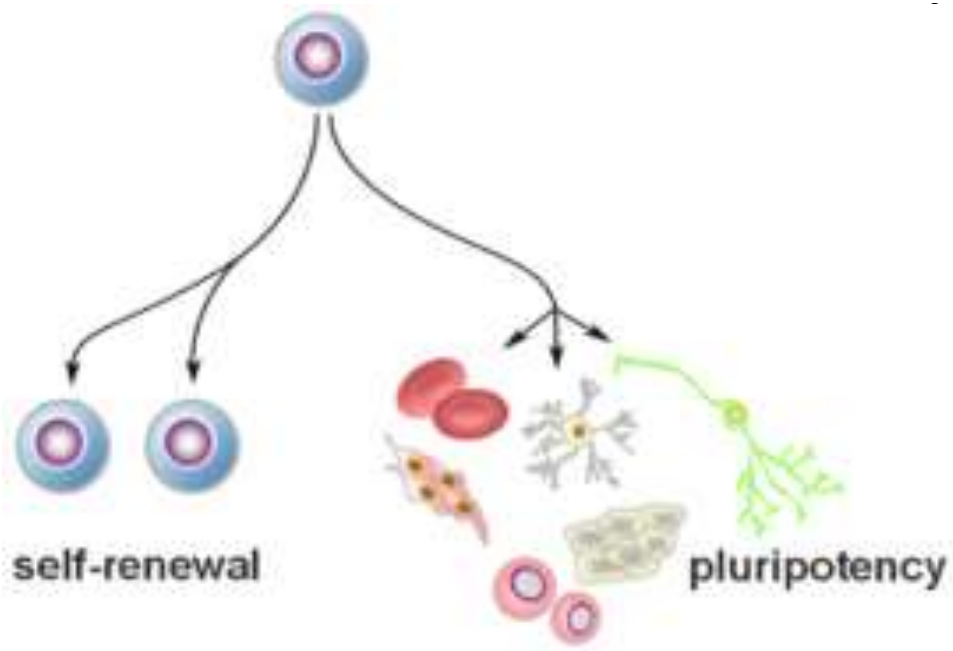
ACQUEST HEALTHCARE AND STEM CELL R&D

SWISS R&D LABORATORIES

Brown Fat Stem Cells (BFSC)

A breakthrough advance in reversing Obesity and Age related disease.

Stem Cell Self-Renewal



- Stem Cells have the capacity to another cell as well as a daughter cell

Stem Cells make a copy of itself to regenerate tissue

Stem Cell Self-Renewal

Review

Mesenchymal stromal cells

Biology of adult mesenchymal stem cells: regulation of niche, self-renewal and differentiation

Catherine M Kolf*, Elizabeth Cho* and Rocky S Tuan

Cartilage Biology and Orthopaedics Branch, National Institute of Arthritis, and Musculoskeletal and Skin Diseases, National Institutes of Health, Department of Health and Human Services, 50 South Drive, Bethesda, MD 20892, USA
*These authors contributed equally to this work

Corresponding author: Rocky S Tuan, tuanr@mail.nih.gov

Published: 19 February 2007
This article is online at http://arthritis-research.com/content/9/1/204

Arthritis Research & Therapy 2007, **9**:204 (doi:10.1186/ar2116)

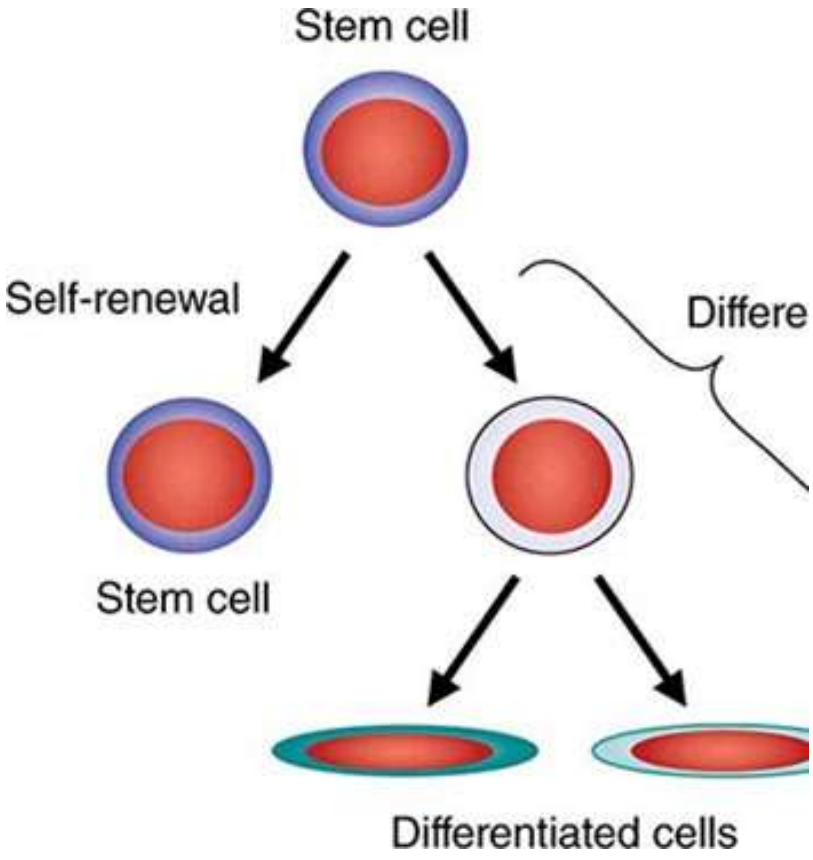
Abstract

Recent advances in understanding the cellular and molecular signaling pathways and global transcriptional regulators of adult mesenchymal stem cells have provided new insights into their biology and potential clinical applications, particularly for tissue repair and regeneration. This review focuses on these advances, specifically in the context of self-renewal and regulation of lineage-specific differentiation of mesenchymal stem cells. In addition we review recent research on the concept of stem cell niche, and its relevance to adult mesenchymal stem cells.

heterogeneous mixture of cells with varying proliferation and differentiation potentials. Although acceptable for cell-based therapeutic applications, a rigorous understanding of the MSC requires a better definition of what an MSC is. Many attempts have been made to develop a cell-surface antigen profile for the better purification and identification of MSCs. Particularly important is whether MSCs isolated from different tissues are identifiable by the same immunophenotype. Table 1 provides information on 16 surface proteins reported in various studies. Most of the studies focused on MSCs from

Stem Cell Differentiation

Stem Cell Differentiation



Stem Cells can specialize or develop into another type of cell

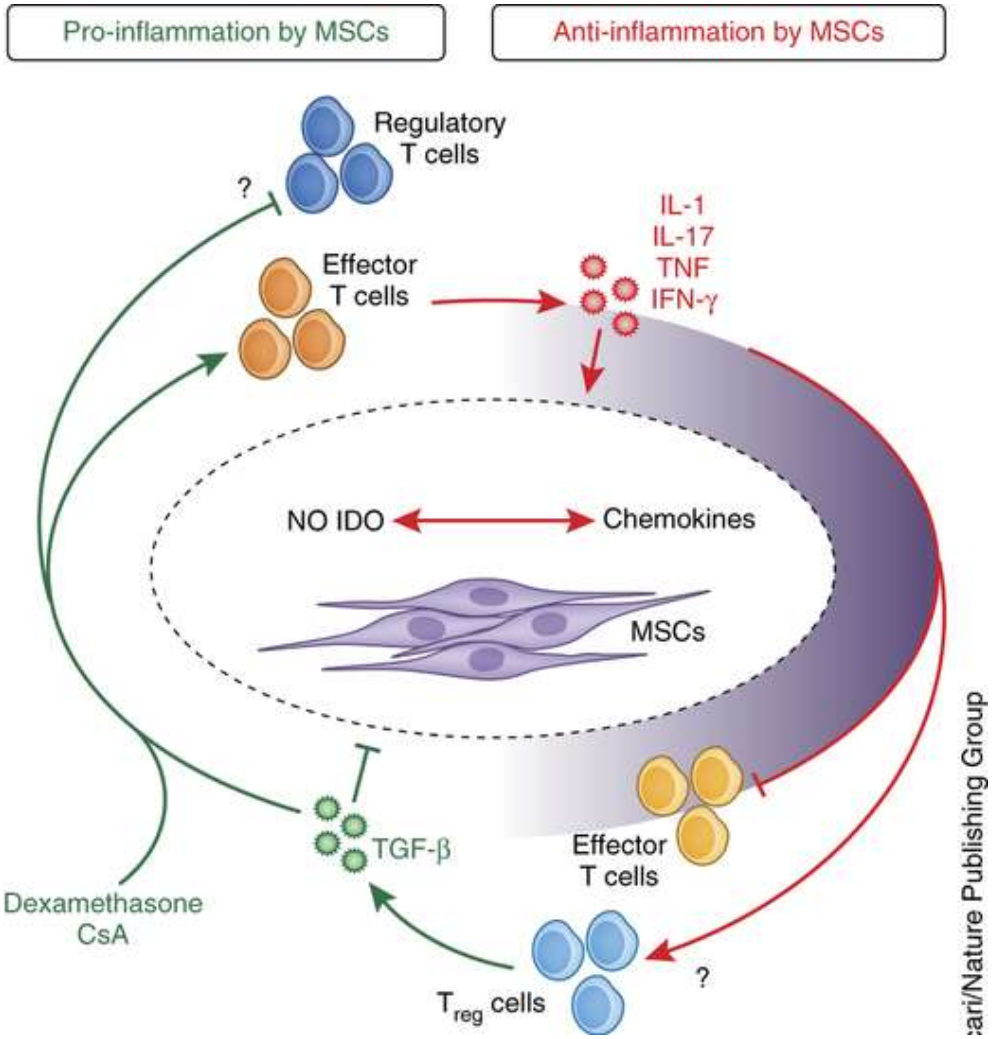
Stem Cell Differentiation

Adipose cell differentiation: evidence for a two-step process in the polyamine-dependent Ob1754 clonal line

Ez-Zoubir AMRI,* Christian DANI,* Alain DOGLIO,* Jacqueline ETIENNE,† Paul GRIMALDI* and Gérard AILHAUD*

*Centre de Biochimie du CNRS (LP 7300), Université de Nice, Parc Valrose, 06034 Nice Cédex, France, and †Laboratoire de Biochimie, Faculté de Médecine Saint-Antoine, 27 rue Chaligny, 75571 Paris Cédex 12, France

A subclone of preadipocyte Ob17 cells has been isolated (Ob1754 clonal line). Confluent Ob1754 cells treated with an inhibitor of spermidine and spermine synthesis, methylglyoxal bis(guanylhydrazone), were totally dependent upon putrescine addition for the expression of glycerol-3-phosphate dehydrogenase which behaved as a late marker of adipose conversion. Under these conditions, the early expression of lipoprotein lipase during growth arrest remained unchanged. Studies at the mRNA level showed that the expression of unidentified pOb24 and pGH3 mRNAs, which was parallel to that of lipoprotein lipase, is independent of polyamine addition whereas the late emergence of glycerol-3-phosphate dehydrogenase mRNA was putrescine-dependent and co-ordinated with the expression of pAL422 mRNA encoding for a myelin-P_2 homologue [Bernlohr, Angus, Lane, Bolanowski & Kelly (1984) Proc. Natl. Acad. Sci. U.S.A. **81**, 5468–5472]. The appearance of lipoprotein lipase preceded DNA synthesis and post-confluent mitoses which were both putrescine-dependent and which took place before the appearance of glycerol-3-phosphate dehydrogenase. Thus the adipose conversion of Ob1754 cells involves the expression of at least two separate sets of markers which are differently regulated.



Stem Cell Plasticity

- Stem Cells have the capacity to become any type of cell in the body
- Stem cells may go on to form any tissue, organ or body structure

Stem Cell Plasticity

Adult stem cell plasticity

Richard Poulsom[1]*, Malcolm R. Alison[1,2], Stuart J. Forbes[1,3] and Nicholas A. Wright[1,4]

[1] Histopathology Unit, Cancer Research UK, London Research Institute, London, UK
[2] Department of Histopathology, ICSTM, Hammersmith Campus, London, UK
[3] Department of Medicine, Faculty of Medicine, Imperial College of Science, Technology and Medicine (ICSTM), St Mary's Hospital, London, UK
[4] Bart's and the Royal London Hospitals, Queen Mary College, London, UK

*Correspondence to:
Richard Poulsom, PhD, MRCPath,
Histopathology Unit, Cancer
Research UK, London Research
Institute, 44 Lincoln's Inn Fields,
London WC2A 3PX, UK.
E-mail: richard.poulsom@
cancer.org.uk

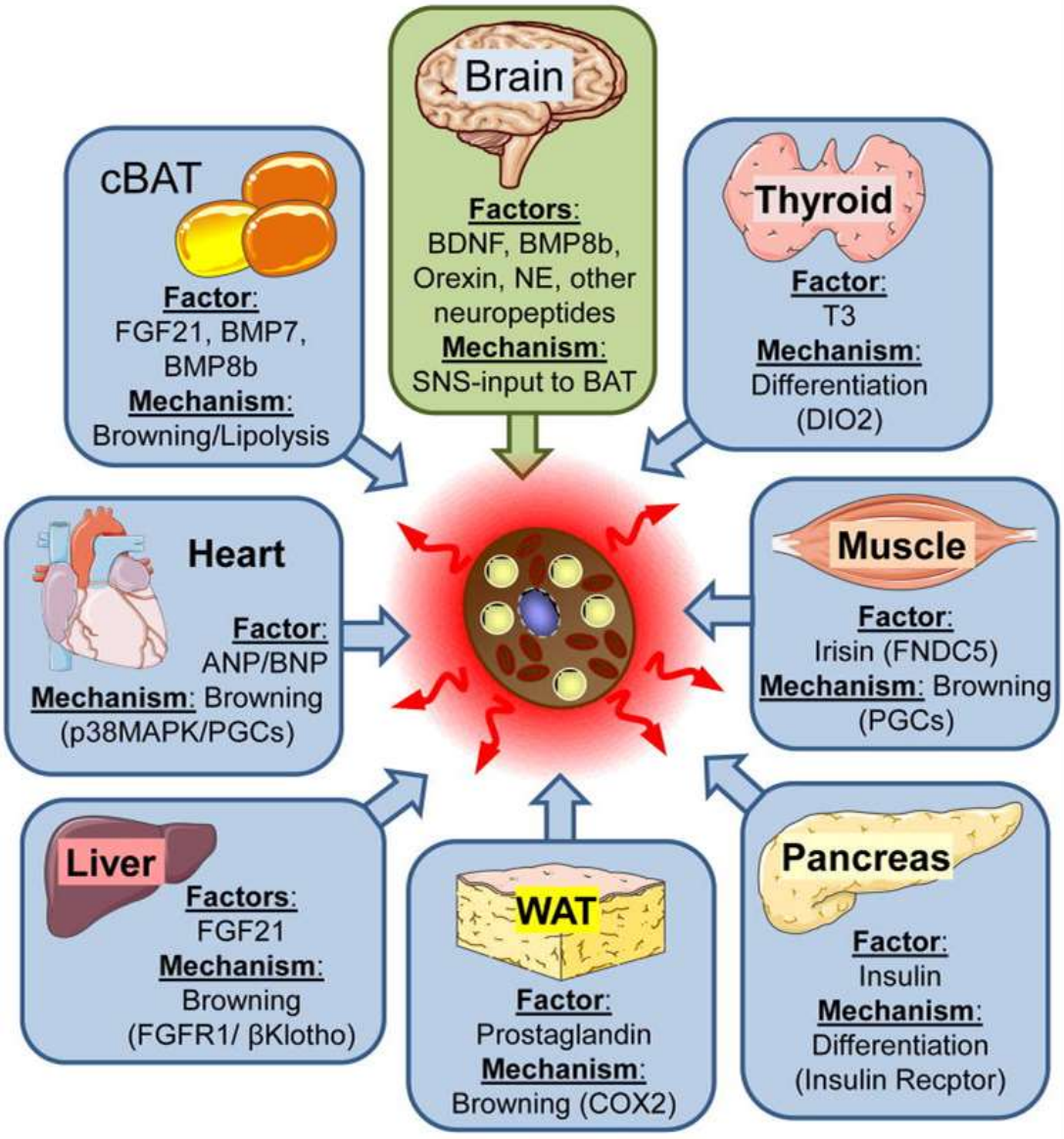
Abstract

Observations made in the last few years support the existence of pathways, in adult humans and rodents, that allow adult stem cells to be surprisingly flexible in their differentiation repertoires. Termed plasticity, this property allows adult stem cells, assumed, until now, to be committed to generating a fixed range of progeny, to switch, when they have been relocated, to make other specialized sets of cells appropriate to their new niche. Reprogramming of some adult stem cells can occur *in vivo*; the stem cells normally resident in bone marrow appear particularly flexible and are able to contribute usefully to multiple recipient organs. This process produces cells with specialized structural and metabolic adaptations commensurate with their new locations. In a few examples, the degree of support is sufficient to assist or even rescue recipient mice from genetic defects. Some studies provide evidence for the expansion of the reprogrammed cells locally, but in most it remains possible that cells arrive and redifferentiate, but are no longer stem cells. Nevertheless, the fact that appropriately differentiated cells are delivered deep within organs simply by injection of bone marrow cells should make us think differently about the way that organs regenerate and repair. Migratory pathways for stem cells in adult organisms may exist that could be exploited to effect repairs using an individual's own stem cells, perhaps after gene therapy. Logical extensions of this concept are that a transplanted organ would become affected by the genetic susceptibilities of the recipient, alleles that re-express themselves via marrow-derived stem cells, and that plasticity after bone marrow transplantation would also transfer different phenotypes, affecting important parameters such as susceptibility to long-term complications of diabetes, or the ability to metabolize drugs in the liver. This article reviews some of the evidence for stem cell plasticity in rodents and man.

Keywords: **stem cells; bone marrow; regeneration and repair**

Brown Fat Treatable Conditions

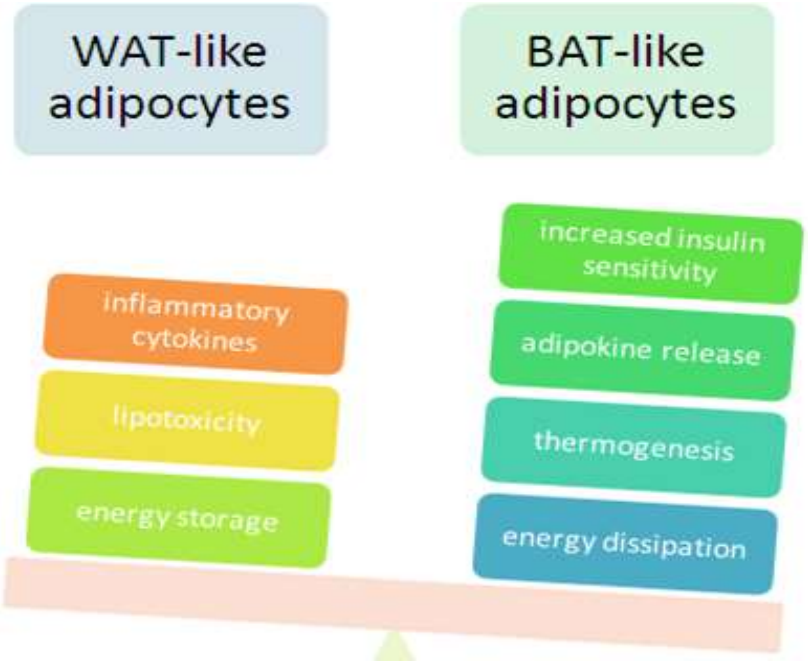
- Diabetes
- Heart Disease
- Obesity
- Arthritis
- Metabolic Disorders



Brown Fat vs. White Fat

Brown Fat vs. White Fat

Brown Fat burns White Fat

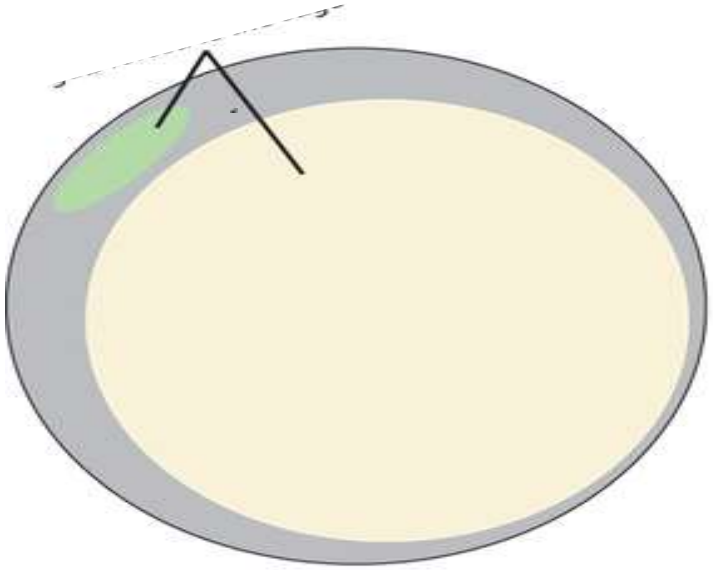


White Fat creates Inflammation

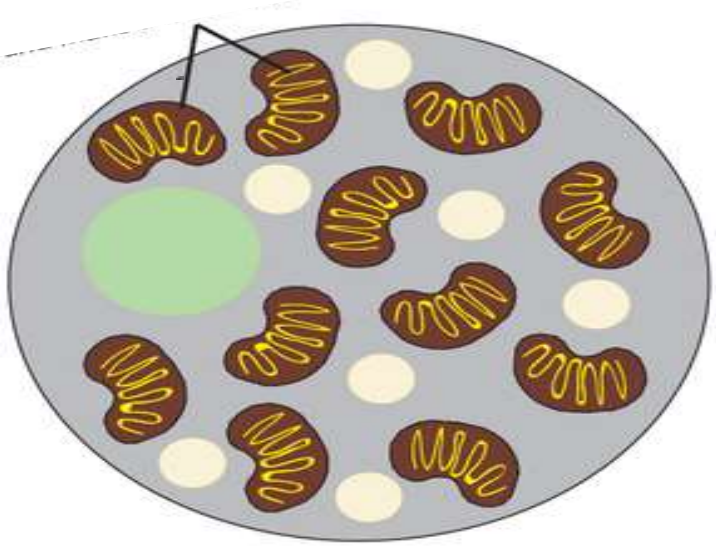
Brown Fat vs. White Fat

Produced heat gets sent to outer membrane

Increased mitochondria creates enough heat to turn the cell brown

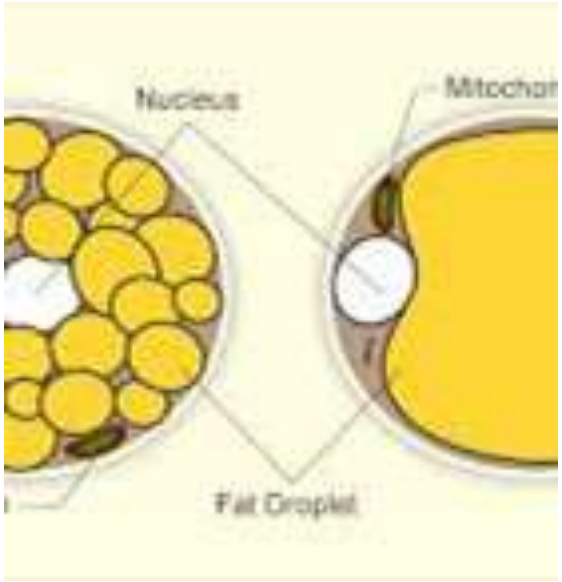


White Fat Cell



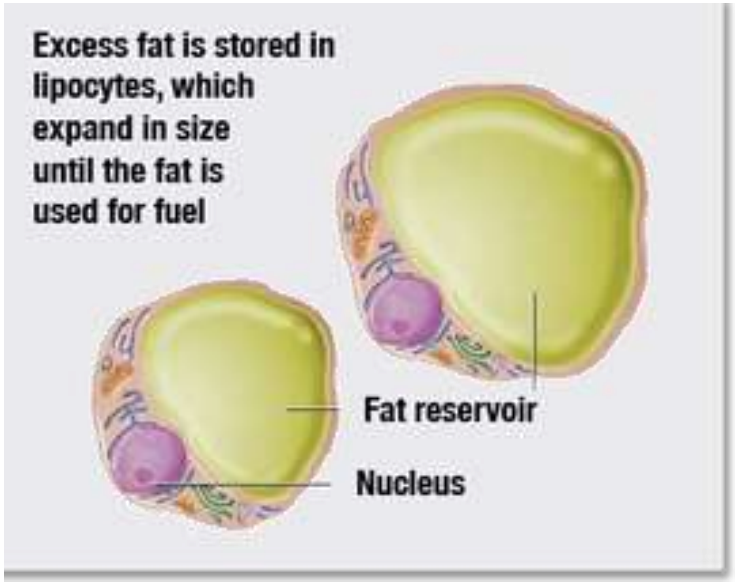
Brown Fat Cell

Brown Fat vs. White Fat



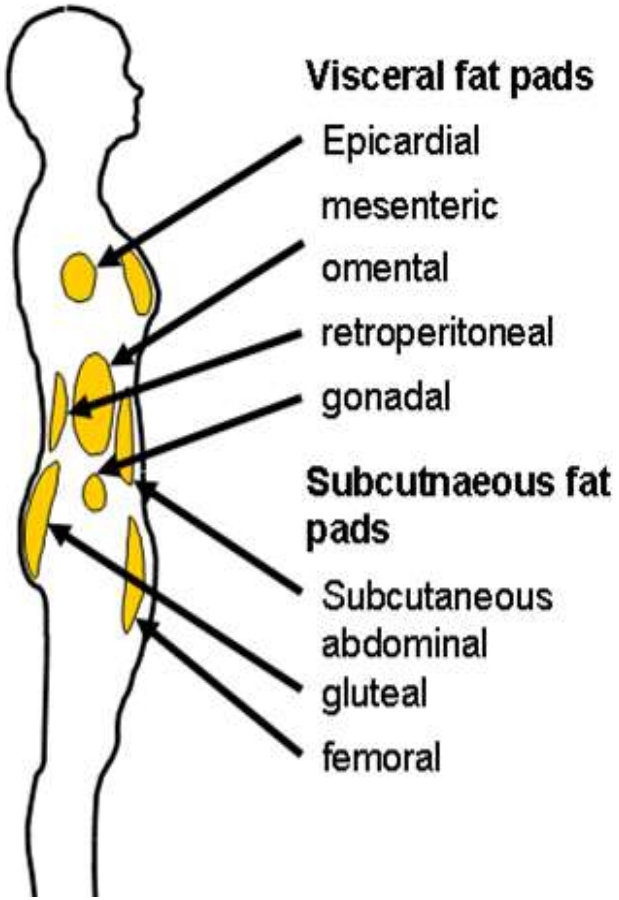
- Triggers Inflammation
- Gives off lots of heat

What is White Fat?



- Single Lipid Droplet
- Largest Energy Reserve in the Body
- Contains small number of Mitochondria

Where is White Fat stored?

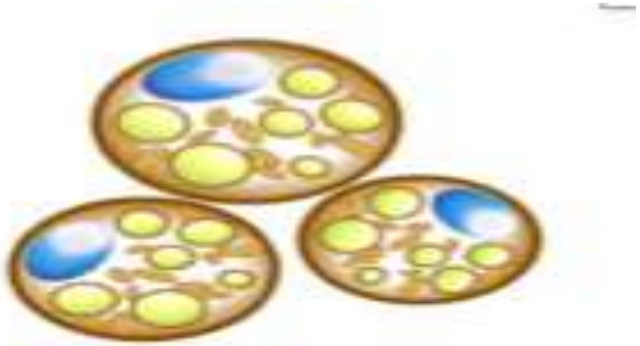


- Visceral Fat Pads
- Subcutaneous Fat Pads

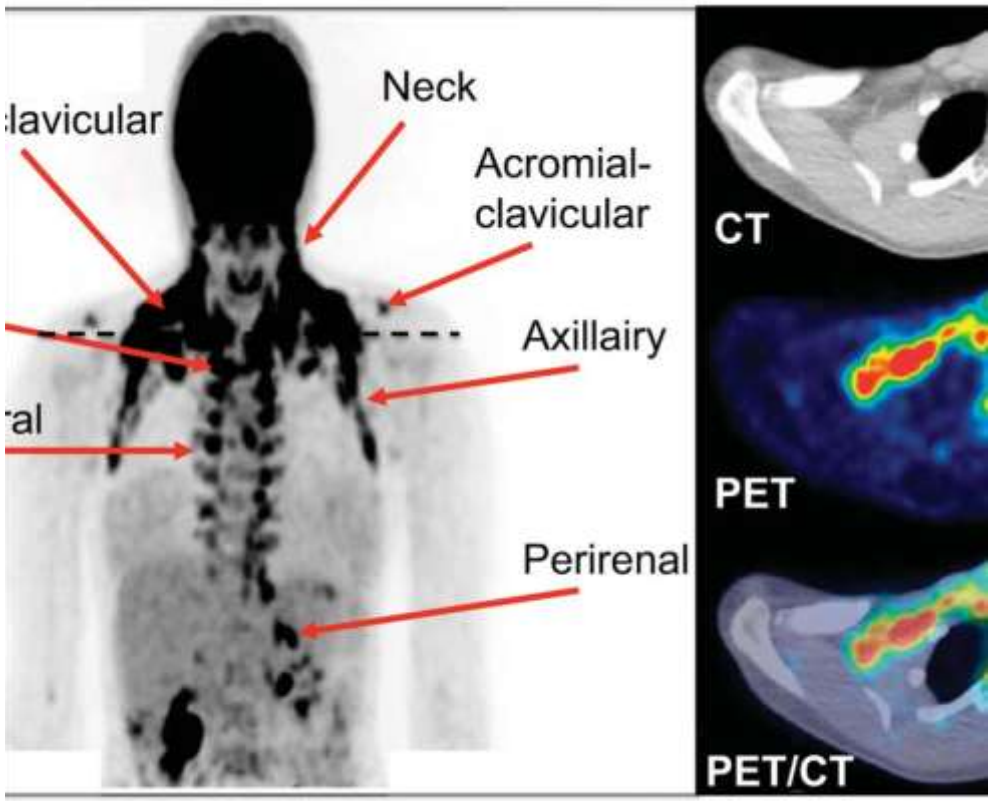
Where is White Fat Stored?

What is Brown Fat?

- Several Small Lipid Droplets
- Burns Calories to Generate Heat
- Contains large number of Mitochondria
- Derived from Muscle Tissue



Where is Brown Fat Stored?

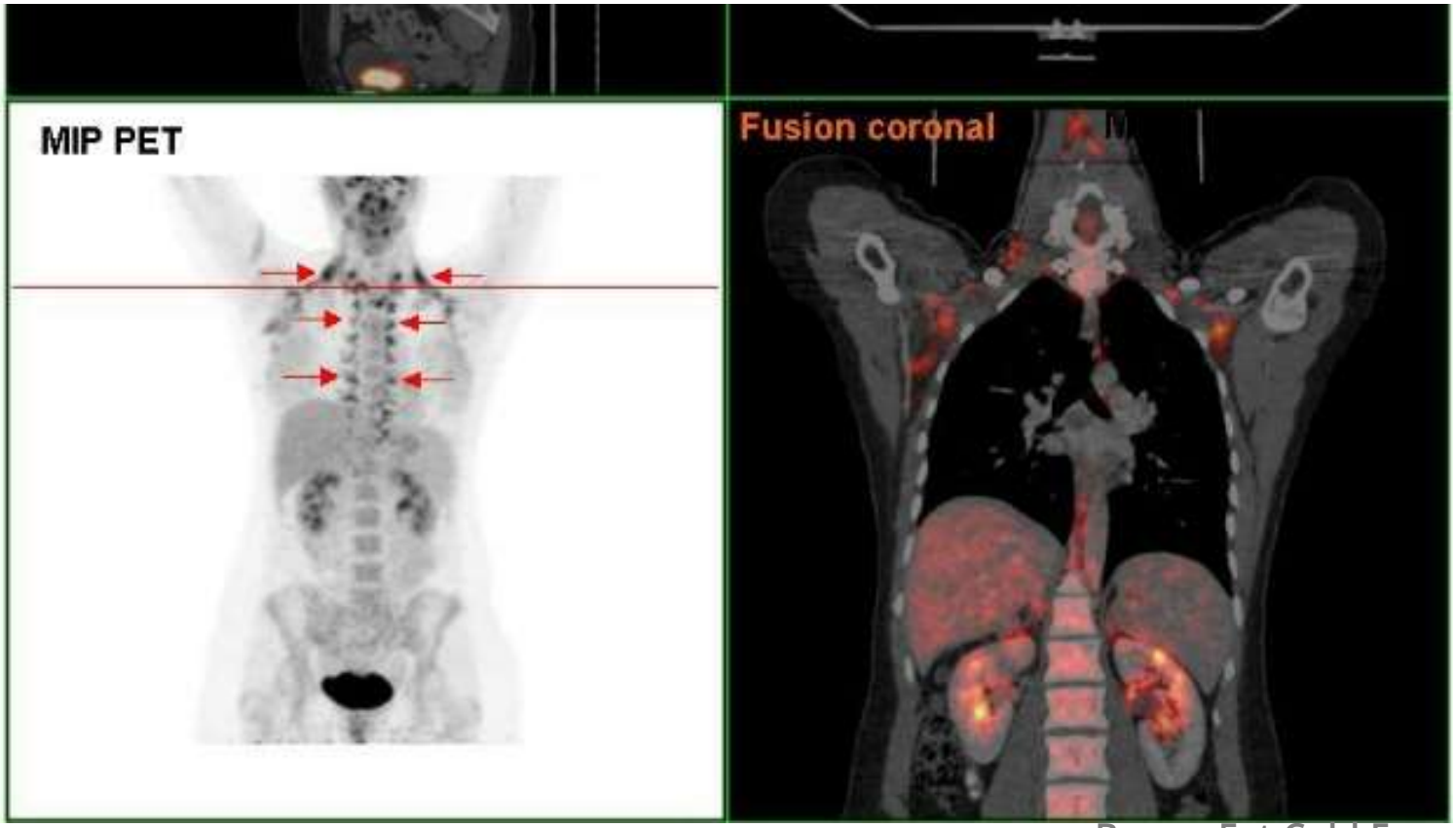


- Neck
- Supraclavicular
- Acromial-Clavicular
- Auxiliary
- Para Aortic
- Paravertebral
- Suprarenal

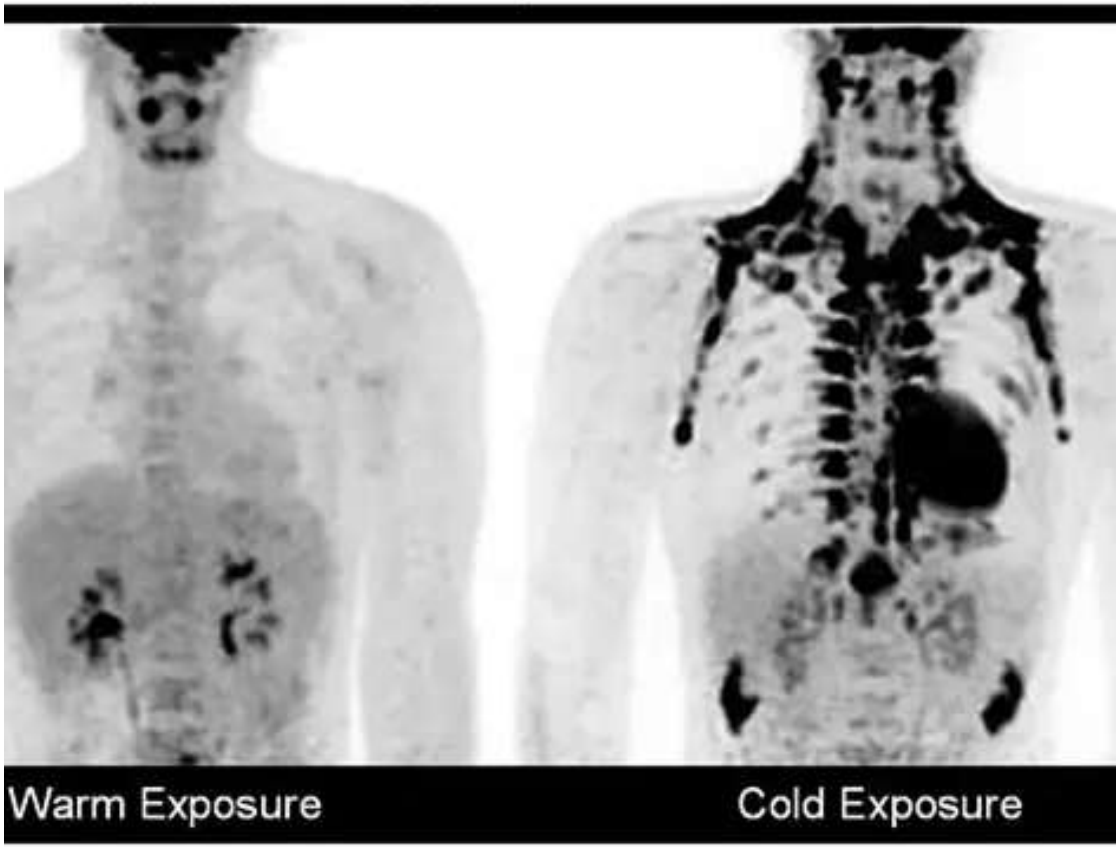
Advantages of Brown Fat

- Creates heats through thermogenesis
- Metabolizes white fat
- Reduces glucose and lipid levels
- Regulates homeostasis-balances metabolism

Brown Fat on PET Scan

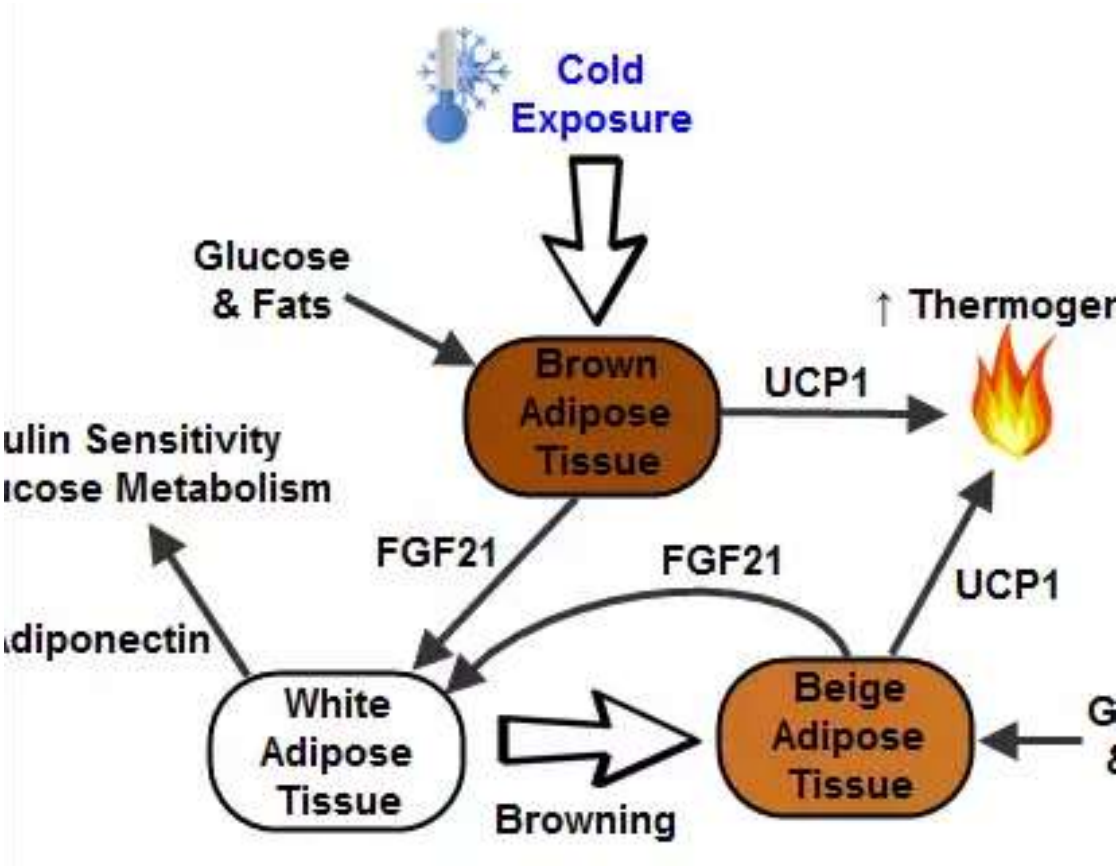


Brown Fat Cold Exposure



Brown Fat And Cold Exposure

- Exposure to cold causes the conversion of white fat to brown fat
- Exposure to cold causes increase brown fat production



Brown Fat And Cold Exposure

- Converts White Fat to Brown Fat
- Increases Thermogenesis resulting in increased heat production
- Increases energy expenditure

Brown Fat And Cold Exposure

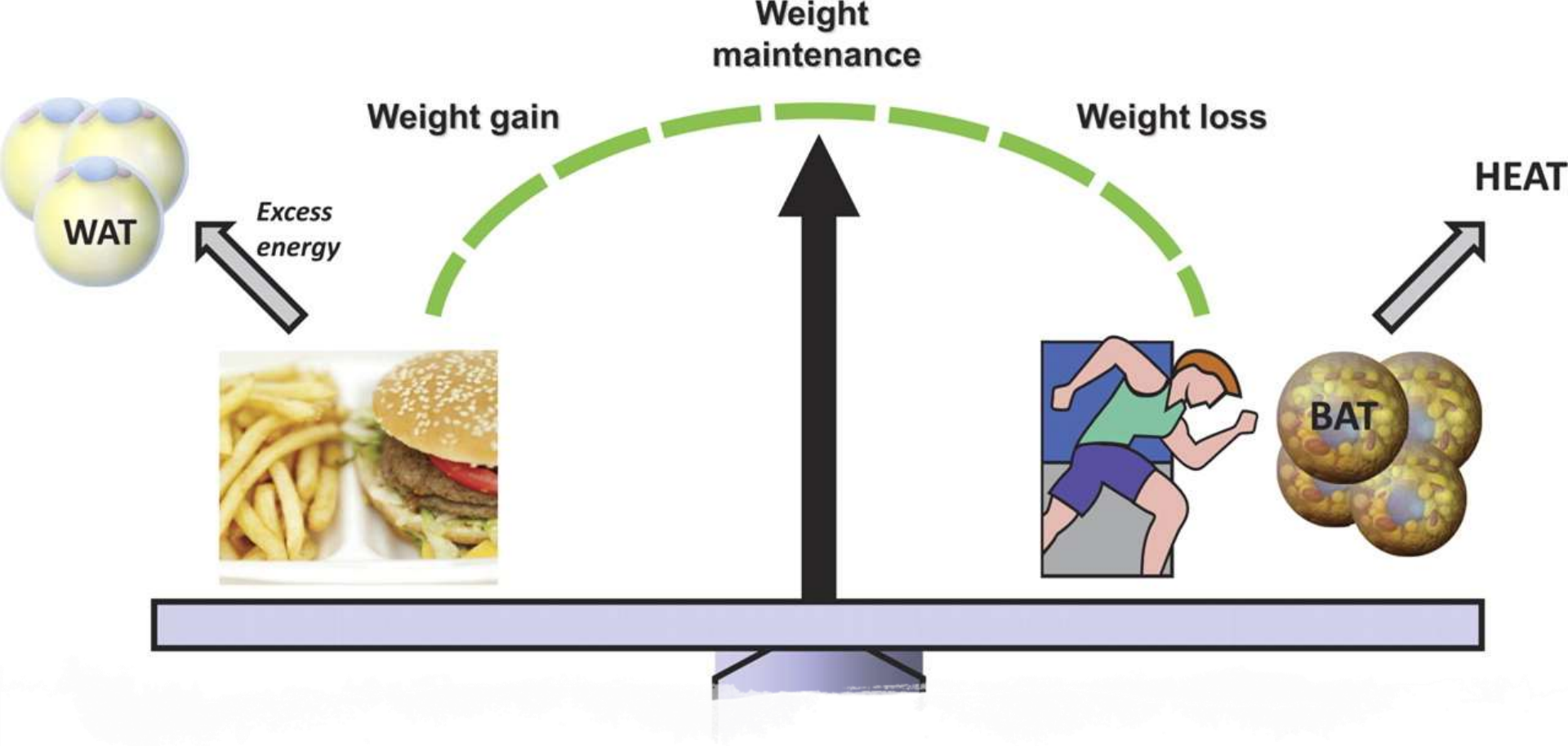
Research article

Cold acclimation recruits human brown fat and increases nonshivering thermogenesis

Anouk A.J.J. van der Lans,[1] Joris Hoeks,[1] Boudewijn Brans,[2] Guy H.E.J. Vijgen,[1,3] Mariëlle G.W. Visser,[2] Maarten J. Vosselman,[1] Jan Hansen,[1] Johanna A. Jörgensen,[1] Jun Wu,[4] Felix M. Mottaghy,[2,5] Patrick Schrauwen,[1] and Wouter D. van Marken Lichtenbelt[1]

[1]Department of Human Biology, NUTRIM School for Nutrition, Toxicology and Metabolism, [2]Department of Nuclear Medicine, and [3]Department of Surgery, Maastricht University Medical Centre+ (MUMC+), Maastricht, Netherlands. [4]Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts, USA. [5]Department of Nuclear Medicine, University Hospital RWTH Aachen, Aachen, Germany.

In recent years, it has been shown that humans have active brown adipose tissue (BAT) depots, raising the question of whether activation and recruitment of BAT can be a target to counterbalance the current obesity pandemic. Here, we show that a 10-day cold acclimation protocol in humans increases BAT activity in parallel with an increase in nonshivering thermogenesis (NST). No sex differences in BAT presence and activity were found either before or after cold acclimation. Respiration measurements in permeabilized fibers and isolated mitochondria revealed no significant contribution of skeletal muscle mitochondrial uncoupling to the increased NST. Based on cell-specific markers and on uncoupling protein-1 (characteristic of both BAT and beige/brite cells), this study did not show "browning" of abdominal subcutaneous white adipose tissue upon cold acclimation. The observed physiological acclimation is in line with the subjective changes in temperature sensation; upon cold acclimation, the subjects judged the environment warmer, felt more comfortable in the cold, and reported less shivering. The combined results suggest that a variable indoor environment with frequent cold exposures might be an acceptable and economic manner to increase energy expenditure and may contribute to counteracting the current obesity epidemic.



Brown Fat Conversion

- Maintain a Cold Environment
- Increase Melatonin Production
- Proper Diet
- Exercise

Brown Fat Conversion

ScienceAlert

Researchers Discover How to Turn Energy-Storing White Fat Into Energy-Burning Brown Fat

And they're figuring out how to get our cells to burn more calories for us.

BEC CREW 5 AUG 2015

For the first time, researchers have discovered a way to convert the white fat cells that sit in unsightly, energy-storing clumps around our bodies into energy-burning brown fat. If they can figure out how to apply this method to medical treatments, obese patients and those with metabolic issues could be given the ability to increase their energy expenditure without having to adjust their exercise routine.

Brown Fat Conversion

Cell Metab. Author manuscript; available in PMC 2013 Mar 7.
Published in final edited form as:
Cell Metab. 2012 Mar 7; 15(3): 395–404.
doi: 10.1016/j.cmet.2012.01.019

PMCID: PMC3410936
NIHMSID: NIHMS355383

PPAR agonists induce a white-to-brown fat conversion through stabilization of PRDM16 protein

Haruya Ohno,[1] Kosaku Shinoda,[1] Bruce M. Spiegelman,[2] and Shingo Kajimura[1]

Author information ► Copyright and License information ►

Increased Mitochondria

Increased Mitochondria

THE PATTERN OF IRON–SULFUR CENTERS IN BROWN ADIPOSE TISSUE MITOCHONDRIA: PREPONDERANCE OF ETF DEHYDROGENASE AND INVARIANCE WITH THE THERMOGENIC STATE

Torgeir FLATMARK*, Frank J. RUZICKA and Helmut BEINERT
Institute for Enzyme Research, University of Wisconsin, Madison, Wisconsin 53706, USA

Received 8 January 1976

1. Introduction

Most of the resonances observed in heart mitochondria by e.p.r. spectroscopy at presently attainable sensitivities have been recently identified (for review, see [1]) including the so-called iron–sulfur (Fe–S) 'center 5' [2], recognized by its low field resonance (g_z = 2.086) in the reduced state of mitochondria from a variety of species and tissues [1]. The assignment of this e.p.r. line was based on the purification of a thus far unknown iron–sulfur (Fe–S) flavoprotein from beef heart mitochondria [3]. Since the purified Fe–S flavoprotein was most readily reduced by fatty acyl-CoA in the presence of acyl-CoA dehydrogenase and electron-transferring flavoprotein (ETF), it was suggested [3] that this Fe–S flavoprotein may function as an electron transfer protein between the fatty acyl-CoA dehydrogenase system [4] and the terminal part of the respiratory chain. In support of this conclusion, we would like to present further experimental

destructive tool for studying aspects of cold-acclimatization related to a change in the rate of mitochondrial biogenesis in this tissue.

2. Methods

2.1. *Animals*

Weaned guinea pigs of an inbred strain from Marvin O'Brien, Rt. 3, Syene Road, Madison, WI were used. Approximately 4 weeks old, the animals were transferred from an environment of 22°C to 5–6°C in which they remained for different lengths of time [6].

2.2. *Isolation of mitochondria*

Brown adipose tissue mitochondria were isolated essentially as described [7,8]. Heart mitochondria were prepared by the nagarse method [9]; the final mitochondrial pellet was washed twice. Protein was determined by the biuret method after precipitation with trichloroacetic acid and dissolution of the pellet in the presence of 2% deoxycholate.

Increased Mitochondria

Biochimica et Biophysica Acta 1817 (2012) 410–418

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbabio

Brown adipose tissue mitochondria oxidizing fatty acids generate high levels of reactive oxygen species irrespective of the uncoupling protein-1 activity state

Peter Schönfeld [a,*], Lech Wojtczak [b]

[a] Institut für Biochemie und Zellbiologie, Medizinische Fakultät, Otto-von-Guericke-Universität Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany
[b] Nencki Institute of Experimental Biology, Pasteura 3, 02-093 Warsaw, Poland

ARTICLE INFO

Article history:
Received 20 September 2011
Received in revised form 9 December 2011
Accepted 18 December 2011
Available online 27 December 2011

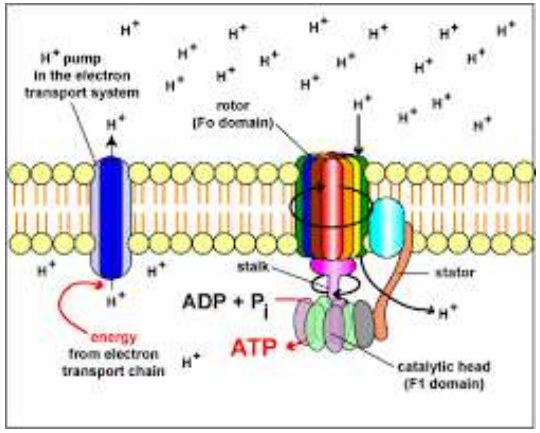
Keywords:
Brown adipose tissue
Mitochondria
Fatty acid oxidation
Reactive oxygen species (ROS)
Reverse electron transfer

ABSTRACT

Mitochondria from brown adipose tissue (BATM) have a high enzymatic capacity for fatty acid oxidation and therefore are an ideal model to examine the sites of reactive oxygen species (ROS) generation during fatty acid oxidation. ROS generation by BATM (isolated from 3-week-old rats) was measured during acylcarnitine oxidation as release of H_2O_2 into the medium and as inactivation of the matrix enzyme aconitase. The following results were obtained: (1) BATM release large amounts of H_2O_2 in the coupled as well as in the uncoupled states, several times more than skeletal muscle mitochondria. (2) H_2O_2 release is especially large with acylcarnitines of medium-chain fatty acids (e.g. octanoylcarnitine). (3) Reverse electron transport does not contribute in a significant extent to the overall ROS generation. (4) Despite the large release of H_2O_2, the ROS-sensitive matrix enzyme aconitase is not inactivated during acylcarnitine oxidation. (5) In contrast to acylcarnitines, oxidation of α-glycerophosphate by BATM is characterized by large H_2O_2 release and a pronounced aconitase inactivation. We hypothesize that acylcarnitine-supported ROS generation in BATM may be mainly associated with acyl-CoA dehydrogenase and electron transferring flavoprotein-ubiquinone reductase rather than with complexes of the respiratory chain.

Increased ATP Energy

Increased ATP Energy



- Brown Fat Mitochondria in the presence of ATP results in an increase of rapid bursts of Energy
- Increased respiration produces increased energy for the cell longevity and function

Increased ATP Energy

European J. Biochem. 11 (1969) 183—192

Oxidative Phosphorylation and Compartmentation of Fatty Acid Metabolism in Brown Fat Mitochondria

K. J. Hittelman, O. Lindberg, and B. Cannon

Wenner-Grens Institut, Kungliga Universitetet i Stockholm

(Received June 6/August 18, 1969)

1. Mitochondria freshly isolated from brown adipose tissue by a standard procedure consistently fail to display normal oxidative phosphorylation. Incubation of these particles with ATP and carnitine in the absence of exogenous substrate results in a rapid burst of respiration which eventually slows to a low resting rate. Oxidation of the endogenous substrate is absolutely dependent upon the presence of both ATP and carnitine and is completely inhibited by rotenone. In the absence of added CoASH, respiration is also inhibited by atractyloside, and this inhibition is completely released by addition of CoASH.

2. After the ATP + carnitine-induced respiration has slowed to a low resting rate, oxidative phosphorylation is observed during the oxidation of added α-ketoglutarate, succinate, or α-glycerophosphate.

3. If the mitochondria are incubated with ATP and carnitine in the presence of rotenone, coupled behavior is also observed upon subsequent oxidation of succinate or α-glycerophosphate.

4. Under appropriate conditions, the time-course of appearance of oxidative phosphorylation corresponds closely to the time-course of appearance of significant levels of acylcarnitine.

5. It is concluded that the endogenous substrate of brown fat mitochondria is free fatty acids which lie initially outside the acyl-CoA barrier, and that these are responsible for the uncoupled behavior of the freshly isolated particles. By providing the mitochondria with the appropriate components for activation and transport of free fatty acids, the redistribution which occurs relieves the uncoupling and hence both oxidative phosphorylation and classical sensitivities to inhibitors become evident.

6. The significance of the fatty acid transport mechanism in these mitochondria is discussed with respect to a possible role in regulating the degree of uncoupling which may occur during active thermogenesis by brown adipose tissue.

Uncoupling Protein 1 (UCP1)

Uncoupling Protein 1 (UCP1)

The role of the uncoupling protein 1 (UCP1) on the development of obesity and type 2 *diabetes mellitus*

Papel da proteína desacopladora 1 (UCP1) no desenvolvimento da obesidade e do diabetes melito tipo 2

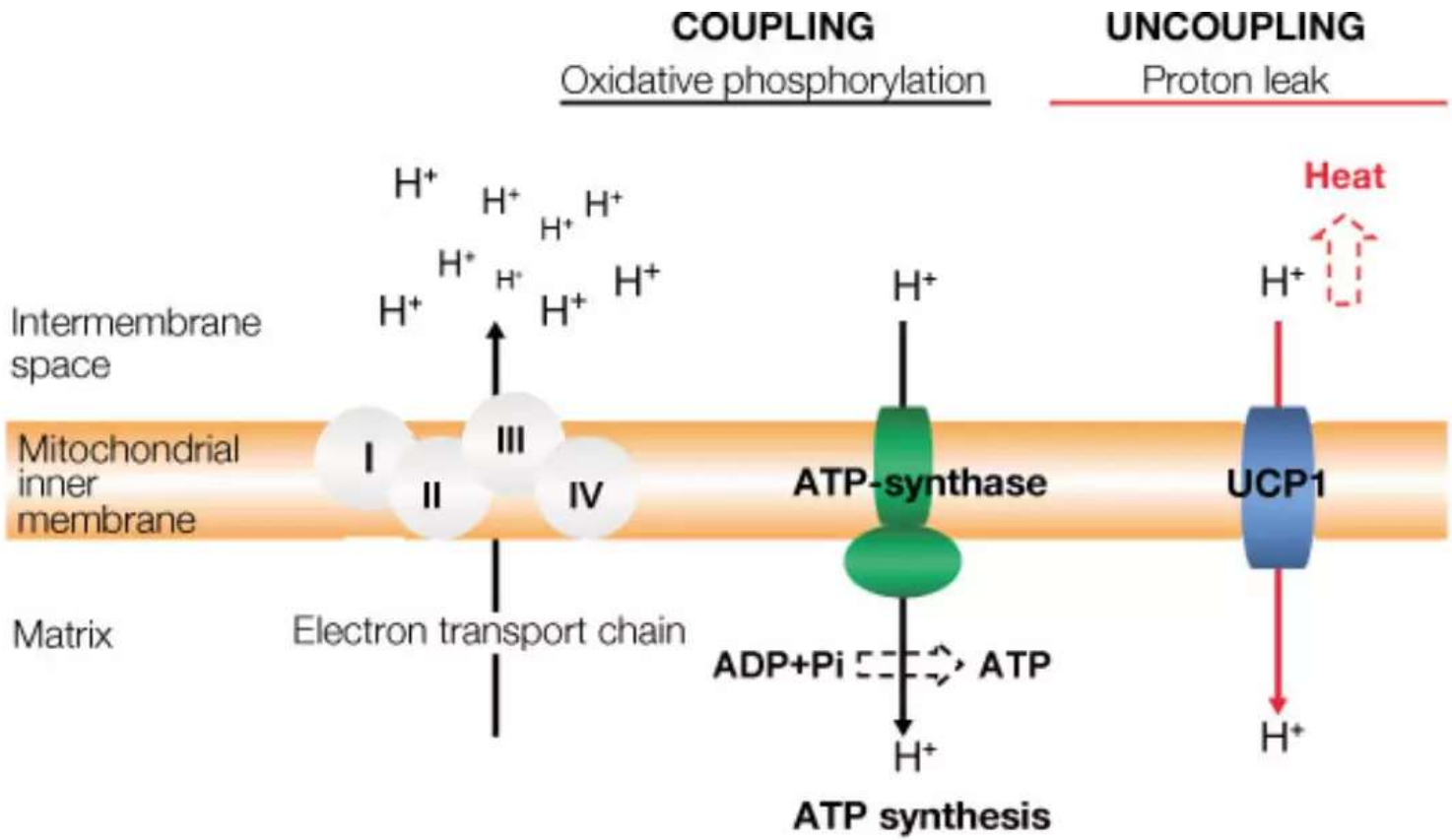
Letícia de Almeida Brondani[1], Taís Silveira Assmann[1], Guilherme Coutinho Kullmann Duarte[1], Jorge Luiz Gross[1], Luís Henrique Canani[1], Daisy Crispim[1]

SUMMARY

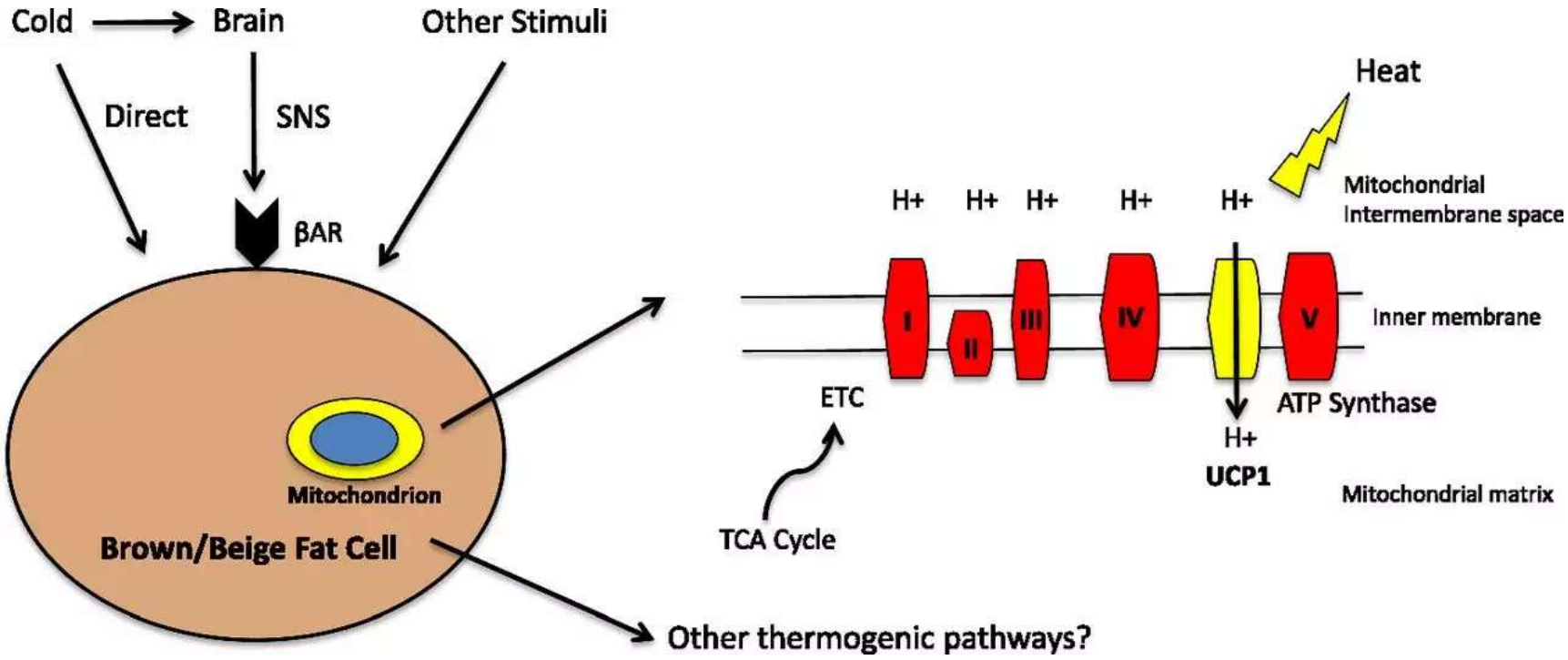
It is well established that genetic factors play an important role in the development of both type 2 *diabetes mellitus* (DM2) and obesity, and that genetically susceptible subjects can develop these metabolic diseases after being exposed to environmental risk factors. Therefore, great efforts have been made to identify genes associated with DM2 and/or obesity. Uncoupling protein 1 (UCP1) is mainly expressed in brown adipose tissue, and acts in thermogenesis, regulation of energy expenditure, and protection against oxidative stress. All these mechanisms are associated with the pathogenesis of DM2 and obesity. Hence, *UCP1* is a candidate gene for the development of these disorders. Indeed, several studies have reported that polymorphisms -3826A/G, -1766A/G and -112A/C in the promoter region, Ala64Thr in exon 2 and Met299Leu in exon 5 of *UCP1* gene are possibly associated with obesity and/or DM2. However, results are still controversial in different populations. Thus, the aim of this study was to review the role of UCP1 in the development of these metabolic diseases. Arq Bras Endocrinol Metab. 2012;56(4):215-25

[1] Endocrinology Division, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul (HC-UFRGS), Porto Alegre, RS, Brazil

Uncoupling Protein 1 (UCP1)



Uncoupling Protein 1 (UCP1)



Thermogenesis

Heat Production

- Basal Metabolism
- Muscular Activing (Shivering)
- Thyroxine and epinephrine (effects on metabolic rate)
- Temperature effect on cells

Heat Loss

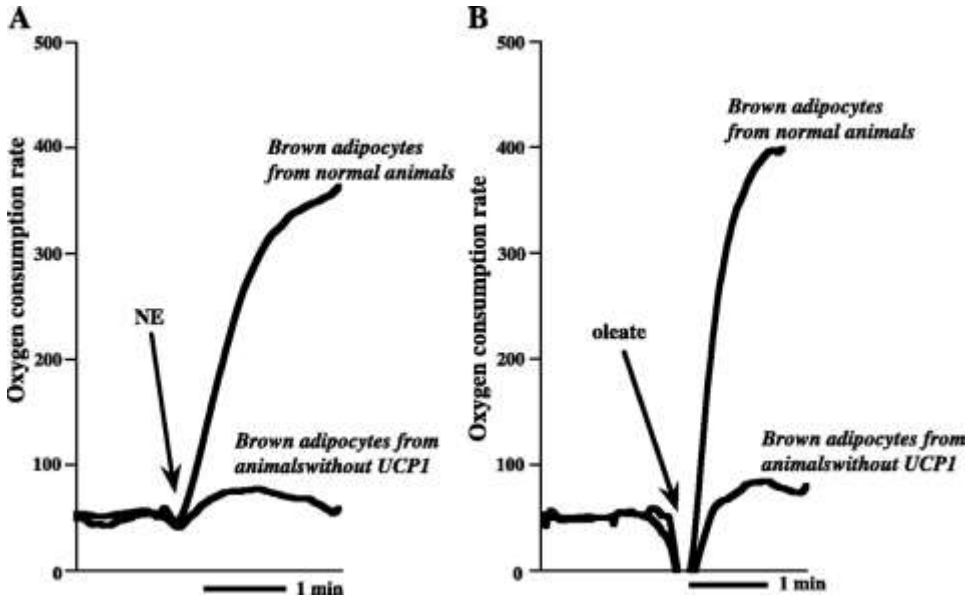
Radiation

Conduction/ Convection

Evaporation

Thermogenesis

• (*A*) or fatty acid (*B*) addition with a nearly 10-fold increase in the rate of oxygen consumption (thermogenesis) is fully dependent on the presence of UCP1

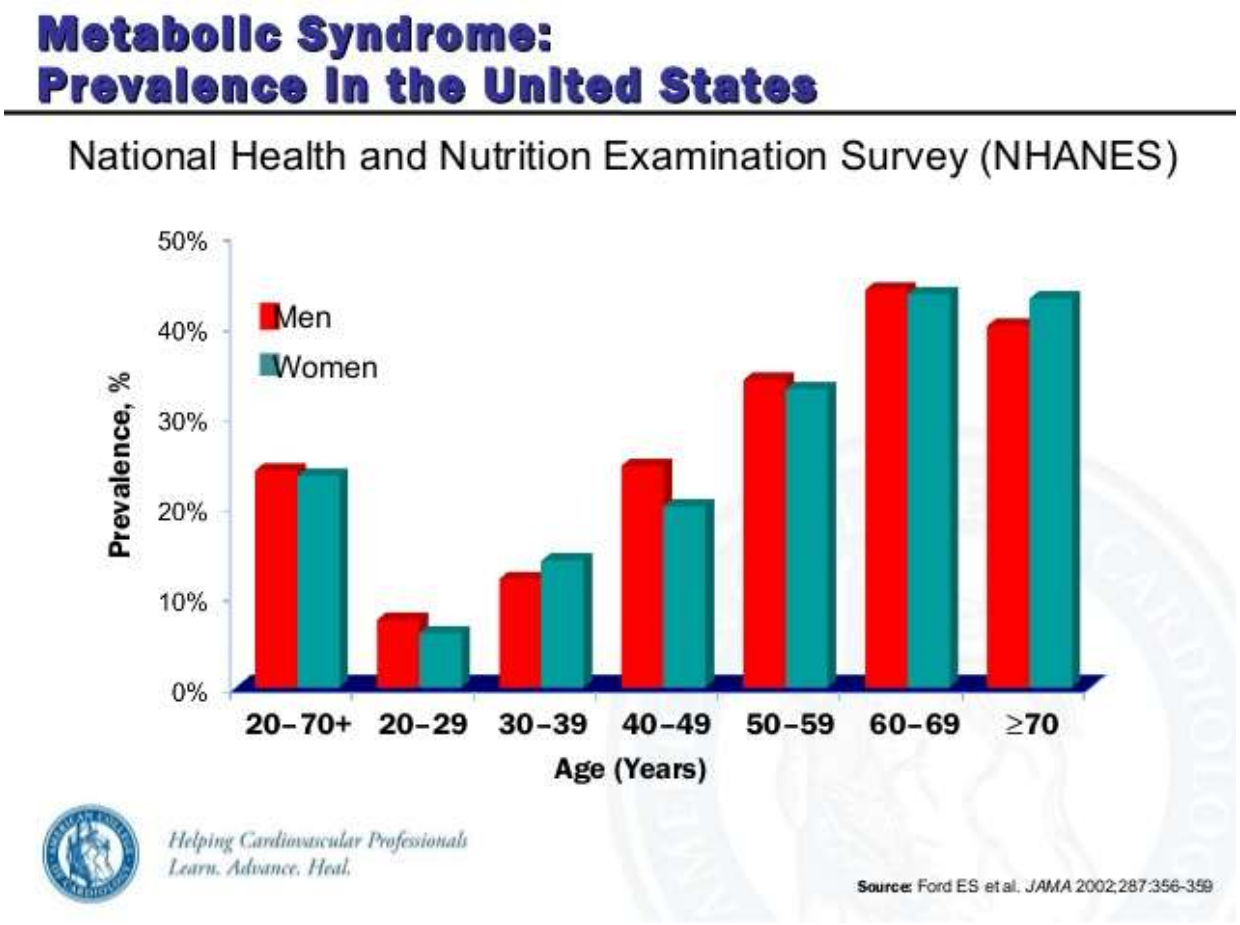


Metabolic Diseases

- **Diabetes Type 2**
- **Heart Disease**
- **Obesity**

Metabolic Diseases : Data USA

Metabolic Disease : Data USA



Metabolic Disease

New Powers of Brown Fat: Fighting the Metabolic Syndrome

Jan Nedergaard,[1,*] Tore Bengtsson,[1] and Barbara Cannon[1]
[1]The Wenner-Gren Institute, Stockholm University, Stockholm 106 91, Sweden
*Correspondence: jan@metabol.su.se
DOI 10.1016/j.cmet.2011.02.009

An understanding of the full powers of brown adipose tissue (BAT) is only successively being accumulated. In a paper in *Nature Medicine*, Bartelt et al. (2011) add further impressive aspects to the potential powers of BAT in the combat against the metabolic syndrome by demonstrating its vast capacity for triglyceride clearance and glucose disposal.

Until very recently, brown adipose tissue (BAT) seemed to attract interest from only a few hibernation researchers and mitochondrial bioenergeticists. This was understandable. BAT is not easily discernable: It has a color and texture that blends into both fat and muscle, and it is found in small depots spread out in different parts of the body, totally amounting to only a small percentage of total body weight (Figure 1A). Yet this organ has the power to be a main player in metabolism. In their recent study in *Nature Medicine*, Bartelt

further energy supplies must come from outside the tissue.

The study of Bartelt et al. (2011) reveals the ability of BAT to import and combust triglycerides from the circulation and demonstrates how this uptake delivers substrate for continued thermogenesis. By exposing mice to cold, Bartelt et al. optimized the acute activity of BAT, and this had dramatic effects on triglyceride levels in the blood. Specifically, plasma triglycerides (mainly in the form of chylomicrons, i.e., the dietary fat) practically

free fatty acids from triglyceride droplets within the brown fat cell, it also induces VEGF (Fredriksson et al., 2005) and lipoprotein lipase (LPL) gene expression (Mitchell et al., 1992; Bartelt et al., 2011). VEGF leads to increased capillary permeability, allowing plasma triglycerides to leave the capillaries (as elegantly video-recorded in vivo by Bartelt et al.). LPL degrades the triglycerides and allows fatty acids to become available for combustion in the tissue through the action of the plasma membrane trans-

Metabolic Disease

NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Format: Abstract

Send to

Stem Cells. 2014 Feb;32(2):572-81. doi: 10.1002/stem.1595.

Metabolically active human brown adipose tissue derived stem cells.

Silva FJ[1], Holt DJ, Vargas V, Yockman J, Boudina S, Atkinson D, Grainger DW, Revelo MP, Sherman W, Bull DA, Patel AN.

Author information

Abstract

Brown adipose tissue (BAT) plays a key role in the evolutionarily conserved mechanisms underlying energy homeostasis in mammals. It is characterized by fat vacuoles 5-10 μm in diameter and expression of uncoupling protein one, central to the regulation of thermogenesis. In the human newborn, BAT depots are typically grouped around the vasculature and solid organs. These depots maintain body temperature during cold exposure by warming the blood before its distribution to the periphery. They also ensure an optimal temperature for biochemical reactions within solid organs. BAT had been thought to involute throughout childhood and adolescence. Recent studies, however, have confirmed the presence of active BAT in adult humans with depots residing in cervical, supraclavicular, mediastinal, paravertebral, and suprarenal regions. While human pluripotent stem cells have been differentiated into functional brown adipocytes in vitro and brown adipocyte progenitor cells have been identified in murine skeletal muscle and white adipose tissue, multipotent metabolically active BAT-derived stem cells from a single depot have not been identified in adult humans to date. Here, we demonstrate a clonogenic population of metabolically active BAT stem cells residing in adult humans that can: (a) be expanded in vitro; (b) exhibit multilineage differentiation potential; and (c) functionally differentiate into metabolically active brown adipocytes. Our study defines a new target stem cell population that can be activated to restore energy homeostasis in vivo for the treatment of obesity and related metabolic disorders.

Diabetes Data : USA

Diagnosed and undiagnosed diabetes among people aged 20 years or older, United States, 2012

	Number with diabetes (millions)	Percentage with diabetes (unadjusted)
Total		
20 years or older	28.9	12.3
By age		
20–44	4.3	4.1
45–64	13.4	16.2
65 years or older	11.2	25.9
By sex		
Men	15.5	13.6
Women	13.4	11.2

Source: 2009–2012 National Health and Nutrition Examination Survey estimates applied to 2012 U.S. Census data.

Diabetes

Published in final edited form as:
Curr Opin Endocrinol Diabetes Obes. 2010 April ; 17(2): 143–149. doi:10.1097/MED.0b013e328337a81f.

Brown fat as a therapy for obesity and diabetes

Aaron M. Cypess and **C. Ronald Kahn**
Joslin Diabetes Center, Harvard Medical School, One Joslin Place, Boston, Massachusetts, 02215, USA

Abstract

Purpose of review—Human fat consists of white and brown adipose tissue (WAT and BAT). Though most fat is energy-storing WAT, the thermogenic capacity of even small amounts of BAT makes it an attractive therapeutic target for inducing weight loss through energy expenditure. This review evaluates the recent discoveries regarding the identification of functional BAT in adult humans and its potential as a therapy for obesity and diabetes.

Diabetes

ORIGINAL ARTICLE

Reversal of Type 1 Diabetes in Mice by Brown Adipose Tissue Transplant

Subhadra C. Gunawardana and David W. Piston

Current therapies for type 1 diabetes (T1D) involve insulin replacement or transplantation of insulin-secreting tissue, both of which suffer from numerous limitations and complications. Here, we show that subcutaneous transplants of embryonic brown adipose tissue (BAT) can correct T1D in streptozotocin-treated mice (both immune competent and immune deficient) with severely impaired glucose tolerance and significant loss of adipose tissue. BAT transplants result in euglycemia, normalized glucose tolerance, reduced tissue inflammation, and reversal of clinical diabetes markers such as polyuria, polydipsia, and polyphagia. These effects are independent of insulin but correlate with recovery of the animals' white adipose tissue. BAT transplants lead to significant increases in adiponectin and leptin, but with levels that are static and not responsive to glucose. Pharmacological blockade of the insulin receptor in BAT transplant mice leads to impaired glucose tolerance, similar to what is seen in nondiabetic animals, indicating that insulin receptor activity plays a role in the reversal of diabetes. One possible candidate for activating the insulin receptor is IGF-1, whose levels are also significantly elevated in BAT transplant mice. Thus, we propose that the combined action of multiple adipokines establishes a new equilibrium in the animal that allows for chronic glycemic control without insulin.
Diabetes 61:674–682, 2012

Type 1 diabetes (T1D) involves autoimmune-mediated destruction of β-cells, which leads to an absolute deficiency of insulin and loss of glycemic control. The ultimate cure for T1D would require permanent renormalization of blood glucose homeostasis. Although insulin is believed to be the major regulator of blood glucose levels, numerous other hormones are also involved (1). In particular, adipose tissue is a versatile endocrine organ secreting a variety of adipokines with both hyperglycemic and hypoglycemic properties (1–3). Two adipokines, adiponectin and leptin, have recently been reported to ameliorate diabetes phenotypes in the absence of exogenous insulin (4–7), indicating that specific adipokines may be able to compensate for a loss of insulin.

In addition to the destruction of pancreatic β-cells, T1D is associated with a loss of adipose tissue. Successful treatment of T1D results in spontaneous recovery of adipose tissue along with the restoration of normal glucose levels and dynamics (8–10). However, a two-way relationship between adipose tissue and blood glucose homeostasis has not yet been documented. Previous data following streptozotocin (STZ)-diabetic mice (a model of T1D) treated by embryonic pancreatic tissue transplants suggest that healthy adipose tissue contributes to the correction of T1D, even when insulin levels are low (11). In some immune-deficient nude mice (NCRNU; Taconic), we observed return to euglycemia and reversal of clinical signs of diabetes despite a lack of any measurable increase in plasma insulin. These animals exhibited a robust recovery of body weight and adipose tissue, as well as a simultaneous increase in plasma adiponectin and visfatin (11,12). Thus, we hypothesized that adipose tissue can compensate for a lack of insulin. Our previous subcutaneous transplants were performed using embryonic pancreatic buds with their surrounding tissue, resulting in remarkable replenishment of recipients' subcutaneous white adipose tissue (WAT) (11,12). To delineate the contributions from different tissue types, we transplanted a panel of embryonic tissues subcutaneously into STZ-treated mice. Pancreatic bud transplants correct T1D as expected. Surprisingly, subcutaneous transplantation of embryonic brown adipose tissue (BAT) into immune-competent C57BL6J T1D recipients results in marked improvement of glucose homeostasis and reversal of diabetes, accompanied by robust regeneration of the recipients' subcutaneous WAT. None of the other transplanted tissue types produce similar results. The positive changes after the BAT transplant do not require exogenous insulin or immunosuppression, which indicates that healthy adipose tissue is sufficient to maintain glucose homeostasis in the absence of insulin.

RESEARCH DESIGN AND METHODS

Embryonic BAT was transplanted in the subcutaneous space of STZ-diabetic recipients. Recipient mice included C57BL6J and NCRNU-M-M nude mice. Donor adipose tissue came from E16–E17 C57BL6J embryos. Weight was recorded and basal-fed blood samples were collected at regular intervals from mice that received BAT transplants as well as normal nondiabetic control mice and untreated diabetic control mice. Intraperitoneal glucose tolerance tests (IPGTTs) were performed before BAT transplants and at monthly intervals after BAT transplants. Metabolic parameters such as blood glucose, insulin response to glucose and arginine, and plasma levels of adipose cue, leptin, glucagon, and IGF-1 were measured from transplant and control groups at regular intervals. Three months after BAT transplant, mice were subjected to an additional glucose tolerance test in the presence of S961, an inhibitor of insulin receptor. One insulin tolerance test was also performed between 2 and 3 months posttransplant. BAT transplant mice were killed at different time points after 3 months and tissues were collected. Pancreata were tested for insulin content by immunohistochemistry and radioimmunoassay, and adipose tissue at and around the transplant site was examined for uncoupling protein-1 (UCP-1), IGF-1, and signs of inflammation by immunohistochemistry.

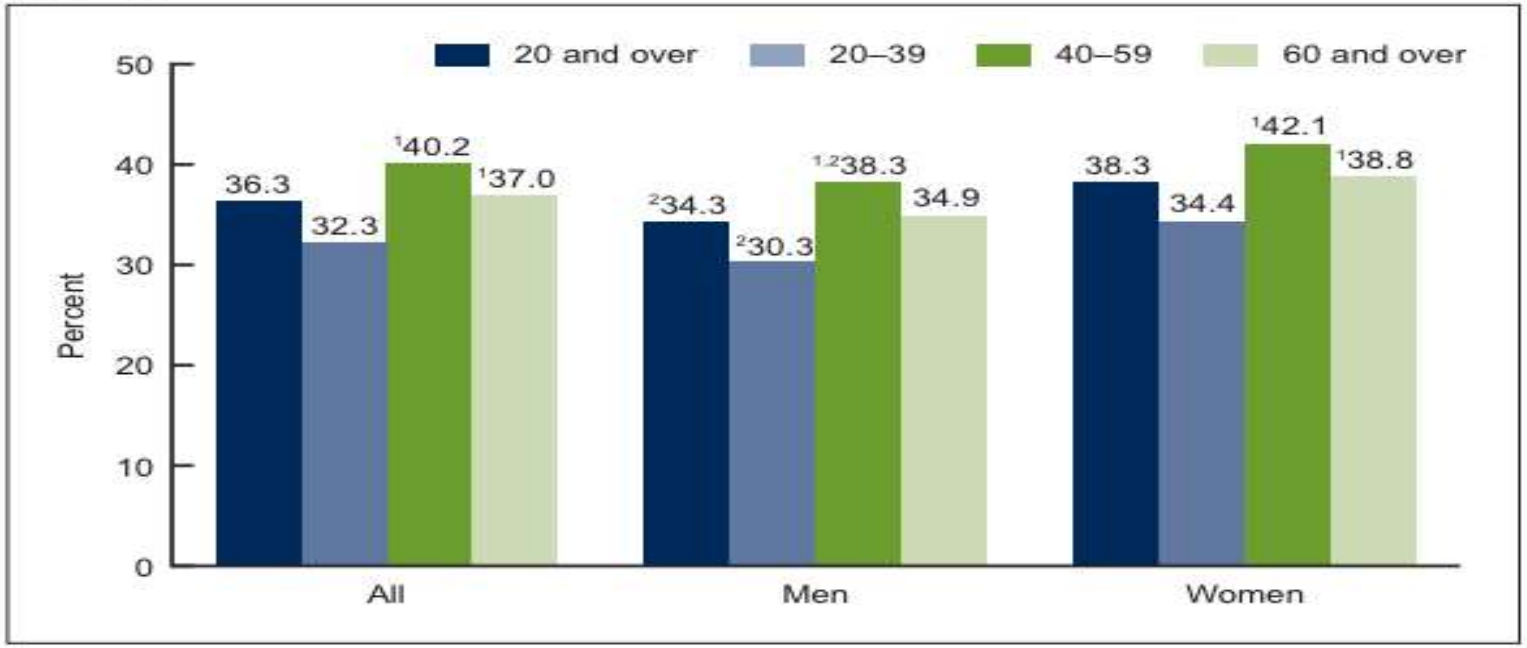
Animals. Recipients were immune-deficient NCRNU-M-M nude mice (Taconic) and immune-competent C57BL6J mice (Jackson Laboratories) rendered diabetic with STZ (125 mg/kg, dissolved in ice-cold Na$^+$ citrate buffer at pH 4.5, injected intraperitoneally, and repeated biweekly until diabetes induced). All recipients were 3–6 months of age at the time of transplants. Donor embryonic BAT was obtained from C57BL6J embryos at gestational age E16.5–E17.5. Parents were purchased from Jackson Laboratories and maintained in the Vanderbilt animal care facility. Animals were fed standard laboratory chow and

From the Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, Tennessee.
Corresponding author: Subhadra C. Gunawardana, subhadra.gunawardana@vanderbilt.edu.
Received 15 April 2011 and accepted 15 December 2011.
DOI: 10.2337/db11-0510
This article contains Supplementary Data online at http://diabetes.diabetesjournals.org/lookup/suppl/doi:10.2337/db11-0510/-/DC1.

Obesity : Data USA

Obesity : Data USA

Figure 1. Prevalence of obesity among adults aged 20 and over, by sex and age: United States, 2011–2014



[1]Significantly different from those aged 20–39.
[2]Significantly different from women of the same age group.
NOTES: Totals were age-adjusted by the direct method to the 2000 U.S. census population using the age groups 20–39, 40–59, and 60 and over. Crude estimates are 36.5% for all, 34.5% for men, and 38.5% for women.
SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2011–2014.

NCHS Data Brief ■ No. 219 ■ November 2015

Obesity


ENDOCRINE ADIPOCYTE
TNF-α
IL-6
MCP-1
PAI-1
Adipisn
Adiponectin
Resistin
Angiotensin
Leptin


TYPE 2 DIABETES
HYPERTENSION
DYSLIPIDEMIA
LIVER DISEASE
OBESITY
CANCER RISK
REPRODUCTIVE DISORDERS
MOOD DISORDERS
HEART DISEASE

Obesity

Blood Sugar and Heart Disease

Blood Sugar and Heart Disease

Harvard Health Publications
HARVARD MEDICAL SCHOOL
Trusted advice for a healthier life

HEART HEALTH | MIND & MOOD | PAIN | STAYING HEALTHY | CANCER

Home » Harvard Health Blog » Tight blood sugar control in type 2 diabetes linked to fewer heart attacks and strokes - Harvard Health Blog

Tight blood sugar control in type 2 diabetes linked to fewer heart attacks and strokes

POSTED JUNE 04, 2015, 2:40 PM
Urmila Parlikar, Senior Content Editor, Harvard Health Publications

Diabetes damages every part of the body, from the brain to the feet. High blood sugar, the hallmark of diabetes, wreaks havoc on blood vessels. It makes sense that keeping blood sugar under control should prevent diabetes-related damage — but how low to push blood sugar is an open question.

A study published in today's issue of *The New England Journal of Medicine* (NEJM) provides reassuring evidence that so-called tight blood sugar control is good for the heart and circulatory system.

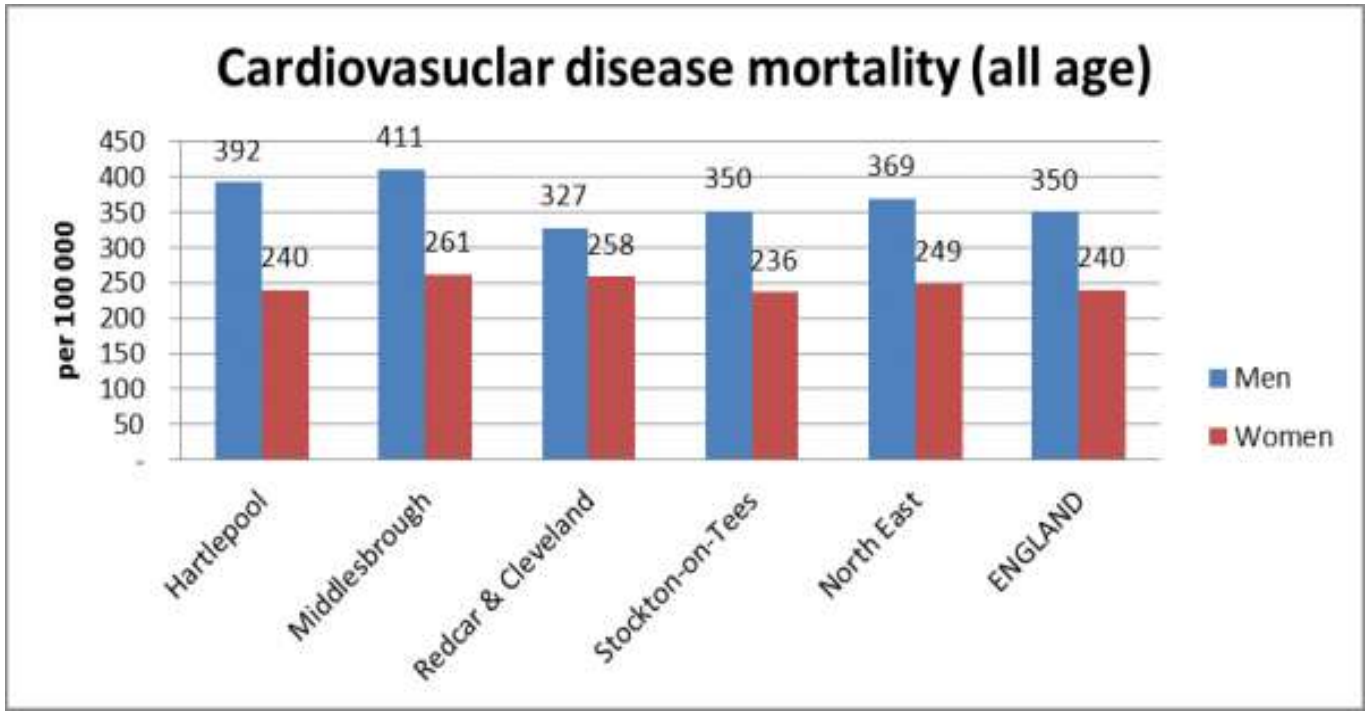
"Tight blood sugar control represents a new age of diabetes care," says Dr. David Nathan, professor of medicine at Harvard Medical School and director of both the General Clinical Research Center and the Diabetes Center at Massachusetts General Hospital.

The hazards of high blood sugar

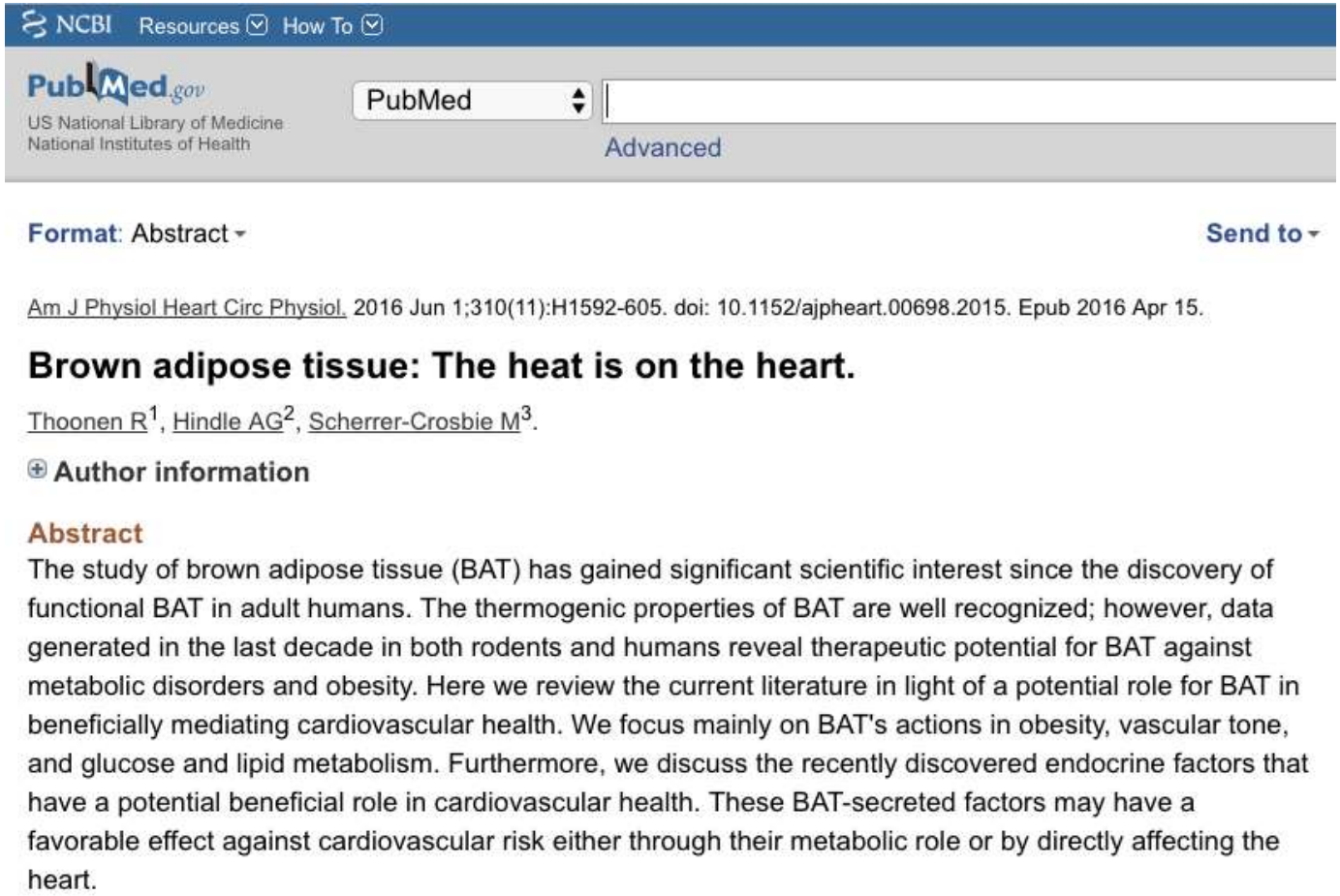
Heart Disease : Data USA

Heart Disease : Data USA

- Number of adults with diagnosed heart disease: 28.4 million
- Percent of adults with diagnosed heart disease: 11.7%



Heart Disease



NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Format: Abstract

Send to

Am J Physiol Heart Circ Physiol. 2016 Jun 1;310(11):H1592-605. doi: 10.1152/ajpheart.00698.2015. Epub 2016 Apr 15.

Brown adipose tissue: The heat is on the heart.

Thoonen R[1], Hindle AG[2], Scherrer-Crosbie M[3].

Author information

Abstract

The study of brown adipose tissue (BAT) has gained significant scientific interest since the discovery of functional BAT in adult humans. The thermogenic properties of BAT are well recognized; however, data generated in the last decade in both rodents and humans reveal therapeutic potential for BAT against metabolic disorders and obesity. Here we review the current literature in light of a potential role for BAT in beneficially mediating cardiovascular health. We focus mainly on BAT's actions in obesity, vascular tone, and glucose and lipid metabolism. Furthermore, we discuss the recently discovered endocrine factors that have a potential beneficial role in cardiovascular health. These BAT-secreted factors may have a favorable effect against cardiovascular risk either through their metabolic role or by directly affecting the heart.

Heart Disease

Activated brown fat reduces cardiovascular disease

André Frankhuizen

Activated brown fat protects from atherosclerosis, which reduces the risk of cardiovascular disease. This was revealed by a recent study published in the online medical journal *Nature Communications*. What is brown fat and how do you activate it?

In 2009 it was discovered that not only babies, but adults too, have brown adipose tissue. Since then, research has gained momentum. Stimulation of brown adipose tissue has been found to be a promising therapeutic strategy for obesity and metabolic syndrome. This has been evidenced by animal research and the effect has also been found in humans. Researchers at the Leiden University Medical Centre have now

Heart Disease

Newly Identified Brown Fat Stem Cells Hold Possibilities for Treating Diabetes

Posted on:29 Dec 2013

Obesity and diabetes have become a global epidemic leading to severe cardiovascular disease. Researchers at the University of Utah believe their recent identification of brown fat stem cells in adult humans may lead to new treatments for heart and endocrine disorders, according to a new studypublished in the peer-reviewed journal *Stem Cells*.

The study was led by Amit N. Patel, MD, MS, director of Clinical Regenerative Medicine and Tissue Engineering and associate professor in the Division of Cardiothoracic Surgery at the University of Utah School of Medicine.

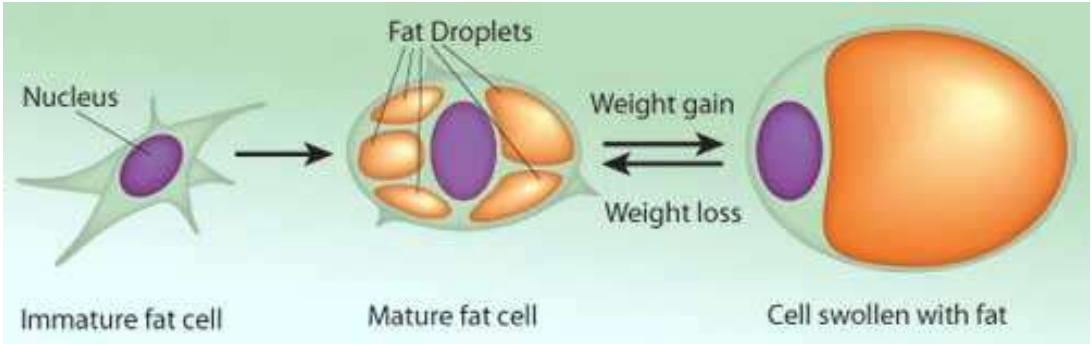
Prior to Patel's study, it was thought that brown fat stem cells did not exist in adults. Children have large amounts of brown fat that is highly metabolically active, which allows them to eat large amounts of food and not gain weight. Patel notes, adults generally have an abundance of white fat in their bodies, which leads to weight gain and cardiovascular disease but this is not seen in brown fat. As people age the amount of white fat increases and brown fat decreases which contributes to diabetes and high cholesterol.

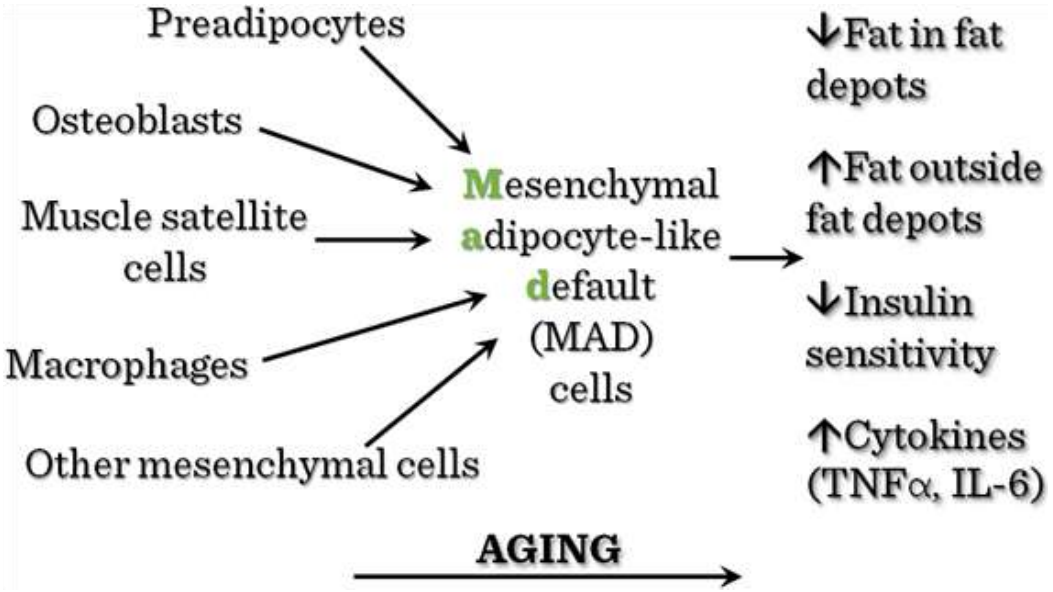
Anti Aging Effects

Brown Fat increases the amount of energy given to cells

Anti Aging Effects

- Brown Fat decreases as age increases
- As Brown Fat decreases thermoregulation is altered
- Decreases in thermoregulation results in altered cellular function

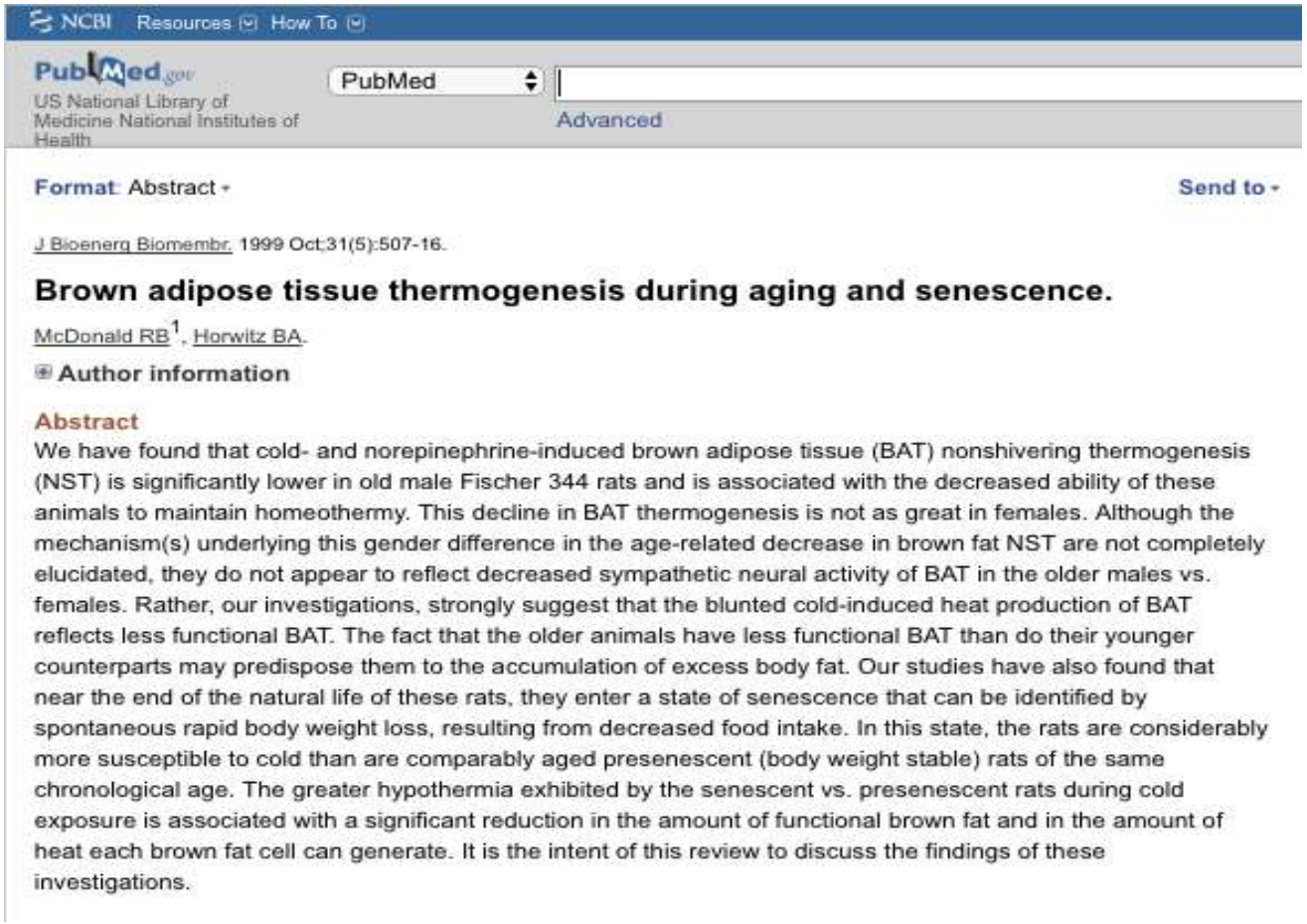




Anti Aging Effects

- Insulin sensitivity increases as Brown Fat decreases
- Cytokine release increase as Brown Fat decreases
- Inflammation levels increase as Brown Fat decreases

Anti Aging Effects



NCBI Resources How To

PubMed.gov
US National Library of Medicine National Institutes of Health

PubMed

Advanced

Format: Abstract

Send to

J Bioenerg Biomembr. 1999 Oct;31(5):507-16.

Brown adipose tissue thermogenesis during aging and senescence.

McDonald RB[1], Horwitz BA.

Author information

Abstract

We have found that cold- and norepinephrine-induced brown adipose tissue (BAT) nonshivering thermogenesis (NST) is significantly lower in old male Fischer 344 rats and is associated with the decreased ability of these animals to maintain homeothermy. This decline in BAT thermogenesis is not as great in females. Although the mechanism(s) underlying this gender difference in the age-related decrease in brown fat NST are not completely elucidated, they do not appear to reflect decreased sympathetic neural activity of BAT in the older males vs. females. Rather, our investigations, strongly suggest that the blunted cold-induced heat production of BAT reflects less functional BAT. The fact that the older animals have less functional BAT than do their younger counterparts may predispose them to the accumulation of excess body fat. Our studies have also found that near the end of the natural life of these rats, they enter a state of senescence that can be identified by spontaneous rapid body weight loss, resulting from decreased food intake. In this state, the rats are considerably more susceptible to cold than are comparably aged presenescent (body weight stable) rats of the same chronological age. The greater hypothermia exhibited by the senescent vs. presenescent rats during cold exposure is associated with a significant reduction in the amount of functional brown fat and in the amount of heat each brown fat cell can generate. It is the intent of this review to discuss the findings of these investigations.

Ageing Res Rev. Author manuscript; available in PMC 2010 Feb 9.
Published in final edited form as:
Ageing Res Rev. 2010 Jan; 9(1): 69.
Published online 2009 Dec 5. doi: 10.1016/j.arr.2009.11.004

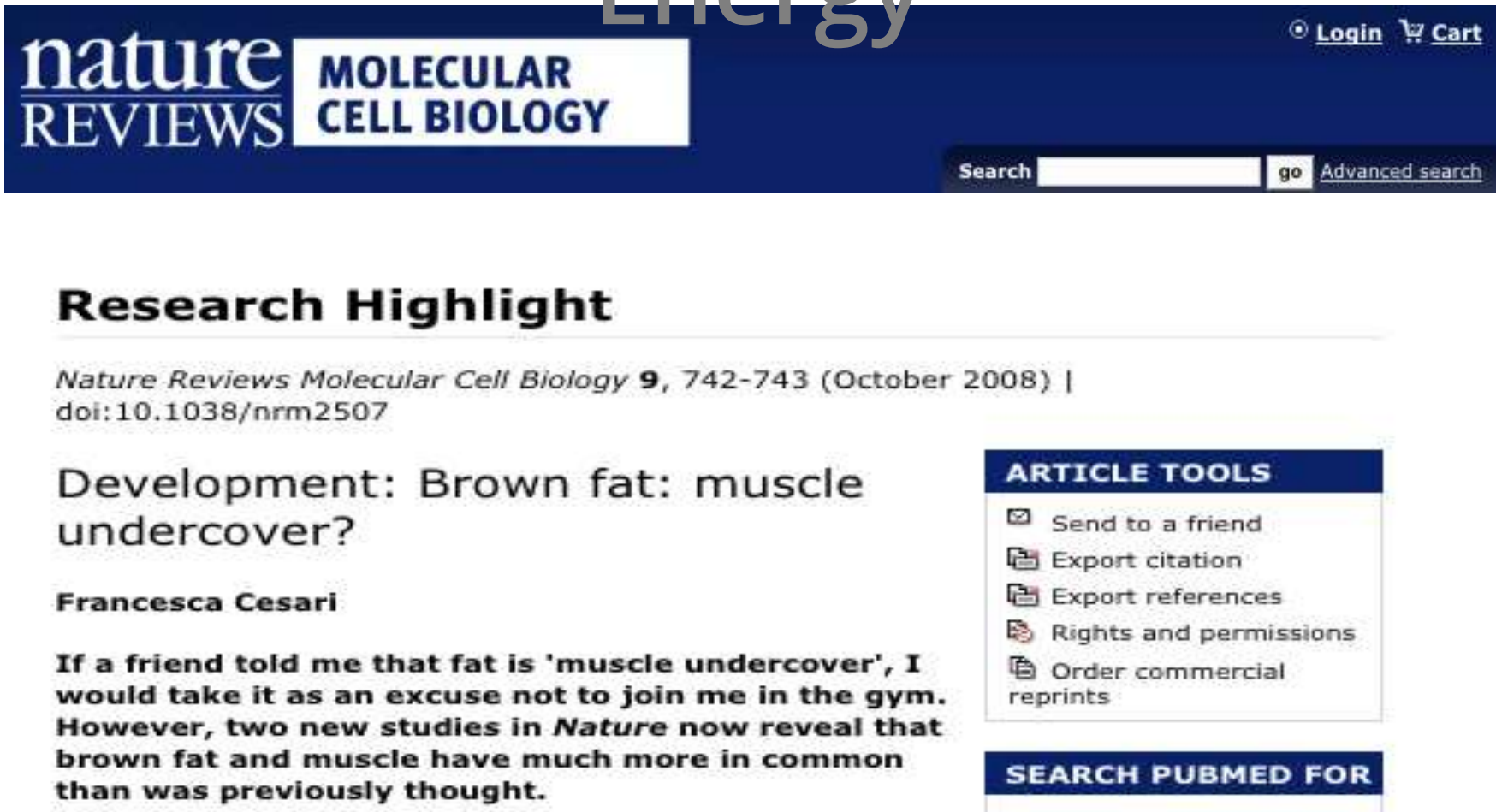
Does Brown Fat Protect Against Diseases of Aging?

Mark P. Mattson

Diet and lifestyle changes, specific regimens of mild intermittent stress, drugs that stimulate BAT formation and activity, induction of brown adipose cell progenitors in muscle and other tissues, and transplantation of brown adipose cells are all potential means of increasing BAT mass and thermogenic activity. In addition, stimulation of UCP expression in non-adipose cells (neurons, muscle cells, hepatocytes and others) may prove an effective means of protecting those cells against severe stress and the adversities of aging. However, while studies of such approaches in animal models of obesity and age-related diseases appear promising, their efficacy and safety in human subjects remains to be established.

Anti Aging Effects

Strength and Energy



Strength and Energy

Published in final edited form as:
Curr Opin Pediatr. 2010 August ; 22(4): 478–484. doi:10.1097/MOP.0b013e32833a8d6e.

The Role and Importance of Brown Adipose Tissue in Energy Homeostasis

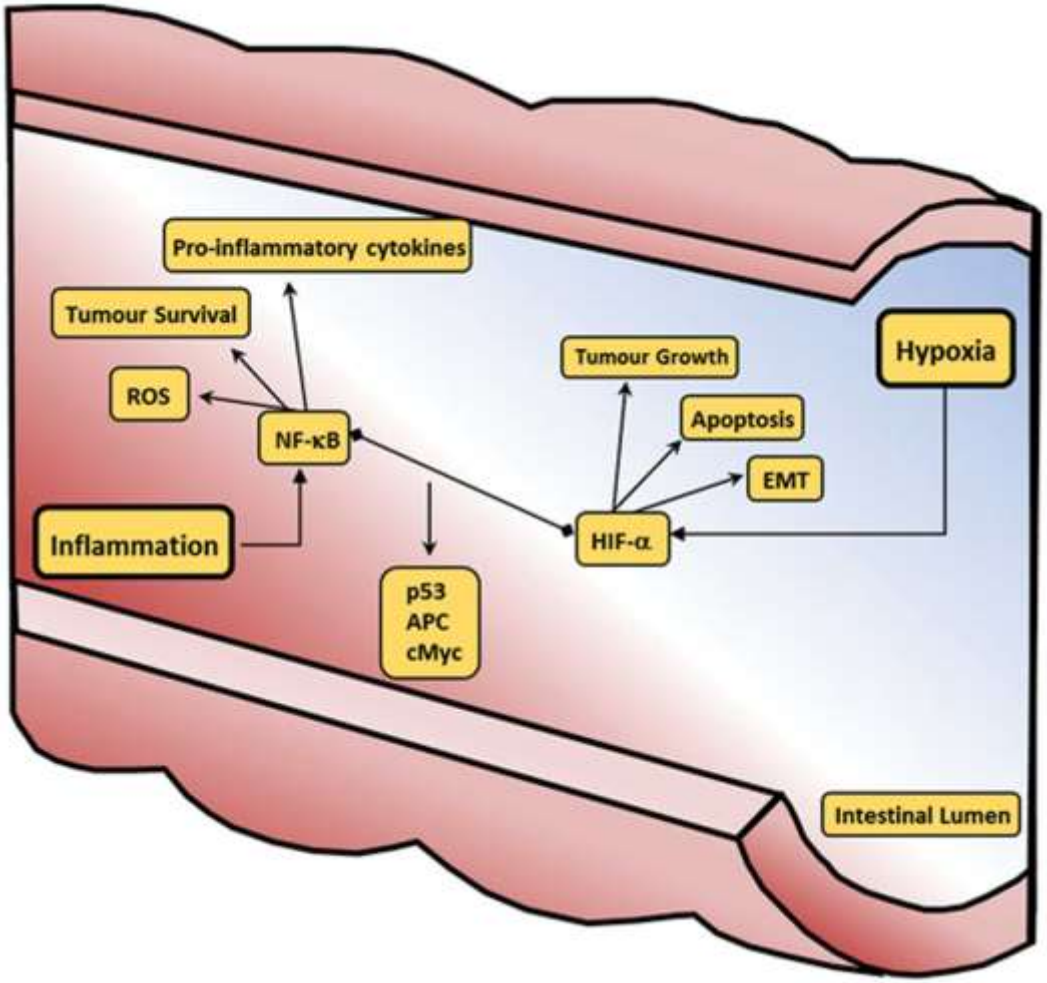
Aaron M. Cypess and **C. Ronald Kahn**
Joslin Diabetes Center, Harvard Medical School, One Joslin Place, Boston, MA 02215

Abstract

Purpose of review—Children and adults have two major types of adipocytes, which represent the predominant cells in white adipose tissue (WAT), which is involved in energy-storage, and brown adipose tissue (BAT) which is responsible for thermogenesis and energy expenditure. This review discusses BAT physiology and evaluates the recent discoveries regarding its development, identification, and function.

Recent findings—This past year multiple independent research teams using combined positron-emission tomography and computed tomography (PET/CT) imaging, immunohistochemistry, and gene and protein expression have proven conclusively that adult humans have functional BAT. In parallel, basic studies defined BAT origins, its transcriptional regulation, and the role of hormones in BAT growth and activation. These methods have begun to be applied to children to understand pediatric BAT anatomy and physiology.

Summary—Adult humans have functional BAT, which plays a role in energy balance. BAT is more prevalent in children, suggesting an even greater physiological role than that seen in adults. Future studies will identify safe ways to quantify BAT mass and activity and which interventions

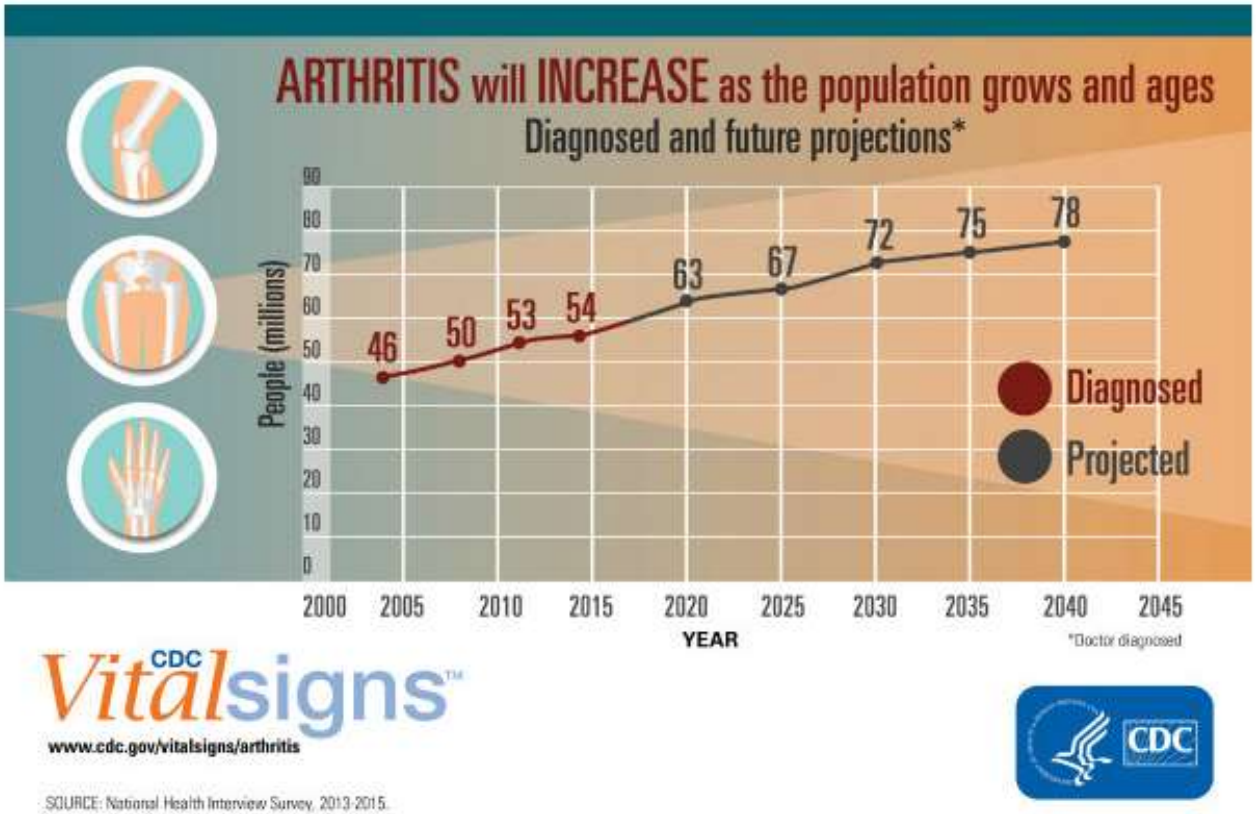


Arthritis / Osteoporosis

- Brown Fat adipocytes remodel the bone matrix
- Brown adipocytes set up hypoxic gradients resulting in increase vascularization

Arthritis : Data USA

National Arthritis Prevalence Projections



Arthritis / Osteoporosis

Published in final edited form as:
Discov Med. 2011 March ; 11(58): 179–185.

Temperatures Rising: Brown Fat and Bone

Katherine J. Motyl[1] and **Clifford J. Rosen**[1,*]
[1]Maine Medical Center Research Institute 81 Research Drive Scarborough, ME 04074

Abstract

Caloric restriction is associated with a reduction in body weight and temperature but a reduction in trabecular bone volume and paradoxically an increase in adipocytes within the bone marrow. The nature of these adipocytes is uncertain, although there is emerging evidence of a direct relationship between bone remodeling and brown adipocytes. For example, in heterotropic ossification, brown adipocytes set up a hypoxic gradient that leads to vascular invasion, chondrocyte differentiation and subsequent bone formation. Additionally, deletion of retinoblastoma protein in an osteosarcoma model leads to increased hibernosarcoma (brown fat tumor). Interestingly, brown adipose tissue (BAT) senescences with age at a time when thermoregulation becomes altered,, bone loss becomes apparent and sympathetic activity increases. Interestingly, heart rate is an unexpected but good predictor of fracture risk in elderly individuals, pointing to a key role for the sympathetic nervous system in senile osteoporosis. Hence the possibility exists that BAT could play an indirect role in age-related bone loss. However, evidence of an indirect effect from thermogenic dysfunction on bone loss is currently limited. Here, we present current evidence for a relationship between brown adipose tissue and bone as well as provide novel insights into the effects of thermoregulation on bone mineral density.

Arthritis / Osteoporosis

ADIPOCYTE
2017, VOL. 0, NO. 0, 1–15
http://dx.doi.org/10.1080/21623945.2017.1295174

Taylor & Francis
Taylor & Francis Group

RESEARCH PAPER

OPEN ACCESS

Alterations to adipose tissue morphology during inflammatory arthritis is indicative of vasculopathology in DBA/1 mice

Katie Sime[a], Ernest H. Choy[a,b], and Anwen S. Williams[a,b]

[a]Division of Infection and Immunity, Department of Rheumatology, Cardiff University School of Medicine, Cardiff, United Kingdom; [b]The Cardiff Regional Experimental Arthritis Treatment and Evaluation Centre (CREATE Centre), Cardiff University School of Medicine, Cardiff, United Kingdom

ABSTRACT

The physiologic function of adipose tissue is altered by the host's inflammatory response; the implications for maintaining human health and regulating inflammation-associated disease progression are ill defined. However, this cannot be investigated in humans, therefore the use of animal models is required. With the aim to determine morphological and molecular alterations to perivascular and organ-associated adipose tissues during inflammatory arthritis, collagen-induced arthritis (CIA) was established in male DBA/1 mice. Emerging evidence from this study signposts CIA in the DBA/1 mouse as a model that is relevant to study the development and treatment of early cardiovascular pathology associated with inflammatory arthritis. Here, we show global morphological changes in adipose tissue and the thoracic aorta in animals induced with CIA compared with the non-immunized controls. In CIA, we concluded that the increased cell count in PVAT was, at least in part, caused by an ingress and/or expansion of macrophages that had a mixed phenotype. A substantial increase of galectin-3 was expressed in PVAT from mice with CIA. Galectin-3 is elevated in the blood of patients with CVDs, however, it has never before been measured in PVAT in rodents or humans. Here, PVAT-associated galectin-3 is identified as a potential biomarker for detecting early vascular pathology in CIA and a promising candidate for translation to RA.

ARTICLE HISTORY
Received 17 August 2016
Revised 7 February 2017
Accepted 8 February 2017

KEYWORDS
Adipose tissue; perivascular adipose tissue; inflammatory arthritis; vasculature; macrophage; galectin-3

Thank You

Summary

Advantages of Brown Fat

- Creates heats through thermogenesis
- Metabolizes white fat
- Reduces glucose and lipid levels
- Regulates homeostasis- balances metabolism

Areas of Treatment

- Diabetes
- Heart disease
- Obesity
- Arthritis
- Metabolic disorders