration of the non-specific alpha-adrenergic blocker (phentolamine) did not alter the blood flow response, whereas local administration of propranolol (non-specific beta-adrenoreceptor blocker) attenuated the effect of adrenaline (epinephrine) (open circles). Figures are adapted from[44] with permission.

EFFECTS OF OBESITY ON ATBF

It was noted above that ATBF increases rapidly after a meal, which may simply be a glucose drink. An extremely consistent finding in the literature is that this response to meal ingestion is diminished, or lost entirely, in obese people (Figure 2). In most studies of obese people, fasting ATBF is also reduced (expressed per kg adipose tissue) compared with lean people. Frayn and Humphreys analyzed a large database of studies on 240 healthy people and found a negative correlation between BMI and ATBF (Spearman correlation coefficient = 0.34, $P \ll 0.001$).[65] The mechanism for the lack of responsiveness to meals has been studied by Ardilouze *et al.*,[32] who concluded that this represents a diminished responsiveness to adrenaline (epinephrine) rather than a diminution of the sympatho-adrenal response itself. There are parallels with the well-documented diminution of fasting or catecholamine-stimulated lipolysis (fat mobilization), when expressed per cell or per kg adipose tissue, in obesity.[66,67] It may well be that in both cases (ATBF and lipolysis downregulation) this can be seen as a physiological adaptation to the increased adipose tissue mass that characterises obesity.[68] At a tissue or cellular level, it would seem reasonable to assume a lowered demand for tissue perfusion in obesity; the adipocyte volumes are increased but this represents an increase in the lipid droplet size, whereas the cytoplasm and metabolic needs per

tissue volume are decreased. The diminution of catecholamine-stimulated lipolysis in obesity *in vivo* may represent increased preponderance of inhibitory α-adrenergic receptors.[69] It has not been thoroughly studied whether the same applies to the downregulation of ATBF in obesity, although Stich *et al.*[70] did not find an effect of locally administered phentolamine on ATBF in obese people, either before or after weight loss.

More detailed investigations of the effect of obesity on ATBF have suggested that this may be a feature of insulin resistance rather than of obesity *per se*.[50] Jansson *et al.*[71]showed a reduction in fasting ATBF, and in the ATBF response to oral glucose, in obese people compared with lean people, with a further reduction in those with type 2 diabetes. Dimitriadis *et al.*[73] have confirmed the reduced ATBF in obesity[72] and in type 2 diabetes and have also shown that this effect is seen even in first-degree relatives of people with diabetes.[73]

It would seem intuitive that the lower baseline blood flow and the relative absence of upregulation after meal intake could contribute to poor tissue perfusion, resulting in adipose tissue hypoxia in obesity. Adipose tissue hypoxia is a feature of some animal models of obesity,[74] and hypoxia has been suggested to be mechanistically related to features of human adipose tissue dysfunction (e.g., impaired insulin-mediated antilipolysis).[75] However, two recent publications using different methodologies to assess tissue oxygenation question the existence of hypoxia in 'normal' human obesity. First, Goossens *et al.*[76]detected normoxic, or even hyperoxygenated states, in obese adipose tissue. Of note, these tissues exhibited the expected inflammatory features and a low degree of capillarization, which is largely an effect of enlarged adipocytes, rather than a deficit of capillaries. Second, Hodson *et al.*[77] searched for metabolic features of hypoxia, for instance by studying the lactate/pyruvate ratio in venous blood draining adipose tissue. This ratio was unrelated to increasing body fat content. It was also noted that the oxygen saturation in the venous effluent from adipose tissue was never observed to be below 85%. We believe a reasonable explanation for these findings is that the oxygen requirement of adipose tissue is very low and reduced still further (when expressed per kg adipose tissue) in obesity because of the enlarged fat cells, and even at low perfusion rates, the delivery of oxygen to the tissue is sufficient to keep the tissue adequately oxygenated.

REGIONAL DIFFERENCES IN ATBF

Adipose depots in different parts of the body have different relationships to metabolic health. In general, accumulation of abdominal fat (both intra-abdominal and subcutaneous) is associated with increased risk of type 2 diabetes and cardiovascular disease. In contrast, accumulation of fat in the lower part of the body (gluteofemoral fat) is associated with protection from these conditions (reviewed in Manolopoulos *et al.*[78]). There have been a number of studies of the metabolic properties of fat cells isolated from these different regions in an attempt to explain these different relationships to metabolic health. A general conclusion is that fat cells in the abdominal region are more metabolically active than those from the gluteofemoral depots: lipolysis is more readily stimulated by beta-adrenergic agents and is less readily suppressed by insulin.[79] This has been broadly borne out by physiological studies of the depots *in vivo*.[80–83] There has been less study of differences in ATBF between different regions. An early study showed lower ATBF in gluteofemoral than abdominal adipose tissue.[84] Gluteal adipose tissue specifically has a considerably lower fasting blood flow than abdominal,[82] perhaps reflecting a special metabolic role. For femoral fat, the difference from abdominal is not so marked, although most studies find lower ATBF in femoral than abdominal (summarised in McQuaid *et al.*[83]), or that the two depots are similar.[83] However, differences between the abdominal and femoral adipose tissue depots become very clear when the regulation by adrenergic stimulation is tested.[44] Although fasting, or baseline, blood flow appears similar in the two depots, systemic administration of adrenaline (epinephrine) reveals profoundly less augmentation of blood flow in femoral compared with abdominal tissue (Figure 3a), whereas the systemic administration of a specific beta-adrenergic agonist (isoprenaline, isoproterenol) gives rise to a similar response between the tissues (Figure 3b). This is apparently due to higher expression of alpha-adrenergic receptors in the femoral

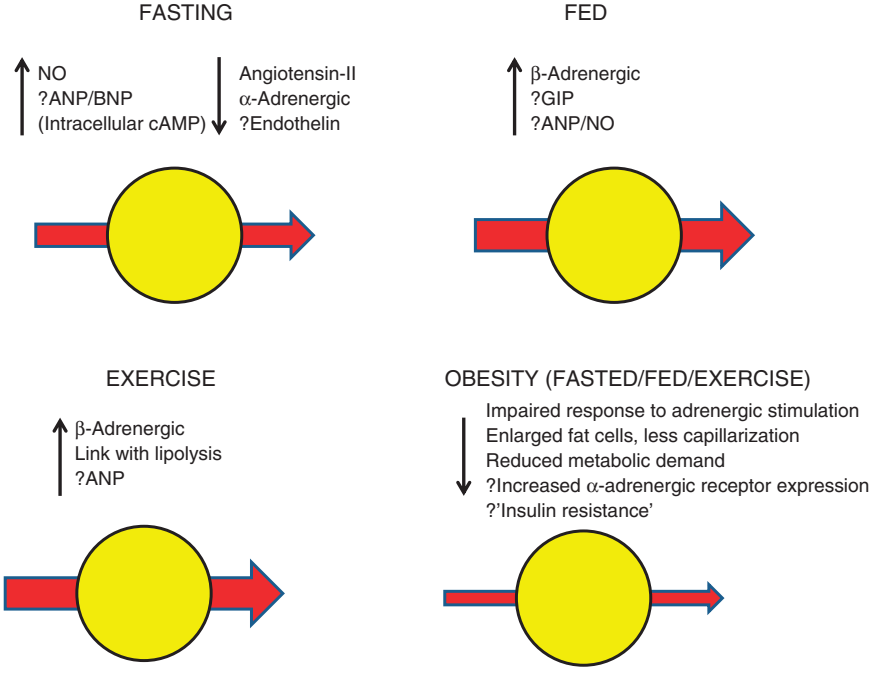

Figure 4. Summary of the regulation adipose tissue blood flow in different states. Question marks denote suggestions from the literature awaiting fuller experimental confirmation.

tissue, as the lower blood flow induced by adrenaline alone can be augmented by local administration of an alpha-adrenergic blocker (phentolamine) (Figure 3c). This effect is not seen in abdominal tissue (Figure 3d), which suggests that the alpha-adrenergic inhibition of adrenergic blood flow stimulation is of limited relevance in the abdominal tissue. In this sense, the differences in adrenergic regulation of blood flow between the tissues appear to match the differences in lipolytic regulation extremely well.[20]

As was discussed above, the increase in abdominal ATBF seen in response to ingestion of a meal varies considerably between individuals. This is also true of femoral fat, with a lack of response in obese individuals.[85] In fact, the ATBF response to a meal of the two depots is correlated across individuals,[83] suggesting similar mechanisms governing this effect.

CONCLUSIONS AND SUMMARY

Subcutaneous ATBF is an integral component of the physiological functioning of the tissue. ATBF changes rapidly when there is a demand for increased delivery of the products of fat cell lipolysis, as in exercise, but also when there is a need for fat storage, as after ingestion of a meal. Pharmacological studies have elucidated many of the regulators of ATBF in different states, and adrenergic effects appear to predominate in many conditions, but these investigations also indicate that the regulation of ATBF is complex, as is the regulation of adipose tissue metabolism. There are apparent defects in ATBF regulation in obesity and insulin resistance, although it is also possible to interpret these as physiological adaptations to increased fat mass. This, together with the main physiologic regulators of ATBF is illustrated in Figure 4. The regulation of ATBF is relatively unexplored compared with the metabolic and secretory functions of adipose tissue, but should not be neglected.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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