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Unexpected evidence for active brown adipose tissue in adult humans

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Nedergaard J, Bengtsson T, Cannon B. Unexpected evidence for active brown adipose tissue in adult humans. *Am J Physiol Endocrinol Metab* 293: E444–E452, 2007. First published May 1, 2007; doi:10.1152/ajpendo.00691.2006.—The contention that brown adipose tissue is absent in adult man has meant that processes attributed to active brown adipose tissue in experimental animals (mainly rodents), i.e., classical nonshivering thermogenesis, adaptive adrenergic thermogenesis, diet-induced thermogenesis, and antiobesity, should be either absent or attributed to alternative (unknown) mechanisms in man. However, serendipidously, as a consequence of the use of fluorodeoxyglucose positron emission tomography (FDG PET) to trace tumor metastasis, observations that may change that notion have recently been made. These tomography scans have visualized symmetrical areas of increased tracer uptake in the upper parts of the human body; these areas of uptake correspond to brown adipose tissue. We examine here the published observations from a viewpoint of human physiology. The human depots are somewhat differently located from those in rodents, the main depots being found in the supraclavicular and the neck regions with some additional paravertebral, mediastinal, para-aortic, and suprarenal localizations (but no interscapular). Brown adipose tissue activity in man is acutely cold induced and is stimulated via the sympathetic nervous system. The prevalence of active brown adipose tissue in normal adult man can be only indirectly estimated, but it would seem that the prevalence of active brown adipose tissue in the population may be at least in the range of some tens of percent. We conclude that a substantial fraction of adult humans possess active brown adipose tissue that thus has the potential to be of metabolic significance for normal human physiology as well as to become pharmaceutically activated in efforts to combat obesity.

fluorodesoxyglucose; positron emission tomography; glucose uptake; nonshivering thermogenesis

IT IS WELL RECOGNIZED THAT BROWN ADIPOSE TISSUE is present and active in human newborns and is responsible for their successful defense of body temperature without shivering [the evidence is summarized in comprehensive reviews (45, 46)]. However, it has been the general contention that brown adipose tissue is rapidly lost postnatally, the implication being that this process is normally concluded within the first (few) years of life, and that humans later in life do not possess more than vestigical amounts of brown adipose tissue [although some evidence to the contrary has been presented, as reviewed in detail (45, 46), but this evidence has been largely ignored].

Thus, that brown adipose tissue is not found in adult man has become a generally accepted dogma. There are several consequences of the tenet that adult man lacks brown adipose tissue. It has meant that any suggestion that brown adipose tissue could be part of the defense against cold in adult man and particularly could increase its thermogenic capacity in response to prolonged cold exposure has been dismissed. This then means either that adult man does not possess classical nonshivering thermogenesis (i.e., the development with time of a heat-producing mechanism to replace shivering, as a consequence of chronic exposure to cold) or that man should possess an alternative method of nonshivering thermogenesis other than that found in experimental animals (rodents), where all classical nonshivering thermogenesis is dependent upon brown adipose tissue (34). Furthermore, this means that adaptive adrenergic thermogenesis [which in rodents originates from brown adipose tissue (33)] must, if it exists, be dependent upon an alternative mechanism in man (50). The alleged absence of brown adipose tissue also precludes that alterations in amount and activity of brown adipose tissue could be an explanatory contributory factor for obesity in humans, in contrast to what seems to be the case in rodents (51). An important applied extension of this issue is that pharmaceutical agents intended to combat obesity (or diabetes) by stimulating brown adipose tissue have now generally been discarded as candidates for human therapy.

However, since 2002, unrelated pursuits within nuclear medicine have unexpectedly produced results that challenge the view that adult man lacks active brown adipose tissue. These results indicate that brown adipose tissue is indeed present and active in (at least a significant fraction of) adult humans and may thus be considered to be an organ of physiological and pharmaceutical importance even in adult man. In the following, we summarize this evidence.

A Symmetry Problem

To localize tumors, markers for cellular activity are used in nuclear medicine. Because tumors in general are glycolytic, increased glucose uptake may indicate the presence of a tumor. A favored substance used to follow glucose uptake is 2-[^{18}F]-fluoro-2-desoxy-glucose (FDG; Fig. 1). FDG possesses the expected characteristics of deoxyglucose in that it is taken up by member(s) of the sodium-independent glucose transporter family [generally by glucose transporter (GLUT)1, but in, e.g., adipose tissue, muscle, and myocardium also by GLUT4 and in cancer cells also by GLUT3] and is then phosphorylated by hexokinase to the 6-phosphate. The deoxyglucose cannot be further metabolized, but the phosphorylation has the consequence that the substance cannot easily leave the cell. In addition to this deoxyglucose property, labeling with ^{18}F means that the localization of FDG accumulation within the body can be detected due to its positron emission; the annihilation of the positron by an electron leads to the formation of two high-energy photons radiating in opposite directions, and these photons are then detected. In clinical positron emission tomography (PET) settings, the detection system allows for

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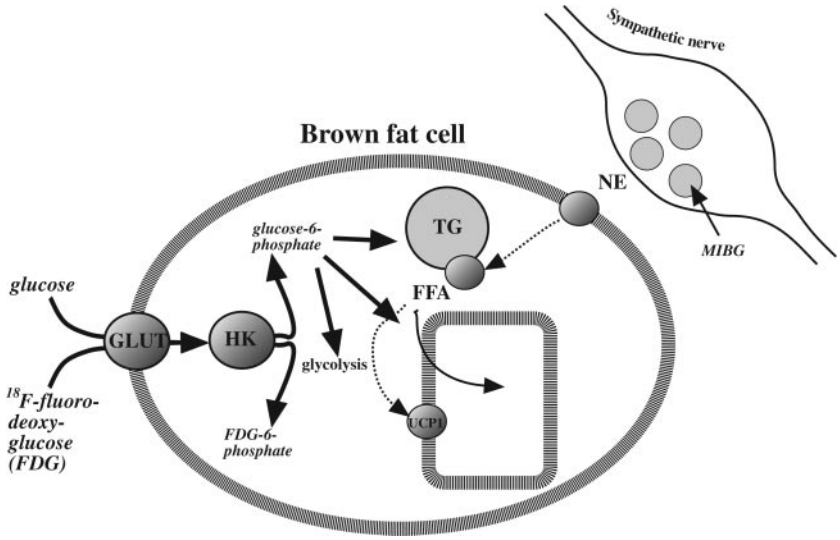

Fig. 1. 2-[^{18}F]fluoro-2-desoxy-glucose (FDG) uptake in brown fat cells. Both FDG and glucose are taken up by members of the glucose transporter family, most likely glucose transporter (GLUT)1 and GLUT4. After phosphorylation by hexokinase (HK) tracer, FDG cannot be further metabolized and is trapped in the cell. Glucose phosphate is, however, further metabolized by several processes in the cell; the 3 arrows symbolize resynthesis of lipid, anaplerotic reactions in the mitochondria, and cytosolic ATP production. Physiologically, the brown fat cell is stimulated by norepinephrine (NE) released from sympathetic nerves [note that the tracer compound metaiodobenzylguanidine (MIBG) is accumulated in the transmitter vesicles of the nerve], and this stimulation with NE leads to triglyceride (TG) breakdown The resulting free fatty acids (FFA) are probably involved in activation of the brown fat-specific uncoupling protein-1 (UCP1). FFA are also the main source for substrate combustion in the mitochondria. The further metabolism of glucose is linked to the ongoing thermogenesis, but the exact mechanism(s) is not known [for general overview concerning brown adipose tissue function and significance we refer to our recent review (11), to which we also refer, for space reasons, in the running text for general statements].

mapping of the origin of the photons and produces two- and three-dimensional maps of the body; however, the resolution of the maps is not very high. In routine procedures, patients are fasted for >4 h to decrease blood glucose levels (glucose competes with FDG for the uptake mechanism). They are then injected with FDG, and after ~1 h the imaging procedure takes place. The images are then analyzed for areas with a high FDG uptake that may represent tumors.

However, as fluorodeoxyglucose positron emission tomography (FDG PET) in principle simply monitors glucose uptake, it is not unexpected that also some nontumor tissues utilizing glucose are labeled by this procedure. Particularly, the brain shows high labeling, along with the heart (if the patients have not been fasted for sufficiently long), as does any muscle that may be active during the imaging process. As the FDG is poorly reabsorbed in the kidneys, the bladder may show a very high apparent "uptake." However, in addition to these expected areas of non-tumor-related uptake, it turned out in the early 1990s that it was not unusual to observe additional areas of uptake, particularly in the neck and shoulder area. What was particular with these areas of uptake was that they were symmetrical in nature (6, 24). As tumors would not be expected to be symmetrically distributed, it was evident that these uptakes did not represent the tumors clinically targeted with this proceedure. Originally, this type of uptake pattern was attributed to muscular uptake, ascribed to tense muscle due to anxiety; this interpretation was apparently supported by observations that diazepam treatment could diminish the disturbing uptake (6).

By using only FDG PET, it is in principle impossible to identify the nature of the tissue where FDG uptake occurs. It was therefore not until it became possible to routinely combine FDG tomography with computer tomography (CT), which visualizes the density and composition of the tissues with higher spatial resolution than PET, that it became clear that the areas of symmetrical uptake were not muscle; the uptake was found in tissue with a lower CT density than that of muscle. Instead, the uptake was in a tissue with the characteristics of adipose tissue. Due to its anatomical location, the main tissue responsible was known for a short time as "USA-fat", the acronym not having its normal meaning here but instead referring to "uptake (of FDG) localizing to the supraclavicular area." At this time, it was finally proposed that this adipose tissue was brown adipose tissue (36, 70).

It may be said in retrospect that the pattern observed (as sketched in Fig. 2) should perhaps already at an early stage have caused observers to contemplate whether this could be brown adipose tissue. Indeed, one may ask, as did Weber (69), why it took so long to recognize that this type of FDG uptake represented brown adipose tissue. This, as he suggests, was probably "because it was generally believed that brown adipose tissue is not present in relevant amounts in adults," making it difficult to see what "is in front of your eyes."

In the context of clinical investigations, the uptake in brown adipose tissue is seen as a disturbing complication. This is because it may interfere with diagnosis both by giving false positives, i.e., indicate as a tumor what is in reality brown adipose tissue, and by its dominance obscuring the ability to identify a true tumor uptake in a given area. Therefore, experimental efforts in nuclear medicine have concentrated on how to eliminate the problem of brown fat uptake. Accordingly, all data concerning FDG uptake in brown adipose tissue have been published in journals addressing nuclear medicine scientists, i.e., journals not normally studied by physiologists. Here, however, we look at the evidence in the positive light of asking what the results presented to date tell us about human brown

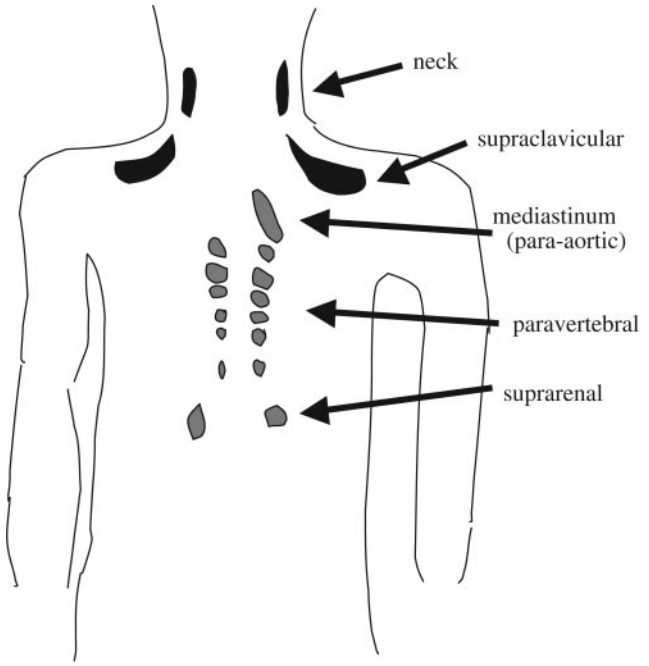

Fig. 2. Sites of FDG uptake corresponding to brown adipose tissue in adult humans. The black areas are those that are most frequently described; the gray areas are not always found, even in humans positive in the black areas. (A 3-dimensional representation of the distribution of brown adipose tissue FDG uptake in adult man is presently available at www.med.harvard.edu/JPNM/chetan/normals/brown_fat/case.html).

adipose tissue and what the significance may be for human physiology.

In total, a few dozen articles have been published discussing FDG uptake in brown adipose tissue in adult man; some of these consist mainly of further examples of brown fat FDG uptake (1, 56, 66), and the present overview is therefore not comprehensive in this respect. Notably, the brown fat uptake is now so recognized in nuclear medicine that it is considered a "normal" uptake in recent reviews and textbooks on FDG analysis (13, 35), and it is therefore unlikely that more than a few further descriptive articles will be published.

Where is Brown Adipose Tissue Found in Adult Humans?

In Fig. 2, we summarize standard observations on the location of brown adipose tissue in adult humans as evidenced by the FDG PET technique.

As implied in the USA-fat name, the most conspicuous brown adipose tissue depot detected in adult man with this technique is a depot localized to the supraclavicular area. Based on studies in experimental rodents, this is not an expected depot of brown adipose tissue, and, accordingly, there are no earlier data examining brown adipose tissue in this area. This fat depot is not generally described as possessing special characteristics; it is otherwise discussed only as being enhanced in Cushing's syndrome.

The neck depots may be said to have their correspondence in rodents. These two depots (supraclavicular and neck) constitute the two most often occurring depots in man; the supraclavicular is the largest brown adipose tissue depot in most persons examined. In general, these two depots are apparently the depots most easily induced in man; the depots mentioned below are often found when the two upper depots are present, whereas the presence of brown adipose tissue in the depots mentioned below in the absence of supraclavicular brown adipose tissue is generally not observed.

A pattern of brown adipose tissue is seen along the spinal cord as a paravertebral depot, also in the mediastinum (67), particularly in the para-aortic area (16), and around the heart, particularly the apex. Also, infradiaphragmatic depots exist (5), particularly in the perirenal area, but this depot is generally weaker than the upper depots (16).

Thus, the distribution pattern, although having similarities to, is not identical to that observed in rodents; there is no interscapular depot (which is the depot that is most prominent, largest, and most experimentally studied in rodents), there is no axillary depot, and the perinephric depot is not very prominent.

It should be pointed out that this distribution of brown adipose tissue in the adult human, as inferred from FDG PET scans, is in very good accordance with classical data on brown adipose tissue in newborn human infants. As also commented by Lean (45), the interscapular depot "is quantitatively unimportant in human infants," and the major depots identified by FDG PET in adult man are in good correspondence to those described in human infants in the classical study by Aherne and Hull (2).

This species-specific distribution of the human depots may partly explain why the presence of functional amounts of brown adipose tissue in adult man has been refuted in earlier studies. In earlier studies in man, two expected depots have particularly been examined. One is the interscapular depot, where it was concluded that no brown adipose tissue was found in adult man (3); the FDG data indeed now confirm this but add to the picture that brown adipose tissue instead is found elsewhere. The second depot is the perirenal depot, where functional studies have concluded that brown adipose tissue may be present (4, 20); however, functional data from this area have been used to calculate total brown adipose tissue capacity in adult man, based on this depot being a major depot, arriving at the conclusion that the capacity was minimal. Based on the FDG PET observations, it would seem likely that such calculations would markedly underestimate total brown adipose tissue capacity.

Confirmation that Brown Adipose Tissue is Visible as Areas of FDG Uptake

Two issues must be addressed concerning the relationship between FDG uptake and brown adipose tissue. One is whether brown adipose tissue really is visible as an FDG uptake, and the other is whether the relevant areas showing FDG uptake really represent brown adipose tissue.

That brown adipose tissue is visualized as FDG uptake is supported by a series of studies in both rodents and man. In mice, excision of brown adipose tissue eliminates the FDG uptake (44). Also, isoflurane anesthesia of mice eliminates FDG uptake (26), in agreement with isoflurane (and other inhalation anesthetics such as halothane) completely blocking norepinephrine-induced thermogenesis (57). It may be noted that this inhibition of thermogenesis occurs downstream of sympathetic stimulation, i.e., stimulation of the tissue can probably occur but the thermogenic process is inhibited, indi-

cating that the uptake is not secondary to sympathetic stimulation per se but requires active thermogenesis to be evident.

Conversely, there are two clinical conditions in adult man where the presence of active brown adipose tissue is already recognized: hibernoma and pheochromocytoma. Hibernomas (tumors, generally benign, with brown fat characteristics, often appearing in unexpected locations such as the thigh) are clearly visible in FDG PET, also indicating that the hibernoma is metabolically active (14, 49, 68). In patients with pheochromocytoma (a neuroendocrine tumor leading to excessive release of norepinephrine in the body), brown adipose tissue is known to become recruited (9, 10, 25, 47, 61; review in Refs. 11, 45, and 46). In FDG PET studies, the uptake in these patients becomes extreme with regard to both intensity and localization (27, 59). However, when the pheochromocytoma tumor is eliminated, this dramatic uptake is also eliminated (27, 59).

Taken together, the above observations demonstrate that active brown adipose tissue can be visualized as an area of enhanced FDG uptake.

Does FDG Uptake Indicate Active Brown Adipose Tissue?

Evidently, the FDG PET method only visualizes glucose uptake as such, and any further implications on what the glucose uptake indicates must be by inference. However, it should be pointed out that there is no doubt that the FDG PET studies demonstrate that glucose uptake is actively ongoing in brown adipose tissue in (a fraction of) the adult population, and the existence of this means of glucose disposal may not be without interest in itself.

Glucose uptake is directly adrenergically stimulated in rodent brown adipocytes in culture (15, 53); this process can occur even in the absence of uncoupling protein-1 (UCP1) (39). It could therefore be hypothesized that the FDG uptake even in vivo mainly reflects a direct stimulation of glucose uptake and may not be associated with a truely high metabolic rate in the tissue. However, in general, the information that glucose is being taken up is normally interpreted to indicate that the tissue is also metabolically active in a broader sense. This is the basis for the use of the FDG PET technique in localization of tumors and for the analysis of brain areas involved in different cognitive activities as well as for examining myocardial activities. Thus, there is general consensus that increased glucose uptake indicates increased metabolism.

Concerning the more specific and relevant question here, i.e., whether the glucose uptake indicates ongoing metabolism in the form of thermogenesis, there is evidence to support this interpretation. Thus, in mature brown fat cells, glucose uptake seems to require fatty acid metabolism (54), and, importantly, in intact mice without UCP1, where norepinephrine is unable to stimulate any thermogenesis in the brown fat cells (55), norepinephrine also loses its ability to increase glucose uptake (40). Thus, at least in mice, stimulated thermogenesis is a prerequiste for FDG uptake in brown adipose tissue in vivo. There is no reason to think that the conclusion from this functional study cannot be extended to man. Thus the FDG uptake seen in brown adipose tissue in adult man implies the existence of thermogenically active tissue in adult man.

The Significance of Glucose Uptake in Brown Adipose Tissue

Thermogenesis as such mainly utilizes lipid for combustion (as indicated in Fig. 1). Although glucose uptake is highly associated with stimulated thermogenesis, the metabolic significance of the glucose is not fully clear. It may play a role through an anaplerotic mechanism forming oxaloacetate from pyruvate (from the glucose) and thus increase the capacity of the citric acid cycle, it may produce cytosolic ATP through glycolysis when the brown fat mitochondria are thermogenic and uncoupled, or it may be imported into the cell to replenish the triglyceride depots either by providing the glycerol phosphate backbone or after having been converted to fatty acids (11). It is clear from the FDG PET studies that brown adipose tissue may be very significant for glucose disposal outside the nervous system, at least under the conditions under which FDG is studied, i.e., when we are at rest and in a fasted condition. These are conditions characterizing nearly one-third of everyday life, implying that brown adipose tissue may not be without significance for glucose metabolism, actively clearing glucose from the circulation.

Are the Human Depots Really Brown Adipose Tissue?

That the depots showing high FDG uptake are not normal adipose tissue depots is clear. Thus, although the uptake areas have a CT density corresponding to adipose tissue, it may particularly be pointed out that FDG uptake is not seen in storage depots of fat, such as under the skin or in omental depots.

The one identifying characteristic of brown adipose tissue is the presence of UCP1 in the tissue. Concerning mitochondria isolated from the perinephric depots of adult humans, one of the depots that show FDG uptake, a series of earlier studies (9, 10, 47, 61) have shown the presence of functional characteristics indicating the presence of UCP1 as well as UCP1 protein or UCP1 mRNA. Initially, such studies were made with perinephric/periadrenal mitochondria from pheochromocytoma patients. The induction of brown adipose tissue by pheochromocytoma is a classical observation (25), and it may therefore be argued that these depots become brown adipose tissue only as an effect of this disease and are not brown adipose tissue in normal man. However, later studies (12, 30, 42, 48) have also indentified UCP1 characteristics [low mitochondrial membrane potential and high respiratory rate, which can be coupled by GDP (20)] and UCP1 protein and mRNA in tissue and mitochondria from patients that are not pheochromocytoma patients, as well as from nonpathological material. UCP1 is also detectable in the para-aortic depots (16). Thus, the perinephric and para-aortic depots are undoubtedly brown adipose tissue even in nonpheochromocytoma patients; unfortunately, it does not seem that the presence of UCP1 in the dominant supraclavicular depot has so far been examined.

Activity is Induced by Acute Exposure to Cold

Thermogenesis in brown adipose tissue (in experimental animals) is a facultative process. This means that, even if the tissue is present and is well differentiated (including having high levels of UCP1), the tissue will be inactive in warm surroundings but will be acutely activated (in a

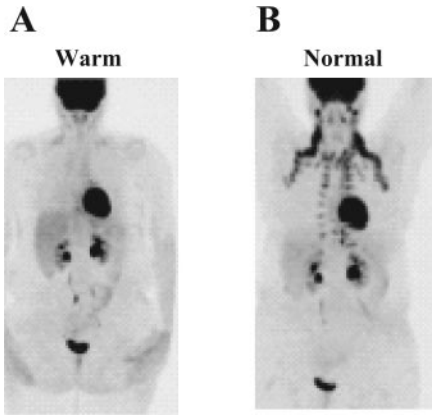

Fig. 3. Cold-induced brown adipose tissue activation in adult man. The same patient was investigated by fluorodeoxyglucose positron emission tomography (FDG PET) twice a few days apart. *A*: efforts had been made to keep the patient under warm conditions before injection and during the time from injection to imaging. The only uptake visible is that into the brain, heart, kidneys, and bladder. *B*: the patient had been examined under routine conditions, i.e., in comparatively cold conditions. Note that the characteristic symmetrical pattern of uptake into the supraclavicular, neck, paravertebral areas, etc., i.e., into brown adipose tissue, is now visible. Reproduced from Christensen et al. (17) with permission.

matter of minutes) when the animals experience a cold environment (11).

If brown adipose tissue in adult man should be thermogenically relevant, it is a basic requirement that its activity is similarly directly regulated by the thermal environment experienced. Several studies (17, 28, 29, 37) have addressed this issue and have found clear differences between patients who have actively been kept warm vs. those who have been exposed to the normal slight cold stress that is associated with the routine FDG PET procedures (Fig. 3). From these studies, it is clear that if the patients are kept warm during the hour from injection of FDG to PET imaging, FDG uptake into brown adipose tissue is fully suppressed. Clinically, the consequence of these observations is that it is now recommended that efforts should be made in routine FDG PET to ensure that the patients are thermally comfortable or even "warm" during the time of uptake. These routines will most probably soon eliminate practically all observations of brown adipose tissue during FDG PET clinical examinations. However, from a physiological point of view, it is a very important and novel demonstration that brown adipose tissue is activated by external cold in adult humans, just as it is in experimental animals.

In rodents, the total amount of brown adipose tissue (and thus the capacity for nonshivering thermogenesis) is regulated mainly by the environmental temperature to which the animal is chronically exposed (referred to as the degree of recruitment of brown adipose tissue). However, the actual acute activity of the tissue is determined by the environmental temperature in the acute conditions; i.e., as stated above, even a cold-acclimated animal will display inactive tissue if acutely transferred to warmth.

Given this fact, it is not surprising that the literature on FDG uptake in human brown adipose tissue in relationship to outdoor temperature diverges; an earlier study (18) indicated a connection (more in winter), and a later study (62) did not find a connection. The latter is probably the more likely outcome; humans in present societies are rarely directly exposed to outdoor temperatures; much of our civilization even has this as its purpose (clothes and houses). It is therefore unlikely that adult civilized man will become markedly cold acclimated in the winter. Rather, as concluded above, it may be the actual temperature in the examination room that determines the degree of FDG uptake. A practical possibility is that outdoor temperature influences the actual temperature in the examination room during the FDG uptake phase, perhaps sometimes even in a paradoxical way; in winter, heating may be on, whereas in summer months air conditioning may be turned on, leading to uncomfortably cold investigation rooms (17). This could even lead to a reversed temperature profile for the examination room compared with the outdoor temperature.

Human Brown Adipose Tissue Activity is Sympathetically Stimulated

In experimental animals, thermogenesis in brown adipose tissue is controlled by norepinephrine released from the sympathetic nervous system; norepinephrine interacts mainly with β-adrenergic receptors to stimulate thermogenesis (11). Accordingly, in rats, the β-adrenergic antagonist propranolol (5 mg/kg body wt) eliminates FDG uptake into brown adipose tissue (65). In man, propranolol (~1 mg/kg) has the same effect (41, 63), clearly indicating that, also in man, glucose uptake (and thus probably thermogenesis) is under β-adrenergic control (Fig. 4).

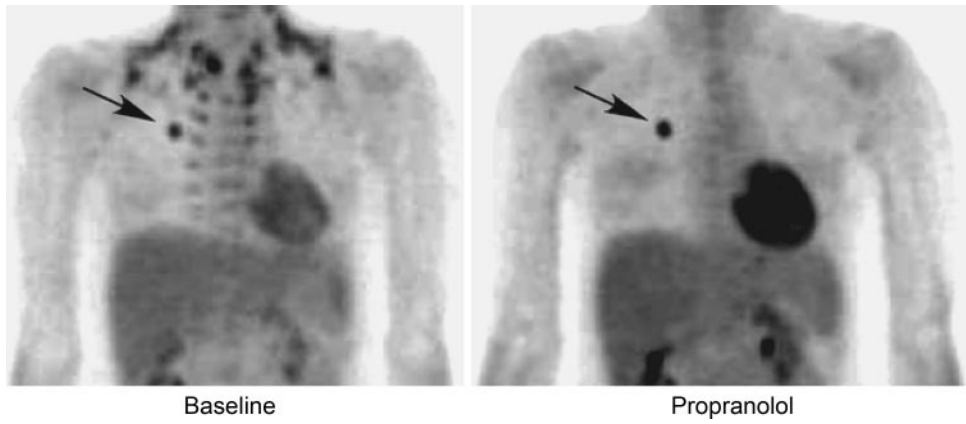

Fig. 4. Sympathetic control of brown adipose tissue activity in adult man. The same patient was examined by FDG PET twice, once at baseline (standard conditions) and then 6 days later when the patient had received 80 mg of propranolol orally 2 h before the examination. Note the total elimination of the brown fat-related uptake by propranolol. The arrow points to a lung metastasis. Reproduced from Soderlund et al. (63) with kind permission of Springer Science and Business Media.

It may be noted that thermogenesis in rodents is stimulated via β_3-adrenoceptors, which are difficult to inhibit with propranolol. Whether the doses used in humans were high enough to block not only β_1- but also β_3-adrenoceptors, or whether human brown adipose tissue is stimulated mainly via β_1-adrenoceptors, has not presently been clarified.

There are some indications that brown adipose tissue activity is blocked by diazepam or other tranquilizers (6, 60), and such treatment is recommended for "nervous" patients (35) [but not all find such effects (21), at least not experimental animals]. The nuclear medicine literature refers to previously observed diazepam-binding sites in brown adipose tissue as an explanation for this effect, but because brown adipose tissue is stimulated by the sympathetic nervous system and because anxiety may activate this system, it is possible that the inhibition of brown fat FDG uptake by diazepam is due to reduced sympathetic activity. However, the ability of a "warm" environment to eliminate FDG uptake in brown adipose tissue (described above) makes it less likely that stress is a common factor for brown adipose tissue activation.

The Prevalence of Brown Adipose Tissue in Adult Man

A natural, but unexpectedly difficult, question concerns the prevalence of brown adipose tissue in adult man, as estimated from the FDG PET data.

When the same patient is examined several times, it becomes evident that the presence or absence of brown adipose tissue FDG uptake is not reproducible. This was observed early on (even before it was realized that the uptake was into brown adipose tissue) (6). The irreproducibility goes both ways; i.e., an uptake into brown adipose tissue observed initially may show "resolution" on a later occasion, or brown fat uptake may occur in a patient who had not demonstrated it earlier. In a remarkable study, 33 women were systematically successively examined five times during an anticancer treatment. Apparently, only six of these women did not demonstrate brown adipose tissue labeling on any of these occasions, and only one woman demonstrated it on all five occasions (62). In this limited population, the prevalence of brown adipose tissue may then be said to be as high as 80%. The uptake was also of different intensity on different occasions. It is likely that the variation is understandable based on the acute regulation of brown adipose tissue activity discussed above. However, the important lesson from this study is that single measurements may seriously underestimate the true prevalence of brown adipose tissue.

This value of about 80% is very much different from what was reported in some of the early retrospective studies, where only a small percentage of patients were judged to show brown adipose tissue. However, in a study of patients with Hodgkin's disease, brown adipose tissue was identified in 25% (21), and in a teenage population the prevalence approched 50% (32). Although finding a decrease over age, one study reported 10–40% prevalence in adults (64). These studies were mainly single-scan studies, and based on the discussions above that the chance of detecting brown adipose tissue may be low in single-scan tests, it is reasonable to estimate that the true prevalence of active brown adipose tissue in the population is higher than a small percentage. It will be understood that brown adipose tissue would be visible only if the examination is performed under conditions where the tissue is physiologically stimulated, i.e., if the patients experienced some degree of cold. In clinical settings where this was not the case, many patients who possess brown adipose tissue would not be detected because the tissue is not acutely activated. Theoretically, it would be necessary to examine a cross section of the population under relative cold conditions to establish the "true" prevalence. This has not been done and is presently not feasible. However, based on the collected evidence, it is our estimate that the true prevalence is at least in the range of some tens of percent and may thus include a significant part of the population.

It may also be pointed out that routine examination procedures include a 4- to 24-h fasting period (to decrease blood glucose that dilutes FDG). However, at least in experimental animals, the stimulation of brown adipose tissue, particularly in animals living at or close to their thermoneutral temperature (where brown fat activity is not needed for thermoregulatory purposes), is largely determined by the feeding status of the animals, with fasting leading to a diminished activity (11). Indeed, in mice there is a very conspicuous scale of FDG uptake in brown adipose tissue, ranging from a very pronounced uptake in fed, cold-stressed mice to very little in fasted, warm-acclimated mice (26). Thus, the apparent prevalence, i.e., the activity, may also be decreased due to the fasting conditions utilized during the examination of patients. Whether this is the case may be difficult to examine, even experimentally, due to the dilution effect of blood glucose on the apparent FDG-specific activity and the resulting decrease in apparent FDG uptake as an effect of increased blood glucose in fed persons; also, an increased glucose uptake into many tissues may partly mask the brown fat component under fed conditions.

Age and Sex

The ages of the persons exhibiting FDG uptake in brown adipose tissue are very diverse and more likely reflect the type of cancer patients examined than the distribution of brown adipose tissue in the population. There is no consistent tendency reported that the distribution is biased towards younger people, and the reports include patients in their 50s, 60s, or even 70s, but a declining proportion with age has been found in one study (64).

There are some reports that females, more than males, exhibit brown adipose tissue (19). Whether this represents a true sex dimorphism is unclear; an alternative would be that the women were in reality experiencing more acute cold stress during the time of FDG uptake.

Brown Adipose Tissue and Body Weight

An important issue is whether the presence of active brown adipose tissue in humans would be protective against obesity, an expectation that some (51) but not all (23) studies with rodents suggest. In other words, does brown adipose tissue in adult man reflect diet-induced thermogenesis? Therefore, in a few larger-scale (retrospective) investigations, attempts have been made to examine whether there is a correlation between the possession of active brown adipose tissue and a low body weight (body mass index). Some of these studies claim such a relationship (16, 62) and even that high brown adipose tissue is

correlated with less insulin resistance (16); others claim that such correlations do not exist (19, 64). However, because the indications above that the real frequency of brown adipose tissue in the examined patients is much underestimated, the material presently available does not really allow for making a valid distinction between two such groups "with" and "without" brown adipose tissue; all patients would need to be examined under "cold" conditions to verify whether they had brown fat, and this is presently not feasible. Dedicated experiments in this respect may, however, be possible.

There are indications from animal experiments (11) that the cachexia associated with cancer is accompanied by recruitment of brown adipose tissue and increased brown adipose tissue activity. The prevalence of brown adipose tissue observed in the human studies could therefore be suggested to reflect the patient group examined, i.e., that the presence of active brown adipose tissue should be induced due to the cancer. However, as the FDG PET analysis is often used for followup control of already treated patients, the majority of all patients reported did not demonstrate any signs (in the images or in clinical examination) of persistent cancer. There are thus no indications that the observations made in humans are secondary to the subjects generally investigated being cancer patients.

Other Indications from Nuclear Medicine of Active Brown Adipose Tissue in Humans

Additional evidence for the presence of brown adipose tissue, particularly in the supraclavicular area, may be seen with other tracers. The substance $^{123/125}$I-labeled metaiodobenzylguanidine (MIBG) accumulates in nerves. MIBG is accumulated in the potential brown fat areas in the body (31), in agreement with the fact that brown adipose tissue is densely innervated. In rodents, uptake is clearly located to brown adipose tissue and disappears when the nerves are destroyed with reserpine or 6-OH-dopamine (58). Accumulation of MIBG in humans was first observed in children but is also observed in adults (8, 22, 52, 58).

The factors determining uptake of ^{99m}Tc-sestamibi are still not fully known, but indications exist that it is taken up in active mitochondria. The substance is avidly taken up in brown adipose tissue in rodents (43). In man, uptake is again localized to expected brown adipose tissue areas (7), and it has even been shown to colocalize with FDG (38).

Is the Human Brown Adipose Tissue of Metabolic Significance?

The data summarized above make it very likely that a significant fraction of adult humans does possess brown adipose tissue, the activity of which is under control of the sympathetic nervous system, very similar to what is the case in, e.g., rodents. The question that cannot be directly answered from this is, how important is this brown adipose tissue metabolically?

Arguments that brown adipose tissue is of low significance in adult humans were largely based on calculations extrapolating from the thermogenic activity in the perirenal depot, which was at that time considered a major depot in adult man. The demonstration from the FDG PET studies is rather that this depot is a very minor depot, with much more active brown adipose tissue being localized in the upper part of the body. Thus, similar estimates today would probably result in a different conclusion.

The amounts of FDG uptake seen in brown adipose tissue are not negligable. Although the data should principally be available in the data collections from the clinical investigations, there are no quantitative estimates of total flux of FDG into brown adipose tissue compared with the total body metabolism. However, simple inspection of the images shown in the literature indicates that, when the tissue is active, the uptake in brown adipose tissue is a main utilizer of glucose in the body, perhaps superceded only by the brain. If this correlates with metabolic activity, it is clear that active brown adipose tissue may play a significant role in the metabolism of at least a significant fraction of adult humans.

Perspectives

Because the occurrence of brown fat FDG uptake is now widely recognized in nuclear medicine, it is unlikely that many more descriptive articles will be published in the future. Furthermore, as some of the techniques to diminish or eliminate uptake into brown adipose tissue have become rather successful, it is also likely that the actual number of observations in clinical studies in oncology will decrease in the future. It is therefore unlikely that further insight into the function and significance of brown adipose tissue in adult man will occur as a result of surplus information from clinical studies. Thus, further analysis of brown adipose tissue activity in humans, utilizing this noninvasive methodology, will probably require dedicated experimental studies. Clearly, many of the issues that are implied here from clinical studies will need experimental confirmation, and other issues, such as the ability of food intake to activate the tissue, have not been examined at all in the clinical settings. In brain research, the use of PET analysis has had a remarkable impact on our understanding of a very complex system. Considering the secondary issues associated with an understanding of the control of human metabolism, it may not be considered unethical to also use PET in experimental analyses of human metabolism in volunteers in the future.

However, already today there are clear scientific implications of the observations already made with the FGD PET technique in humans. The main point is that it would now seem to be defensible to consider that much of the knowledge on the function and significance of brown adipose tissue acquired from studies in experimental animals is also relevant to adult man. Although complete demonstrations of the quantitative effects of alterations in the thermogenic capacity and activity of brown adipose tissue in adult man will be lacking for some years to come, the mere recognition that active brown adipose tissue is present in adult man may lead physiological and therapeutic efforts in a direction that has been considered to be without avail for many years, opening new avenues for understanding and treatment of metabolic diseases.

GRANTS

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