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Cold-Induced Activation of Brown Adipose Tissue: Molecular Mechanisms of Non-Shivering Thermogenesis in Adult Humans

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Abstract

Brown adipose tissue (BAT) is a specialised thermogenic organ that plays a central role in maintaining human body temperature through non-shivering thermogenesis (NST). In contrast to white fat that stores energy, brown fat has a high concentration of mitochondria with a special protein called uncoupling protein 1 (UCP1). UCP1 helps in converting the proton gradient from oxidative phosphorylation into heat rather than ATP production. While BAT was thought to be important only in infants in the past, modern imaging techniques have shown that active BAT is present in adults, especially in specific regions like the neck, chest, and back. Cold exposure is the strongest trigger for activating BAT, which involves a coordinated response from the brain, nerves, hormones, and cell signals to increase heat production. This review examines the molecular and physiological mechanisms underlying cold-induced BAT activation in adult humans, with particular emphasis on the regulation of non-shivering thermogenesis. The review covers how the body senses temperature, activates the nervous system, uses specific signals, and relies on UCP1 for producing heat in BAT. Additionally, the metabolic adaptations supporting thermogenesis—including intracellular lipolysis, fatty acid oxidation, glucose uptake, mitochondrial biogenesis, and enhanced oxidative metabolism—are comprehensively evaluated. The review also looks at important regulators like PPARγ, PRDM16, PGC-1α, and other molecules that control how BAT develops and functions. Additionally, the review talks about how thyroid hormones, insulin, fibroblast growth factor 21 (FGF21), irisin, and environmental factors affect BAT activity to regulate its function. Current evidence demonstrates that BAT functions as a highly dynamic endocrine and metabolic organ rather than merely a site of heat production. Through coordinated neural, hormonal, and cellular mechanisms, cold-induced BAT activation contributes significantly to energy expenditure, metabolic flexibility, glucose homeostasis, and thermal adaptation. By synthesising recent experimental and clinical findings, this review provides a comprehensive overview of the physiological processes governing BAT activation and identifies important gaps in current knowledge regarding the variability of BAT function among adults. A deeper understanding of these molecular mechanisms may enhance future investigations into human thermoregulation and metabolic physiology while providing a robust foundation for subsequent translational research. This study may pave the way for developing novel treatments for metabolic disorders and related conditions, offering new therapeutic options.

Keywords: Brown Adipose Tissue (BAT), Non-shivering Thermogenesis, Cold Exposure, Uncoupling Protein 1 (UCP1), Brown Adipocyte Activation, β_3-Adrenergic Signaling, Mitochondrial Biogenesis, Human Thermoregulation

1. Introduction

Brown adipose tissue (BAT) is a specialised thermogenic adipose tissue that plays a fundamental role in maintaining body temperature through adaptive, non-shivering thermogenesis (NST). Unlike white adipose tissue (WAT), whose principal function is long-term energy storage in the form of triglycerides, BAT is metabolically active and specialised for heat production. This unique capability arises from its exceptionally high mitochondrial density, extensive vascularisation, and abundant sympathetic innervation, all of which enable rapid responses to environmental temperature changes. One of BAT's main features is the presence of UCP1, a protein in the mitochondria that converts energy from food into heat instead of storing it as ATP. This mechanism represents one of the most efficient physiological adaptations for maintaining core body temperature in mammals exposed to cold environments. For many decades, BAT was considered physiologically significant only during infancy and early childhood. Neonates possess relatively large BAT depots that protect against hypothermia because their limited skeletal muscle mass restricts the capacity for shivering thermogenesis. Consequently, BAT was traditionally believed to regress with age and become functionally insignificant in adults. However, this long-standing paradigm changed following the introduction of positron emission tomography combined with computed tomography (18F-FDG PET/CT), which demonstrated metabolically active BAT in healthy adult humans. These studies consistently identified BAT

depots in the supraclavicular, cervical, paravertebral, mediastinal, and perirenal regions, establishing BAT as an important component of adult human physiology rather than a transient developmental tissue. Since these discoveries, interest in BAT has expanded considerably, leading to extensive investigations into its physiological regulation, molecular characteristics, and contribution to systemic energy metabolism.

Cold exposure triggers BAT activation by stimulating peripheral thermoreceptors in the skin that send signals to the hypothalamus, which regulates body temperature. Integration of these neural inputs initiates activation of the sympathetic nervous system, resulting in the release of norepinephrine from sympathetic nerve terminals that densely innervate BAT. Norepinephrine binds predominantly to β_3-adrenergic receptors on brown adipocytes, activating intracellular signalling cascades involving cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), and downstream transcriptional regulators. These signalling events stimulate intracellular lipolysis, mobilise fatty acids, enhance mitochondrial respiration, and activate UCP1-mediated proton leak across the mitochondrial inner membrane. The coordinated activation of these molecular pathways enables BAT to rapidly convert stored chemical energy into heat without generating mechanical muscle contractions, thereby preserving core body temperature during acute and chronic cold exposure.

Non-shivering thermogenesis is a highly regulated physiological process that complements shivering thermogenesis during cold adaptation. While shivering relies on involuntary skeletal muscle contractions that substantially increase metabolic demand, prolonged shivering is energetically inefficient and cannot be sustained indefinitely. BAT-mediated thermogenesis provides a more metabolically efficient alternative by generating heat directly within specialised adipocytes through mitochondrial uncoupling. This adaptation allows maintenance of thermal homeostasis while minimising muscular fatigue. In adult humans, repeated cold exposure can further enhance BAT activity through adaptive mechanisms, including mitochondrial biogenesis, increased UCP1 expression, angiogenesis, and enhanced sympathetic responsiveness, collectively improving thermogenic capacity over time.

At the cellular level, brown adipocytes possess several structural adaptations that distinguish them from white adipocytes. Brown adipocytes contain numerous small lipid droplets (multilocular morphology), abundant iron-rich mitochondria, and an extensive capillary network that facilitates efficient delivery of oxygen and metabolic substrates while rapidly distributing generated heat throughout the circulation. The abundant mitochondrial content not only sustains elevated oxidative metabolism but also forms the structural foundation for UCP1-mediated thermogenesis. Moreover, BAT exhibits remarkable metabolic flexibility, simultaneously oxidising intracellular triglycerides, circulating free fatty acids, glucose, branched-chain amino acids, and other substrates to sustain heat production during prolonged cold exposure. Consequently, BAT functions as an important metabolic organ capable of integrating neural, endocrine, and nutritional signals to regulate whole-body energy homeostasis.

The differentiation, maintenance, and activation of BAT are governed by a complex network of transcription factors and signalling molecules. Among these, peroxisome proliferator-activated receptor gamma (PPARγ), PR domain-containing protein 16 (PRDM16), and peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) represent master regulators of brown adipocyte identity and mitochondrial biogenesis. These transcriptional regulators coordinate the expression of genes involved in lipid metabolism, mitochondrial function, oxidative phosphorylation, and thermogenic protein synthesis. Additional endocrine mediators, including thyroid hormones, insulin, fibroblast growth factor 21 (FGF21), irisin, and natriuretic peptides, further modulate BAT activity by interacting with sympathetic signalling pathways and influencing mitochondrial metabolism. Comprehending the interactions among these molecular regulators is crucial for revealing the physiological foundation of cold-induced thermogenesis.

Recent progress in molecular biology, imaging technologies, transcriptomics, metabolomics, and single-cell sequencing has significantly advanced the comprehension of BAT physiology. These approaches have revealed that BAT is not merely a thermogenic tissue but also an active endocrine organ capable of secreting biologically active molecules, collectively termed batokines, which exert systemic effects on metabolism and inter-organ communication. Nevertheless, substantial variability exists in BAT abundance and activity among adult individuals. Factors including age, sex, genetic background, body composition, seasonal variation, environmental temperature, and habitual cold exposure all influence BAT function, highlighting the complexity of its physiological regulation. Furthermore, many molecular mechanisms underlying long-term BAT adaptation to repeated cold exposure remain incompletely understood, emphasising the need for continued investigation.

This review aims to thoroughly examine how cold exposure activates brown fat in adults, focusing on the underlying physiological and molecular processes. Particular emphasis is placed on the neural regulation of BAT activation, β_3-adrenergic signalling pathways, mitochondrial uncoupling mediated by UCP1, substrate metabolism, transcriptional control of thermogenesis, and the hormonal and environmental factors that modulate BAT activity. By integrating recent experimental and clinical evidence, this review aims to provide an updated understanding of non-shivering thermogenesis and the physiological adaptations that enable humans to maintain thermal homeostasis during cold exposure, while identifying important areas for future research. Furthermore, the review discusses the potential therapeutic implications of targeting BAT activation for metabolic disorders such as obesity and diabetes. Overall, this comprehensive analysis sheds light on the complex

mechanisms underlying thermogenesis and highlights the importance of further investigating BAT function in human health and disease.

2. Brown Adipose Tissue Activation in Response to Cold Exposure

2.1. Physiological Response to Cold Exposure

Maintenance of a relatively constant core body temperature is essential for optimal enzymatic activity, cellular metabolism, and overall physiological homeostasis. In adult humans, the thermoregulatory system functions through an intricate network involving peripheral thermoreceptors, central nervous system integration, autonomic nervous system responses, endocrine regulation, and effector organs such as skeletal muscle, blood vessels, sweat glands, and brown adipose tissue (BAT). Among these effectors, BAT serves as the principal site of adaptive non-shivering thermogenesis (NST), allowing heat generation without mechanical muscle contractions. Cold exposure begins when environmental temperatures fall below the thermoneutral zone, resulting in heat loss from the body's surface. Specialised cold-sensitive transient receptor potential (TRP) ion channels, particularly TRPM8 and TRPA1, located within cutaneous sensory neurones, detect reductions in skin temperature. Activation of these receptors initiates afferent neural signals that travel through the dorsal root ganglia to the spinal cord and subsequently ascend to thermoregulatory centres within the brainstem and hypothalamus. The preoptic area (POA) of the hypothalamus acts as the primary thermoregulatory centre by integrating peripheral temperature information with core body temperature signals. Once a decrease in body temperature is detected, the hypothalamus coordinates autonomic and behavioural responses aimed at minimising heat loss and maximising heat production.

Initially, the body employs heat-conserving mechanisms, including peripheral vasoconstriction, piloerection (which has minimal functional significance in humans), and behavioural adaptations such as seeking warmer environments or increasing clothing insulation. When these mechanisms are insufficient to maintain thermal homeostasis, thermogenic responses are activated. Although shivering thermogenesis contributes to rapid heat production through involuntary skeletal muscle contractions, prolonged shivering is metabolically inefficient, increases fatigue, and cannot be sustained for extended periods. Consequently, BAT-mediated NST becomes increasingly important during prolonged or repeated cold exposure.

Unlike skeletal muscle, BAT produces heat through mitochondrial uncoupling rather than ATP-dependent contraction. This mechanism enables continuous heat generation while minimising muscular fatigue, making BAT particularly effective during chronic cold adaptation. Studies in humans utilising ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) consistently show significant rises in BAT glucose uptake after mild cold exposure (usually 16–19°C), verifying the ongoing metabolic activity of BAT in healthy adults. Cold acclimation over several days or weeks further enhances BAT volume, glucose uptake, mitochondrial density, and thermogenic capacity, demonstrating the remarkable plasticity of this tissue.

2.2. Central Neural Regulation of Brown Adipose Tissue

Cold-induced BAT activation is primarily mediated through the sympathetic nervous system (SNS), which serves as the principal neural pathway linking environmental temperature changes to thermogenic responses. Following thermal information processing in the hypothalamus, excitatory neurones within the dorsomedial hypothalamus (DMH) activate sympathetic premotor neurones located in the rostral raphe pallidus (rRPa) of the medulla oblongata. Descending projections from the rRPa travel through the spinal cord to sympathetic preganglionic neurones within the intermediolateral cell column. These neurones synapse within sympathetic ganglia before postganglionic fibres innervate BAT.

Brown adipose tissue is among the most densely sympathetically innervated tissues in the human body. Each brown adipocyte receives multiple sympathetic nerve terminals capable of rapidly releasing norepinephrine in response to cold stimulation. This dense neural network allows precise regulation of thermogenic activity according to both the intensity and duration of cold exposure. Recent neurophysiological studies have demonstrated that BAT activation is subject to continuous modulation by higher brain centres involved in circadian rhythm regulation, nutritional status, emotional stress, and sleep-wake cycles. Consequently, BAT activity reflects not only environmental temperature but also whole-body physiological state.

2.3. Sympathetic Nervous System Activation and Norepinephrine Release

Norepinephrine (NE) represents the principal neurotransmitter responsible for initiating BAT thermogenesis. Upon cold exposure, sympathetic nerve terminals release NE directly into BAT, where it binds predominantly to **β_3-adrenergic receptors (β_3-ARs)** expressed on the surface of brown adipocytes.

Binding of NE activates the stimulatory G protein (Gs), which stimulates **adenylyl cyclase,** leading to increased intracellular cyclic adenosine monophosphate **(cAMP)** concentrations. Elevated cAMP subsequently activates **protein kinase A (PKA**), initiating one of the most important signalling cascades in BAT physiology.

Activated PKA phosphorylates numerous downstream targets, including:

- Hormone-sensitive lipase (HSL)
- Perilipin-1
- cAMP response element-binding protein (CREB)
- Mitogen-activated protein kinases (MAPKs)

Phosphorylation of HSL and perilipin promotes rapid hydrolysis of intracellular triglyceride droplets into free fatty acids (FFAs) and glycerol. These FFAs serve two essential physiological functions. First, they provide the primary fuel substrate for mitochondrial β-oxidation. Second,

they directly activate UCP1 by overcoming inhibitory interactions between UCP1 and purine nucleotides, thereby initiating mitochondrial proton leak and heat generation. Simultaneously, CREB activation promotes transcription of genes involved in mitochondrial biogenesis, oxidative metabolism, and thermogenic protein synthesis. Thus, sympathetic stimulation induces both immediate thermogenic activation and long-term adaptive remodelling of BAT.

2.4. Cellular Metabolic Adaptations During Cold Exposure

Activation of BAT requires substantial metabolic support to sustain continuous heat production. Consequently, cold exposure induces coordinated increases in nutrient uptake and mitochondrial metabolism.

2.5. Increased Glucose Uptake

Cold stimulation markedly enhances glucose uptake into brown adipocytes through insulin-independent and insulin-dependent mechanisms. Translocation of **GLUT1** and **GLUT4** transporters increases cellular glucose availability, supporting glycolysis, oxidative phosphorylation, and synthesis of metabolic intermediates necessary for sustained thermogenesis. Although glucose contributes to BAT metabolism, fatty acids remain the dominant oxidative substrate during prolonged cold exposure.

2.6. Enhanced Lipolysis

Brown adipocytes contain numerous multilocular lipid droplets that serve as readily accessible intracellular energy stores. Activation of HSL and adipose triglyceride lipase (ATGL) rapidly mobilises triglycerides into free fatty acids. Lipolysis occurs within minutes following sympathetic stimulation, ensuring immediate substrate availability before circulating nutrients become fully mobilised.

2.7. Fatty Acid Oxidation

Released fatty acids enter mitochondria through the carnitine shuttle, involving carnitine palmitoyltransferase-1 (CPT1) and CPT2.

Within mitochondria, β-oxidation generates:

- NADH
- $FADH_2$
- Acetyl-CoA

These metabolites enter the electron transport chain, generating the proton gradient ultimately dissipated by UCP1 to produce heat.

2.8. Increased Oxygen Consumption

BAT activation substantially increases whole-body oxygen consumption due to accelerated mitochondrial respiration. Human indirect calorimetry studies consistently demonstrate increased resting energy expenditure during mild cold exposure, reflecting elevated BAT oxidative metabolism. Unlike ATP synthesis in most tissues, BAT mitochondria intentionally uncouple respiration from ATP production, allowing oxygen consumption to continue at exceptionally high rates while maximising heat production.

2.9. Activation of Uncoupling Protein 1 (UCP1)

The defining event in cold-induced BAT activation is stimulation of uncoupling protein 1 (UCP1). UCP1 is an integral protein located exclusively within the inner mitochondrial membrane of brown adipocytes. Under resting conditions, protons pumped into the mitochondrial intermembrane space during oxidative phosphorylation return to the matrix primarily through ATP synthase, driving ATP production. Cold-induced sympathetic activation fundamentally alters this process. Following norepinephrine-mediated lipolysis, free fatty acids activate UCP1, creating an alternative pathway for proton re-entry into the mitochondrial matrix. Instead of powering ATP synthase, the electrochemical energy stored within the proton gradient is released as thermal energy.

This process is referred to as mitochondrial uncoupling because substrate oxidation continues independently of ATP synthesis.

Several characteristics distinguish UCP1-mediated thermogenesis:

- Rapid activation within minutes of cold exposure.
- High metabolic efficiency for heat generation.
- Ability to sustain prolonged thermogenesis.
- Minimal mechanical energy production.
- Reduced reactive oxygen species generation compared with maximally coupled respiration.

Repeated cold exposure also increases **UCP1 gene expression,** mitochondrial number, cristae density, and oxidative enzyme activity, thereby enhancing the tissue's long-term thermogenic capacity.

2.10. Adaptive Remodelling During Chronic Cold Exposure

Cold acclimation induces structural and molecular remodelling of BAT beyond acute activation.

These adaptations include:

- Increased mitochondrial biogenesis mediated by **PGC-1α.**
- Enhanced capillary density to improve oxygen and nutrient delivery.
- Greater sympathetic innervation.
- Expansion of brown adipocyte volume.
- Increased expression of oxidative enzymes.
- Elevated UCP1 protein abundance.
- Improved fatty acid oxidation capacity.

Repeated cold exposure can also stimulate the emergence of **beige (brite) adipocytes** within white adipose tissue depots, a process termed **browning**. Although beige adipocytes originate from distinct precursor cells, they acquire thermogenic characteristics resembling classical brown adipocytes following sympathetic stimulation. This adaptive response increases total thermogenic capacity during prolonged cold exposure. Collectively, these neural, cellular, and metabolic adaptations demonstrate that BAT is an exceptionally dynamic organ capable of rapidly responding to environmental temperature changes while undergoing long-term remodelling to optimise heat production. Rather than functioning solely as a passive heat-generating tissue,

BAT integrates neural, endocrine, and metabolic signals to maintain thermal homeostasis and whole-body energy balance during cold stress. These physiological events establish the foundation for the intracellular molecular mechanisms of non-shivering thermogenesis, which are discussed in the following section. BAT plays a crucial role in regulating body temperature and energy expenditure, making it a key player in overall metabolic health. Insight into the complex processes within BAT can offer valuable perspectives on potential therapeutic approaches for metabolic disorders like obesity and diabetes.

3. Molecular Mechanisms of Non-Shivering Thermogenesis

3.1. Uncoupling Protein 1 (UCP1): The Central Effector of Non-Shivering Thermogenesis

The hallmark of brown adipose tissue (BAT) is its remarkable ability to convert chemical energy directly into heat through a process known as **non-shivering thermogenesis (NST).** Unlike most mammalian tissues, where mitochondrial respiration is tightly coupled to adenosine triphosphate (ATP) synthesis, BAT possesses a specialised mechanism that deliberately uncouples oxidative phosphorylation from ATP production. This unique thermogenic capability is mediated almost exclusively by **uncoupling protein 1 (UCP1),** a protein located within the inner mitochondrial membrane that serves as the molecular hallmark of functional brown adipocytes. UCP1 is therefore widely regarded as the principal determinant of BAT thermogenic capacity and the defining molecular signature distinguishing brown adipocytes from white adipocytes.

3.1.1. Structure and Localisation of UCP1

UCP1 belongs to the mitochondrial anion carrier protein family and is expressed almost exclusively in classical brown adipocytes and inducible beige adipocytes. Structurally, UCP1 is an approximately 33-kDa transmembrane protein composed of six α-helical domains that span the inner mitochondrial membrane. These transmembrane domains create a channel capable of transporting protons from the mitochondrial intermembrane space back into the matrix independently of ATP synthase. Brown adipocytes contain an exceptionally large number of mitochondria, giving BAT its characteristic brown colouration due to the abundance of iron-containing cytochromes. The high mitochondrial density provides an extensive surface area for UCP1 expression, enabling BAT to sustain remarkably high rates of oxidative metabolism during cold exposure. Consequently, BAT exhibits one of the highest oxygen consumption rates of any tissue in the human body during maximal activation.

3.1.2. Oxidative Phosphorylation Under Physiological Conditions

To appreciate the function of UCP1, it is essential to understand normal mitochondrial energy metabolism. Under physiological conditions, nutrients such as glucose and fatty acids are metabolised to generate reducing equivalents, primarily **NADH and $FADH_2$.** These molecules donate electrons to the mitochondrial electron transport chain (ETC), where sequential electron transfer through Complexes I–IV drives the active transport of protons (H^+) from the mitochondrial matrix into the intermembrane space. This process establishes an electrochemical proton gradient, commonly referred to as the **proton motive force,** which stores potential energy across the inner mitochondrial membrane. Normally, protons return to the mitochondrial matrix through ATP synthase (Complex V), and the released energy is used to phosphorylate adenosine diphosphate (ADP) into ATP.

Thus, in most tissues, mitochondrial respiration is efficiently coupled to ATP production, ensuring maximal conservation of metabolic energy.

3.1.3. Mechanism of Mitochondrial Uncoupling

Cold exposure fundamentally alters this process within BAT. Following sympathetic stimulation, intracellular lipolysis releases large quantities of long-chain free fatty acids (FFAs). These FFAs perform two complementary functions. First, they provide oxidative substrates for mitochondrial β-oxidation. Second, they directly activate UCP1 by displacing inhibitory purine nucleotides that normally suppress its activity. Once activated, UCP1 forms an alternative pathway for proton re-entry into the mitochondrial matrix. Rather than passing through ATP synthase, protons leak through UCP1, dissipating the proton gradient without generating ATP. Consequently, the potential energy stored within the electrochemical gradient is released almost entirely as thermal energy. This phenomenon is termed **mitochondrial uncoupling** because oxygen consumption and substrate oxidation continue independently of ATP synthesis. As the proton gradient continuously dissipates, the electron transport chain accelerates to restore it, dramatically increasing mitochondrial respiration, fatty acid oxidation, glucose utilisation, and oxygen consumption. The net result is rapid heat generation that contributes directly to maintenance of core body temperature during cold exposure.

3.1.4. Sympathetic Regulation of UCP1 Activity

Activation of UCP1 is tightly controlled by the sympathetic nervous system. Cold exposure stimulates hypothalamic thermoregulatory centres, increasing sympathetic outflow to BAT. Norepinephrine released from sympathetic nerve terminals binds predominantly to β_3-adrenergic receptors expressed on brown adipocytes. Activation of these receptors stimulates the Gs protein–adenylyl cyclase pathway, increasing intracellular cyclic AMP (cAMP) concentrations and activating protein kinase A (PKA). PKA phosphorylates hormone-sensitive lipase (HSL) and perilipin, initiating rapid triglyceride hydrolysis and release of FFAs. Simultaneously, PKA activates transcription factors such as CREB, enhancing transcription of genes involved in mitochondrial biogenesis and thermogenesis, including **UCP1, PGC-1α**, and oxidative enzymes. Thus, sympathetic stimulation mediates both immediate activation of existing UCP1 molecules and long-term increases in UCP1 expression through transcriptional regulation.

3.1.5. Regulation of UCP1 Gene Expression

Although acute thermogenesis depends on activation of pre-existing UCP1 proteins, prolonged cold exposure induces

significant increases in UCP1 gene expression.nOne of the most important regulators is **peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α),** which acts as a master regulator of mitochondrial biogenesis and oxidative metabolism. During cold exposure, β_3-adrenergic signalling markedly increases PGC-1α expression, which subsequently coactivates multiple nuclear transcription factors, including nuclear respiratory factors (NRF-1 and NRF-2), oestrogen-related receptors (ERRs), and peroxisome proliferator-activated receptor gamma (PPARγ). These transcriptional complexes promote expression of genes involved in mitochondrial replication, oxidative phosphorylation, fatty acid oxidation, and UCP1 synthesis, thereby increasing the thermogenic capacity of BAT during chronic cold adaptation.

3.1.6. Functional Significance of UCP1-Mediated Thermogenesis

UCP1-mediated thermogenesis provides several important physiological advantages over shivering thermogenesis. First, heat is generated continuously without requiring skeletal muscle contraction, thereby minimising muscular fatigue. Second, BAT produces heat with exceptional speed because mitochondrial uncoupling can occur within minutes following sympathetic activation. Third, repeated cold exposure enhances UCP1 expression, mitochondrial density, vascularisation, and sympathetic innervation, allowing progressive increases in thermogenic capacity through adaptive remodelling. In addition to maintaining body temperature, UCP1-mediated thermogenesis substantially increases whole-body energy expenditure. Activation of BAT accelerates oxidation of fatty acids and glucose, contributing to metabolic flexibility during cold adaptation. Human PET/CT studies consistently demonstrate marked increases in BAT glucose uptake and oxygen consumption following mild cold exposure, confirming that UCP1 remains functionally significant throughout adulthood.

3.1.7. Mitochondrial Adaptations Supporting Thermogenesis

Cold acclimation induces profound mitochondrial remodelling within brown adipocytes.

Repeated sympathetic stimulation increases mitochondrial biogenesis, enlarges mitochondrial cristae surface area, enhances expression of electron transport chain complexes, and increases oxidative enzyme activity. These structural adaptations allow BAT to sustain prolonged thermogenesis while maintaining adequate ATP production for essential cellular functions independent of UCP1-mediated heat generation. Emerging evidence also suggests that reactive oxygen species (ROS), once considered merely harmful metabolic by-products, function as signalling molecules that participate in BAT activation by modulating redox-sensitive signalling pathways involved in UCP1 regulation and mitochondrial adaptation. Similarly, recent studies have identified additional proteins that interact with UCP1, including components of mitochondrial calcium handling and metabolic sensing pathways, indicating that thermogenesis is regulated through highly integrated mitochondrial signalling networks rather than by UCP1 alone.

3.2. Summary

UCP1 represents the molecular foundation of adaptive non-shivering thermogenesis in adult humans. Through cold-induced sympathetic activation, β_3-adrenergic signalling, and mitochondrial proton leak, UCP1 enables BAT to convert chemical energy directly into heat while simultaneously increasing substrate oxidation and oxygen consumption. The coordinated regulation of UCP1 activity, mitochondrial biogenesis, and transcriptional remodelling allows BAT to respond rapidly to acute cold exposure and to undergo long-term adaptation during repeated cold stimulation. These mechanisms solidify UCP1 as the pivotal effector of BAT thermogenesis and lay the physiological groundwork for the subsequent metabolic processes explored in the following section on lipolysis and fatty acid oxidation.

3.2.1. Lipolysis and Fatty Acid Oxidation: Metabolic Fuelling of Non-Shivering Thermogenesis

While uncoupling protein 1 (UCP1) serves as the molecular effector of non-shivering thermogenesis (NST), sustained heat production depends on a continuous supply of metabolic substrates capable of supporting the exceptionally high energy demands of activated brown adipose tissue (BAT). Among these substrates, **fatty acids are the primary fuel** for thermogenesis. They not only provide reducing equivalents for mitochondrial respiration but also directly activate UCP1, making lipid metabolism indispensable for BAT function. Consequently, cold exposure induces rapid activation of intracellular lipolysis, increased uptake of circulating lipids and glucose, enhanced mitochondrial β-oxidation, and coordinated metabolic remodelling to sustain prolonged heat production. Recent evidence indicates that BAT is one of the most metabolically active tissues in the human body during cold exposure, exhibiting substantial increases in oxygen consumption, nutrient uptake, and oxidative capacity.

3.2.2. Activation of Lipolysis During Cold Exposure

The first metabolic event following sympathetic stimulation is the mobilisation of intracellular triglyceride stores. Brown adipocytes contain numerous multilocular lipid droplets, which differ structurally from the large unilocular lipid droplets characteristic of white adipocytes. This **multilocular organisation** increases the surface area available for enzymatic degradation, allowing rapid mobilisation of stored lipids in response to cold.

Cold exposure stimulates the release of **norepinephrine (NE**) from sympathetic nerve terminals densely innervating BAT. Binding of NE to β_3-adrenergic receptors activates the Gs protein–adenylyl cyclase signalling pathway, leading to increased intracellular cyclic adenosine monophosphate (cAMP) concentrations and activation of **protein kinase A (PKA).** PKA phosphorylates several proteins involved in lipid metabolism, most notably perilipin-1 and **hormone-sensitive lipase (HSL),** and indirectly activates **adipose triglyceride lipase (ATGL)**. Perilipin phosphorylation alters the surface structure of lipid droplets, allowing lipases

to access stored triglycerides. ATGL initiates triglyceride hydrolysis by converting triglycerides into diacylglycerol, while HSL subsequently hydrolyses diacylglycerol into monoacylglycerol. Monoacylglycerol lipase (MGL) completes the process by releasing glycerol and free fatty acids (FFAs). The rapid activation of these enzymes ensures that intracellular lipid stores can be mobilised within minutes of cold exposure, providing an immediate supply of fatty acids required for thermogenesis. Unlike white adipose tissue, where lipolysis primarily serves to release fatty acids into the circulation, BAT preferentially oxidises liberated fatty acids locally to generate heat.

3.2.3. Dual Functions of Free Fatty Acids

The free fatty acids generated during lipolysis perform two indispensable physiological functions. First, they act as the **principal oxidative fuel** for mitochondrial β-oxidation. Long-chain fatty acids are transported into mitochondria and sequentially oxidised to generate acetyl-CoA, nicotinamide adenine dinucleotide (NADH), and flavin adenine dinucleotide ($FADH_2$), which supply electrons to the electron transport chain (ETC). These reducing equivalents drive proton pumping across the inner mitochondrial membrane, creating the electrochemical gradient required for UCP1-mediated heat production.

Second, free fatty acids function as **allosteric activators of UCP1.** Under resting conditions, UCP1 activity is inhibited by purine nucleotides such as ATP, ADP, GDP, and GTP. During sympathetic stimulation, increased intracellular concentrations of fatty acids overcome this inhibition by binding directly to UCP1 and promoting proton conductance across the inner mitochondrial membrane. Therefore, fatty acids simultaneously provide the energy source for thermogenesis and activate the molecular machinery responsible for heat generation. This dual role highlights the central importance of lipid metabolism in BAT physiology. Without sufficient fatty acid availability, UCP1 remains largely inactive, and mitochondrial respiration cannot sustain effective non-shivering thermogenesis.

3.2.3. Mitochondrial β-Oxidation

Following lipolysis, long-chain fatty acids are transported into mitochondria through the **carnitine shuttle,** a highly regulated transport system comprising **carnitine palmitoyltransferase-1 (CPT1),** carnitine-acylcarnitine translocase (CACT), and **carnitine palmitoyltransferase-2 (CPT2).**

CPT1, located on the outer mitochondrial membrane, catalyses the formation of fatty acyl-carnitine, which is subsequently transported across the inner mitochondrial membrane by CACT. CPT2 reconverts fatty acyl-carnitine into fatty acyl-CoA within the mitochondrial matrix, enabling entry into the β-oxidation pathway. Each cycle of β-oxidation shortens the fatty acid chain by two carbon atoms while generating one molecule each of acetyl-CoA, NADH, and $FADH_2$. Acetyl-CoA enters the tricarboxylic acid (TCA) cycle, whereas NADH and $FADH_2$ donate electrons to the ETC. In BAT, however, the energy stored in the proton gradient is dissipated by UCP1 rather than being used primarily for ATP synthesis, allowing continuous conversion of chemical energy into heat. The exceptionally high rates of β-oxidation observed in activated BAT explain the dramatic increase in oxygen consumption during cold exposure. Human indirect calorimetry studies consistently demonstrate significant elevations in resting energy expenditure following mild cold exposure, reflecting increased mitochondrial substrate oxidation within BAT.

3.2.4. Uptake of Circulating Lipids

Although intracellular triglycerides provide an immediate source of fuel, prolonged thermogenesis requires continuous replenishment of metabolic substrates from the circulation. BAT expresses high levels of **lipoprotein lipase (LPL**) on its capillary endothelium. LPL hydrolyses triglycerides present in circulating chylomicrons and very-low-density lipoproteins (VLDL), releasing fatty acids that are subsequently taken up by brown adipocytes. This process enables BAT to utilise dietary lipids and circulating triglycerides as additional energy sources during sustained cold exposure. Specific membrane transport proteins, including **cluster of differentiation 36 (CD36)** and **fatty acid transport proteins (FATPs),** facilitate efficient cellular uptake of circulating fatty acids. Once inside the cell, these fatty acids may either undergo immediate oxidation or be temporarily stored within lipid droplets for later utilisation. Maintaining this dynamic equilibrium between lipid uptake, storage, mobilisation, and oxidation guarantees that BAT retains ample fuel reserves even during extended activation.

3.2.5. Glucose Metabolism During Thermogenesis

Although fatty acids constitute the principal fuel for BAT, glucose metabolism also increases markedly during cold exposure. Human ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) studies consistently demonstrate substantial increases in glucose uptake within BAT following acute cold exposure, making BAT one of the most glucose-consuming tissues under these conditions.

Glucose enters brown adipocytes primarily through GLUT1 and GLUT4 transporters. β_3-adrenergic signalling stimulates glucose uptake independently of insulin, while insulin further enhances glucose transport during the postprandial state. Once inside the cell, glucose contributes to glycolysis, producing pyruvate that enters the mitochondria for oxidative metabolism. Glucose-derived intermediates also support glycerol synthesis, nucleotide production, and other biosynthetic pathways required for sustained cellular activity. The simultaneous utilisation of glucose and fatty acids demonstrates the remarkable metabolic flexibility of BAT. Rather than relying exclusively on a single substrate, brown adipocytes rapidly adjust fuel utilisation according to nutrient availability and thermogenic demand.

3.2.6. Integration of Lipid and Glucose Metabolism

Cold-induced BAT activation requires precise coordination

between carbohydrate and lipid metabolism. Fatty acid oxidation provides the majority of reducing equivalents required for heat generation, whereas glucose supports rapid ATP production for essential cellular processes, replenishes tricarboxylic acid cycle intermediates, and contributes to lipid synthesis when necessary. Recent metabolomic studies have further demonstrated that BAT can oxidise additional substrates, including **branched-chain amino acids (BCAAs)**, lactate, acetate, ketone bodies, and certain amino acids, particularly during prolonged cold exposure. This metabolic versatility allows BAT to maintain thermogenesis even when the availability of individual substrates fluctuates. Furthermore, enhanced mitochondrial biogenesis and increased expression of oxidative enzymes during chronic cold acclimation improve substrate utilisation efficiency, enabling BAT to sustain elevated rates of heat production while minimising metabolic stress.

3.2.7. Physiological Significance

Efficient lipolysis and fatty acid oxidation are fundamental to the thermogenic function of BAT. By rapidly mobilising intracellular triglycerides, increasing uptake of circulating nutrients, and accelerating mitochondrial oxidation, BAT generates the enormous quantities of reducing equivalents required for continuous UCP1-mediated proton leak. These metabolic adaptations not only preserve body temperature during cold exposure but also substantially increase whole-body energy expenditure and contribute to systemic metabolic homeostasis. Current evidence suggests that the coordinated regulation of lipid metabolism, glucose utilisation, and mitochondrial function enables BAT to operate as a highly specialised metabolic organ rather than merely a passive heat-producing tissue. Understanding these pathways provides critical insight into the molecular physiology of thermogenesis and establishes the basis for the transcriptional regulatory mechanisms that govern BAT differentiation, maintenance, and adaptive remodelling, discussed in the following section.

3.3. Transcriptional Regulation of Brown Adipose Tissue Thermogenesis

Acute activation of brown adipose tissue (BAT) during cold exposure depends primarily on sympathetic stimulation and uncoupling protein 1 (UCP1)-mediated mitochondrial uncoupling. However, prolonged or repeated cold exposure requires more than transient activation of existing thermogenic machinery. Brown adipocytes must undergo extensive transcriptional and structural remodelling to sustain elevated heat production over time. This adaptive response is orchestrated by a highly integrated network of transcription factors, coactivators, and epigenetic regulators that coordinate mitochondrial biogenesis, lipid metabolism, angiogenesis, and thermogenic gene expression. Rather than functioning independently, these regulators form interconnected signalling networks that determine brown adipocyte identity and maintain the thermogenic phenotype throughout adult life.

3.1. Peroxisome Proliferator-Activated Receptor Gamma (PPARγ)

Among the transcriptional regulators of adipose tissue biology, **peroxisome proliferator-activated receptor gamma (PPARγ)** is regarded as the master regulator of adipocyte differentiation. PPARγ belongs to the nuclear receptor superfamily and is expressed in both white and brown adipocytes. While it is indispensable for the formation of all adipose tissue, its activity in BAT is modified through interactions with brown fat-specific cofactors that direct differentiation toward a thermogenic phenotype. PPARγ functions by binding to specific DNA sequences known as **peroxisome proliferator response elements (PPREs)** within the promoter regions of target genes. Following ligand activation, PPARγ forms heterodimers with the retinoid X receptor (RXR), recruiting transcriptional coactivators that initiate expression of genes involved in lipid uptake, triglyceride synthesis, fatty acid metabolism, mitochondrial function, and insulin sensitivity. During cold exposure, β_3-adrenergic signalling enhances PPARγ activity both directly and indirectly through increased expression of transcriptional coactivators such as **PGC-1α** and **PRDM16.** This interaction promotes the expression of thermogenic genes, including **UCP1, CIDEA, FABP4,** and enzymes involved in fatty acid oxidation. Consequently, PPARγ not only maintains adipocyte differentiation but also contributes significantly to the metabolic remodelling necessary for sustained thermogenesis.

3.2. PR Domain-Containing Protein 16 (PRDM16)

One of the defining molecular regulators distinguishing brown adipocytes from white adipocytes is **PR domain-containing protein 16 (PRDM16).** PRDM16 is considered the principal determinant of brown adipocyte lineage commitment and thermogenic identity.

Unlike PPARγ, which is broadly expressed in adipose tissue, PRDM16 exhibits relatively selective expression in thermogenic adipocytes. It functions as a transcriptional coregulator rather than a conventional DNA-binding transcription factor. PRDM16 interacts with multiple transcription factors, including PPARγ, CCAAT/enhancer-binding proteins (C/EBPs), and PGC-1α, forming transcriptional complexes that activate brown fat-specific genes while simultaneously suppressing white adipocyte gene expression. Experimental studies have demonstrated that overexpression of PRDM16 can convert white adipocyte precursors into thermogenically active beige adipocytes, whereas deletion of PRDM16 significantly impairs BAT development, mitochondrial biogenesis, and UCP1 expression. During prolonged cold exposure, sympathetic activation increases PRDM16 activity, promoting maintenance of brown adipocyte morphology, mitochondrial abundance, and oxidative capacity. PRDM16 also suppresses inflammatory and fibrotic signalling pathways that could otherwise compromise BAT function. This dual role—promoting thermogenesis while inhibiting detrimental cellular programmes ghlights its importance in preserving BAT integrity during chronic cold adaptation.

3.3. Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1 Alpha (PGC-1α)

Among the molecular regulators of thermogenesis, **PGC-1α** occupies a central position because it links sympathetic stimulation directly to mitochondrial adaptation. Unlike conventional transcription factors, PGC-1α does not bind DNA directly; instead, it functions as a transcriptional coactivator that interacts with numerous nuclear receptors and transcription factors. Cold exposure rapidly increases PGC-1α expression through activation of the β_3-adrenergic–cAMP–protein kinase A (PKA) signalling pathway. Activated PKA phosphorylates cAMP response element-binding protein (CREB), which subsequently stimulates transcription of the **PPARGC1A** gene encoding PGC-1α.

Once synthesised, PGC-1α coordinates multiple aspects of BAT physiology, including:

- Induction of UCP1 transcription.
- Stimulation of mitochondrial biogenesis.
- Enhancement of oxidative phosphorylation.
- Promotion of fatty acid oxidation.
- Increased expression of antioxidant enzymes.
- Regulation of glucose metabolism.
- Improvement of mitochondrial respiratory efficiency.

PGC-1α interacts with nuclear **respiratory factors 1 and 2 (NRF-1 and NRF-2)**, stimulating expression of numerous mitochondrial proteins encoded by nuclear DNA. It also activates **mitochondrial transcription factor A (TFAM)**, which regulates replication and transcription of mitochondrial DNA. These coordinated actions substantially increase mitochondrial number, respiratory capacity, and thermogenic potential during chronic cold exposure.

3.4. CCAAT/Enhancer-Binding Proteins (C/EBPs)

The **CCAAT/enhancer-binding protein (C/EBP)** family, particularly **C/EBPβ,** plays an essential role during the early stages of brown adipocyte differentiation. C/EBPβ cooperates closely with PRDM16 to promote commitment of precursor cells toward the brown adipocyte lineage. It activates genes involved in adipogenesis, lipid storage, and mitochondrial metabolism while simultaneously enhancing expression of PPARγ and PGC-1α. xperimental studies demonstrate that reduced C/EBPβ expression significantly impairs BAT development and decreases UCP1 expression, indicating that this transcription factor is required not only during embryonic development but also for maintaining BAT function throughout adulthood.

3.5. Nuclear Respiratory Factors and Mitochondrial Biogenesis

Efficient thermogenesis requires an exceptionally large mitochondrial population capable of sustaining high rates of oxidative metabolism. This demand is met through coordinated regulation by **NRF-1, NRF-2,** and **TFAM.**

Following activation by PGC-1α, NRF-1 and NRF-2 stimulate transcription of genes encoding electron transport chain complexes, mitochondrial ribosomal proteins, ATP synthase subunits, and enzymes involved in oxidative phosphorylation. TFAM subsequently promotes replication and maintenance of mitochondrial DNA, ensuring adequate synthesis of mitochondrially encoded respiratory proteins. Cold acclimation therefore results in a dramatic increase in mitochondrial density, enlarged cristae surface area, and enhanced respiratory enzyme activity, allowing BAT to sustain prolonged thermogenesis without compromising cellular energy homeostasis.

3.6. Epigenetic Regulation of Brown Adipocyte Identity

Recent advances in epigenomics have demonstrated that BAT function is regulated not only by transcription factors but also by **epigenetic mechanisms,** including DNA methylation, histone modifications, chromatin remodelling, and non-coding RNAs. Histone acetyltransferases promote transcription by increasing chromatin accessibility around thermogenic genes, whereas histone deacetylases (HDACs) suppress expression of UCP1 and other mitochondrial genes. Cold exposure shifts this balance toward increased histone acetylation, facilitating transcription of thermogenic pathways.

MicroRNAs (miRNAs) further regulate BAT differentiation by controlling translation of key transcription factors. For example:

- **miR-133** suppresses PRDM16 expression and inhibits brown adipocyte differentiation.
- **miR-155** negatively regulates thermogenic gene expression.
- **miR-196a** promotes beige adipocyte formation by suppressing inhibitory signalling pathways.

These epigenetic mechanisms provide an additional level of regulation that enables BAT to adapt dynamically to prolonged environmental changes.

3.7. Transcriptional Integration During Cold Acclimation

Rather than acting independently, the transcription factors described above function as components of an integrated regulatory network.

Cold exposure activates sympathetic signalling, leading to increased cAMP production and activation of PKA. PKA phosphorylates CREB, stimulating expression of PGC-1α. PGC-1α then cooperates with PPARγ and PRDM16 to activate UCP1 transcription, mitochondrial biogenesis, oxidative metabolism, and fatty acid oxidation. Simultaneously, C/EBPβ supports adipocyte differentiation, while NRF-1, NRF-2, and TFAM expand mitochondrial content. Epigenetic regulators modify chromatin accessibility to ensure sustained transcriptional activation during prolonged cold exposure This coordinated regulatory system enables BAT to undergo adaptive remodelling characterised by:

- Increased UCP1 expression.
- Expansion of mitochondrial number.
- Enhanced oxidative enzyme activity.
- Greater fatty acid oxidation.
- Improved vascularisation.
- Increased sympathetic responsiveness.
- Maintenance of brown adipocyte phenotype.

Collectively, these adaptations significantly enhance thermogenic efficiency during repeated cold exposure.

3.8. Summary

The remarkable thermogenic capacity of BAT depends not only on acute activation of UCP1 but also on an intricate transcriptional network that establishes and maintains the brown adipocyte phenotype. PPARγ governs adipocyte differentiation; PRDM16 specifies thermogenic identity; PGC-1α coordinates mitochondrial biogenesis and oxidative metabolism, while C/EBPβ, NRFs, TFAM, and epigenetic regulators collectively ensure sustained expression of thermogenic genes. Through these integrated mechanisms, BAT exhibits extraordinary cellular plasticity, allowing rapid adaptation to repeated cold exposure and long-term maintenance of non-shivering thermogenesis. Understanding this transcriptional architecture provides the molecular basis for appreciating how endocrine signals and environmental factors further modulate BAT activity, which will be explored in the next section.

3.9. Emerging Molecular Regulators and Integration of Thermogenesis

Although the sympathetic nervous system and uncoupling protein 1 (UCP1) remain the central components of brown adipose tissue (BAT) thermogenesis, recent advances in molecular biology have demonstrated that heat production is regulated by a far more complex and interconnected network than previously recognised. Over the past decade, transcriptomic, proteomic, metabolomic, and single-cell sequencing studies have revealed numerous molecular regulators that coordinate mitochondrial function, cellular metabolism, endocrine communication, and tissue remodelling during cold exposure. These discoveries have transformed the understanding of BAT from a passive heat-producing organ into a highly dynamic metabolic and endocrine tissue capable of integrating neural, hormonal, nutritional, and environmental signals to maintain thermal homeostasis.

3.10. Reactive Oxygen Species as Physiological Signalling Molecules

Reactive oxygen species (ROS) were traditionally regarded as harmful by-products of mitochondrial respiration that caused oxidative damage to proteins, lipids, and DNA. However, contemporary research has demonstrated that moderate increases in mitochondrial ROS serve as essential intracellular signalling molecules during BAT activation. Cold exposure markedly accelerates mitochondrial respiration due to increased substrate oxidation and UCP1-mediated proton leak. Although mitochondrial uncoupling generally reduces excessive electron leakage, transient increases in ROS production occur during the initiation of thermogenesis. Rather than inducing cellular injury, these ROS activate redox-sensitive signalling pathways that promote adaptive responses.

ROS influence several key regulators of BAT physiology, including the following:

- Activation of PGC-1α-mediated mitochondrial biogenesis.
- Enhancement of antioxidant defence systems.
- Regulation of mitochondrial protein turnover.
- Modulation of lipid metabolism.
- Maintenance of mitochondrial quality control.

To prevent oxidative damage during sustained thermogenesis, BAT expresses high levels of endogenous antioxidant enzymes, including **superoxide dismutase (SOD), catalase,** and **glutathione peroxidase.** This antioxidant network maintains redox homeostasis while allowing ROS to function as physiological signalling molecules rather than toxic metabolic products.

3.11. Mitochondrial Dynamics and Quality Control

The remarkable thermogenic capacity of BAT depends not only on mitochondrial number but also on continuous regulation of mitochondrial morphology and quality.

Mitochondria undergo constant cycles of fusion and fission, processes collectively referred to as mitochondrial dynamics. Fusion allows exchange of mitochondrial contents, improving respiratory efficiency and protecting against oxidative stress, whereas fission facilitates removal of damaged mitochondria through selective autophagy (mitophagy).

Several proteins regulate these processes:

- **Mitofusin-1 (MFN1)**
- **Mitofusin-2 (MFN2)**
- **Optic atrophy protein 1 (OPA1)**
- **Dynamin-related protein 1 (DRP1)**

Cold exposure promotes dynamic remodelling of mitochondrial networks, ensuring that mitochondria remain structurally intact despite exceptionally high rates of oxidative metabolism. Simultaneously, damaged mitochondria are selectively removed through **PINK1–Parkin-mediated mitophagy,** preventing accumulation of dysfunctional organelles that could impair thermogenic efficiency. These quality-control mechanisms preserve mitochondrial integrity during prolonged cold acclimation and contribute significantly to sustained BAT function.

3.12. Calcium Signalling in Brown Adipocytes

Intracellular calcium (Ca^{2+}) has emerged as another important regulator of BAT activation.

Cold-induced β_3-adrenergic stimulation influences intracellular calcium concentrations through multiple signalling pathways. Calcium regulates:

- Mitochondrial enzyme activity.
- ATP production.
- Lipolysis.
- Gene transcription.
- Mitochondrial biogenesis.

Within mitochondria, calcium stimulates several enzymes of the tricarboxylic acid (TCA) cycle, increasing production of NADH and $FADH_2$ required for oxidative phosphorylation. Calcium also activates calcium/calmodulin-dependent protein kinase (CaMK), which enhances expression of PGC-1α and promotes mitochondrial adaptation during chronic cold exposure. Recent studies suggest that coordinated interactions between calcium signalling and β_3-adrenergic pathways optimise thermogenic efficiency while maintaining

cellular energy balance.

3.13. Endocrine Function of Brown Adipose Tissue: Batokines

One of the most significant recent discoveries in BAT physiology is its recognition as an endocrine organ. Activated BAT secretes numerous biologically active signalling molecules collectively termed 'batokines', which exert autocrine, paracrine, and endocrine effects on distant organs. Unlike classical hormones produced by endocrine glands, batokines are released in response to thermogenic activation and contribute to systemic metabolic regulation.

Several batokines have been identified, including:

- **Fibroblast growth factor 21 (FGF21)**.
- **Neuregulin 4 (NRG4)**.
- **nInterleukin-6 (IL-6).**
- **nCXCL14.**
- **nGrowth differentiation factor 15 (GDF15).**

These molecules influence multiple physiological processes, including hepatic lipid metabolism, skeletal muscle energy utilisation, pancreatic insulin secretion, immune cell function, and central regulation of energy balance. Although the precise physiological importance of individual batokines remains under investigation, increasing evidence indicates that BAT communicates extensively with other organs, allowing coordinated metabolic adaptation during cold exposure.

3.14. Integration of Nutrient Sensing Pathways

Thermogenesis requires continuous adjustment according to nutrient availability.

BAT integrates multiple nutrient-sensing pathways, including:

- **AMP-activated protein kinase (AMPK).**
- **Mechanistic target of rapamycin (mTOR).**
- **Sirtuin-1 (SIRT1).**
- **Insulin signalling.**

AMPK functions as the cellular energy sensor. During increased energy demand, AMPK stimulates fatty acid oxidation, enhances mitochondrial biogenesis, and promotes glucose uptake while inhibiting energy-consuming anabolic pathways. Conversely, mTOR coordinates protein synthesis, mitochondrial growth, and cellular remodelling when nutrients are abundant.

SIRT1 further regulates BAT by deacetylating PGC-1α, thereby increasing mitochondrial function and oxidative metabolism during prolonged cold exposure. The coordinated interaction among AMPK, mTOR, and SIRT1 enables BAT to adjust thermogenic activity according to both environmental temperature and nutritional status.

3.15. Browning of White Adipose Tissue

Chronic cold exposure not only activates classical BAT but also induces the formation of **beige (brite) adipocytes** within white adipose tissue (WAT), a process commonly referred to as **browning.** Beige adipocytes originate from distinct precursor populations rather than from classical brown adipocyte lineages. Following sustained sympathetic stimulation, these cells begin expressing:

- UCP1.
- PGC-1α.
- PRDM16.
- Mitochondrial oxidative enzymes.

Although beige adipocytes generally exhibit lower basal thermogenic activity than classical brown adipocytes, they significantly expand whole-body thermogenic capacity during prolonged cold adaptation.

The browning response illustrates the remarkable plasticity of adipose tissue and highlights the body's ability to recruit additional thermogenic cells in response to environmental demands.

3.16. Integrated Regulation of Thermogenesis

Current understanding indicates that BAT thermogenesis cannot be explained by a single signalling pathway. Instead, effective heat production results from the integration of multiple physiological systems. Cold exposure activates cutaneous thermoreceptors, initiating hypothalamic signalling and sympathetic stimulation. Norepinephrine released from sympathetic nerve terminals activates β_3-adrenergic receptors, leading to cAMP production, protein kinase A activation, lipolysis, and UCP1-mediated mitochondrial uncoupling. Simultaneously, transcriptional regulators including PPARγ, PRDM16, and PGC-1α increase mitochondrial biogenesis and thermogenic gene expression. ROS and calcium signalling further optimise mitochondrial function, while AMPK, SIRT1, and mTOR coordinate cellular metabolism according to nutrient availability. Batokines mediate communication between BAT and peripheral organs, whereas mitochondrial quality-control mechanisms preserve organelle integrity during prolonged thermogenesis.

The interaction of these pathways enables BAT to respond rapidly to acute cold exposure while maintaining efficient heat production during chronic cold acclimation.

3.17. Summary

Recent advances in molecular physiology have revealed that BAT is far more than a collection of UCP1-rich mitochondria. It is a highly adaptive endocrine and metabolic organ regulated by complex interactions among mitochondrial dynamics, redox signalling, calcium homeostasis, nutrient-sensing pathways, transcriptional networks, and inter-organ communication. These integrated molecular mechanisms ensure that thermogenesis remains efficient, sustainable, and responsive to changing environmental and metabolic conditions. Understanding these emerging regulatory pathways not only advances knowledge of human thermoregulation but also provides a foundation for future investigations into the physiological adaptability of brown adipose tissue and its role in maintaining whole-body energy homeostasis.

4. Regulation of Brown Adipose Tissue Activation

4.1. Cold-Induced Signalling Pathways in Brown Adipose Tissue Activation

The activation of brown adipose tissue (BAT) during cold exposure is governed by a highly coordinated network of neural, intracellular, and molecular signalling pathways that collectively ensure efficient non-shivering thermogenesis (NST). While the sympathetic nervous system (SNS) serves as the primary initiator of BAT activation, sustained thermogenesis depends on the integration of multiple intracellular signalling cascades that regulate gene transcription, mitochondrial metabolism, lipid mobilisation, and cellular adaptation. These signalling pathways enable brown adipocytes to rapidly respond to acute decreases in environmental temperature while simultaneously undergoing long-term structural and functional remodelling during repeated cold exposure.

4.2. Cold Sensing and Central Thermoregulatory Signalling

Cold-induced BAT activation begins with the detection of environmental temperature changes by **cutaneous thermoreceptors** located within the skin. These specialised sensory receptors express members of the **transient receptor potential (TRP) ion channel family,** particularly **TRPM8,** which responds to moderate cooling (approximately 10–28°C), and **TRPA1**, which is activated under more extreme cold conditions. Activation of these receptors generates action potentials that are transmitted through primary sensory neurones to the dorsal horn of the spinal cord. From the spinal cord, thermal information ascends to several brain regions involved in thermoregulation, with the **preoptic area (POA**) of the anterior hypothalamus serving as the principal integrative centre. The POA continuously compares peripheral skin temperature with core body temperature and initiates appropriate autonomic responses when heat loss exceeds heat production. Neurones within the POA project to the **dorsomedial hypothalamus (DMH),** which amplifies thermogenic signals under cold conditions. The DMH subsequently activates sympathetic premotor neurones located in the **rostral raphe pallidus (rRPa)** of the medulla oblongata. Descending pathways from the rRPa synapse with sympathetic preganglionic neurones in the intermediolateral cell column of the thoracic spinal cord. These neurones then activate postganglionic sympathetic fibres that densely innervate BAT, establishing the neural pathway responsible for cold-induced thermogenesis.

This central thermoregulatory network ensures that BAT activation is proportional to the severity and duration of cold exposure, preventing unnecessary energy expenditure while maintaining core body temperature.

4.3. β_3-Adrenergic Receptor Signalling

The **β_3-adrenergic receptor (β_3-AR)** is the principal receptor responsible for mediating sympathetic activation of BAT. Following cold exposure, sympathetic nerve terminals release **norepinephrine (NE)** directly into BAT. NE binds predominantly to β_3-ARs expressed on the plasma membrane of brown adipocytes, initiating one of the most extensively studied signalling pathways in thermogenic physiology. β_3-AR belongs to the G protein-coupled receptor (GPCR) superfamily. Upon ligand binding, the receptor activates the stimulatory G protein (Gs), which in turn stimulates **adenylyl cyclase.** Activated adenylyl cyclase catalyses the conversion of ATP into **cyclic adenosine monophosphate (cAMP),** a second messenger that coordinates numerous intracellular responses. Elevated intracellular cAMP concentrations **activate protein kinase A (PKA),** initiating a signalling cascade that simultaneously regulates metabolism, mitochondrial function, and gene expression.

4.4. Protein Kinase A (PKA) as the Central Intracellular Regulator

PKA functions as the master intracellular regulator of BAT activation by phosphorylating numerous downstream target proteins involved in thermogenesis. One of its earliest actions is phosphorylation of **perilipin-1**, a protein coating intracellular lipid droplets. Phosphorylated perilipin undergoes conformational changes that permit lipolytic enzymes to access stored triglycerides. PKA also phosphorylates **hormone-sensitive lipase (HSL),** increasing its catalytic activity and promoting hydrolysis of triglycerides into free fatty acids (FFAs). These FFAs serve both as mitochondrial fuel and as direct activators of UCP1. Beyond lipid metabolism, PKA phosphorylates the cAMP response element-binding protein **($_c$REB). Activated CREB** translocates to the nucleus, where it binds specific DNA sequences known as cAMP response elements (CREs), promoting transcription of genes involved in thermogenesis, mitochondrial biogenesis, and oxidative metabolism. Among the most important CREB-regulated genes are **PGC-1α, UCP1,** and enzymes required for fatty acid oxidation. Through these coordinated actions, PKA links acute sympathetic stimulation with both immediate heat production and long-term transcriptional adaptation.

4.5. Mitogen-Activated Protein Kinase (MAPK) Signalling

Cold exposure also activates the mitogen-activated protein kinase (MAPK) family, including:

- Extracellular signal-regulated kinase (ERK)
- c-Jun N-terminal kinase (JNK)
- p38 MAPK

Among these pathways, **p38 MAPK** is particularly important for BAT thermogenesis.

PKA-mediated activation of p38 MAPK enhances phosphorylation of transcription factors and coactivators involved in mitochondrial biogenesis, most notably **PGC-1α** and **activating transcription factor 2 (ATF2).** Phosphorylated ATF2 binds to regulatory regions of the **UCP1** gene, increasing transcription and expanding thermogenic capacity during prolonged cold exposure. MAPK signalling also contributes to mitochondrial remodelling, angiogenesis, and cellular adaptation during chronic cold acclimation, demonstrating that thermogenesis requires coordinated regulation of multiple intracellular pathways rather than simple activation of UCP1 alone.

4.6. cAMP–CREB–PGC-1α Signalling Axis

Among the numerous intracellular pathways activated

during cold exposure, the **cAMP–CREB–PGC-1α** signalling axis represents one of the most critical regulators of long-term BAT adaptation. Following phosphorylation by PKA, CREB stimulates expression of **PGC-1α,** a transcriptional coactivator that coordinates mitochondrial biogenesis and oxidative metabolism. PGC-1α subsequently interacts with multiple nuclear transcription factors, including PPARγ, oestrogen-related receptors (ERRs), and nuclear respiratory factors (NRFs), promoting expression of genes involved in the following:

- Mitochondrial DNA replication.
- Electron transport chain assembly.
- Fatty acid β-oxidation.
- Oxidative phosphorylation.
- UCP1 synthesis.
- Antioxidant defence mechanisms.

The result is a substantial increase in mitochondrial content, respiratory capacity, and thermogenic efficiency during repeated cold exposure.

4.7. AMP-Activated Protein Kinase (AMPK) Signalling

Because BAT consumes enormous quantities of metabolic substrates during thermogenesis, intracellular energy status must be continuously monitored. This role is performed primarily by **AMP-activated protein kinase (AMPK),** which functions as the cellular energy sensor.

During prolonged thermogenesis, ATP consumption increases while intracellular AMP concentrations rise. Elevated AMP activates AMPK, which restores energy balance through several mechanisms:

- Stimulation of fatty acid oxidation.
- Increased glucose uptake.
- Promotion of mitochondrial biogenesis.
- Inhibition of fatty acid synthesis.
- Suppression of energy-consuming anabolic pathways.

AMPK also enhances PGC-1α activity, providing an important link between cellular energy availability and mitochondrial adaptation.

4.8. PI3K–Akt Signalling Pathway

Although β_3-adrenergic signalling predominates during cold exposure, **the phosphatidylinositol 3-kinase (PI3K)–Akt pathway** also contributes to BAT regulation, particularly in the presence of insulin. Activation of PI3K stimulates phosphorylation of **Akt (protein kinase B)**, which promotes the following:

- Glucose transporter (GLUT4) translocation.
- Increased glucose uptake.
- Glycogen metabolism.
- Cell survival.
- Protein synthesis.

Cross-talk between insulin signalling and β_3-adrenergic pathways allows BAT to integrate nutritional status with thermogenic demand, ensuring sufficient substrate availability during prolonged cold exposure.

4.9. Integration of Cold-Induced Signalling Networks

Although each signalling pathway has distinct physiological functions, effective BAT activation requires their coordinated interaction. Cold exposure initiates sympathetic stimulation, leading to β_3-adrenergic receptor activation and increased cAMP production. PKA simultaneously stimulates lipolysis, activates CREB, phosphorylates MAPKs, and increases mitochondrial metabolism. AMPK continuously monitors intracellular energy availability, whereas PI3K–Akt signalling adjusts glucose utilisation according to nutritional status. Together, these pathways converge on transcriptional regulators such as **PGC-1α, PPARγ,** and **PRDM16,** ultimately increasing UCP1 expression, mitochondrial biogenesis, and oxidative capacity. This integrated signalling network enables BAT to generate heat efficiently while maintaining cellular energy homeostasis and adapting to prolonged cold exposure. Rather than functioning as isolated pathways, these molecular mechanisms operate as a coordinated physiological system that links environmental temperature sensing to mitochondrial thermogenesis.

4.10. Summary

Cold-induced activation of BAT is initiated by neural detection of reduced environmental temperature and propagated through sympathetic β_3-adrenergic signalling. Intracellular pathways involving cAMP, PKA, MAPKs, CREB, AMPK, and PI3K–Akt collectively regulate lipolysis, mitochondrial metabolism, gene transcription, and cellular remodelling. The integration of these signalling networks ensures that brown adipocytes respond rapidly to acute cold exposure while maintaining long-term thermogenic competence through adaptive molecular remodelling. These pathways also establish the framework through which endocrine factors modulate BAT activity, which will be discussed in the following subsection on hormonal regulation.

4.10.1. Hormonal Regulation of Brown Adipose Tissue Activation

Although the sympathetic nervous system (SNS) is the primary physiological regulator of brown adipose tissue (BAT) activation during cold exposure, optimal thermogenesis depends on the coordinated actions of several endocrine factors. Hormones regulate virtually every aspect of BAT physiology, including brown adipocyte differentiation, mitochondrial biogenesis, substrate utilisation, lipid mobilisation, glucose metabolism, and uncoupling protein 1 (UCP1) expression. Rather than functioning independently, these hormonal signals interact extensively with β_3-adrenergic signalling pathways, allowing BAT to integrate environmental temperature with the body's nutritional and metabolic status. The endocrine regulation of BAT ensures that thermogenesis is not only initiated rapidly during acute cold exposure but also maintained efficiently during prolonged cold acclimation.

4.11. Thyroid Hormones

Among all endocrine regulators of BAT, **thyroid hormones** are considered the most important modulators of thermogenic capacity. The biologically active hormone **triiodothyronine (T3)** and its precursor **thyroxine (T4)** exert profound effects

on basal metabolic rate, mitochondrial function, and heat production. Cold exposure stimulates the hypothalamic–pituitary–thyroid (HPT) axis, increasing thyroid hormone availability. Within BAT, the enzyme type **II iodothyronine deiodinase (DIO2)** converts circulating T4 into the more biologically active T3. This local conversion is particularly important because intracellular T3 concentrations within BAT often exceed circulating plasma levels during cold acclimation. T3 enters the nucleus and binds to **thyroid hormone receptors (TRα and TRβ)**, which function as ligand-activated transcription factors. These receptors regulate numerous thermogenic genes, including:

- **Uncoupling protein 1 (UCP1)**
- **Peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α)**
- **Carnitine palmitoyltransferase-1 (CPT1)**
- **Mitochondrial respiratory enzymes**
- **Fatty acid oxidation enzymes**

Thyroid hormones also increase mitochondrial number, enhance oxidative phosphorylation, stimulate lipolysis, and improve mitochondrial respiratory efficiency. Furthermore, T3 potentiates sympathetic responsiveness by increasing β_3-adrenergic receptor expression on brown adipocytes, thereby amplifying norepinephrine-mediated thermogenesis. Experimental studies have demonstrated that hypothyroidism significantly reduces BAT activity, UCP1 expression, and adaptive thermogenesis, whereas hyperthyroidism enhances heat production and resting energy expenditure. These observations underscore the indispensable role of thyroid hormones in maintaining normal BAT function.

4.12. Insulin

Although BAT activation is classically associated with fasting-independent sympathetic stimulation, insulin plays a critical role in regulating substrate availability for thermogenesis. **Insulin** binds to its receptor on brown adipocytes, activating the **phosphatidylinositol 3-kinase (PI3K)–Akt** pathway, which promotes translocation of **GLUT4** glucose transporters to the plasma membrane. Increased glucose uptake supplies glycolytic intermediates, supports mitochondrial respiration, and provides glycerol phosphate required for triglyceride synthesis and lipid turnover.

In addition to stimulating glucose metabolism, insulin enhances:

- Lipid uptake from the circulation.
- Glycogen synthesis (to a limited extent).
- Protein synthesis.
- Cell survival.
- Mitochondrial metabolism.

Unlike white adipose tissue, where insulin primarily promotes energy storage, BAT utilises insulin-mediated glucose uptake to sustain thermogenesis during prolonged cold exposure. Recent human imaging studies demonstrate that activated BAT exhibits exceptionally high insulin sensitivity, highlighting its importance in systemic glucose homeostasis.

Furthermore, insulin signalling interacts synergistically with β_3-adrenergic pathways, ensuring adequate substrate delivery during periods of increased thermogenic demand.

4.13. Catecholamines

The catecholamines **norepinephrine (NE)** and **epinephrine** represent the immediate hormonal mediators of cold-induced BAT activation. Although norepinephrine is released primarily as a neurotransmitter from sympathetic nerve terminals, it also functions as a local neurohormone within BAT. Binding of NE to β_3-adrenergic receptors initiates the cAMP–protein kinase A (PKA) signalling cascade responsible for:

- Lipolysis.
- Fatty acid oxidation.
- UCP1 activation.
- Mitochondrial uncoupling.
- Mitochondrial biogenesis.
- Increased glucose uptake.

Circulating epinephrine released from the adrenal medulla contributes to systemic metabolic responses during prolonged cold exposure, including hepatic glycogenolysis, increased cardiac output, and enhanced lipolysis in white adipose tissue, thereby supplying additional substrates for BAT. Together, catecholamines coordinate both local BAT activation and whole-body metabolic adaptation to cold.

4.14. Fibroblast Growth Factor 21 (FGF21)

Fibroblast growth factor 21 (FGF21) has emerged as one of the most important endocrine regulators of adaptive thermogenesis. Originally identified as a liver-derived hormone, FGF21 is now recognised as a **batokine,** being produced by activated BAT as well as the liver and skeletal muscle. Cold exposure markedly increases FGF21 expression through sympathetic stimulation and activation of PGC-1α.

FGF21 binds to fibroblast growth factor receptors (FGFRs) in the presence of the co-receptor **β-Klotho,** activating intracellular pathways that promote:

- Mitochondrial biogenesis.
- UCP1 expression.
- Fatty acid oxidation.
- Glucose uptake.
- Browning of white adipose tissue.
- Improved metabolic flexibility.

FGF21 also facilitates communication between BAT and other organs, including the liver, pancreas, skeletal muscle, and central nervous system. This endocrine cross-talk coordinates nutrient metabolism during prolonged cold exposure and enhances whole-body energy homeostasis.

4.15. Irisin

Irisin is a peptide hormone released predominantly from skeletal muscle during physical exercise but is also influenced by cold exposure. Irisin is generated through proteolytic cleavage of **fibronectin type III domain-containing protein 5 (FNDC5)** and is regulated by PGC-1α. Experimental studies indicate that irisin stimulates the

differentiation of beige adipocytes within white adipose tissue by increasing expression of:

- PRDM16.
- PGC-1α.
- UCP1.
- Mitochondrial oxidative enzymes.

Although the physiological significance of circulating irisin in humans remains an area of active investigation, current evidence suggests that it contributes to adaptive thermogenesis by expanding whole-body thermogenic capacity during chronic cold exposure.

4.16. Glucocorticoids

The influence of glucocorticoids, particularly cortisol, on BAT is considerably more complex than that of other hormones. Acute increases in glucocorticoid concentrations may transiently support energy mobilisation during stress by increasing circulating glucose and free fatty acid availability. However, chronic elevations in cortisol generally suppress BAT activity by:

- Reducing UCP1 expression.
- Inhibiting mitochondrial biogenesis.
- Decreasing β_3-adrenergic sensitivity.
- Promoting lipid accumulation.
- Suppressing thermogenic gene transcription.

Consequently, prolonged glucocorticoid excess is associated with reduced adaptive thermogenesis and impaired metabolic flexibility.

4.17. Natriuretic Peptides

Cardiac-derived **atrial natriuretic peptide (ANP)** and **brain natriuretic peptide (BNP)** have recently been recognised as important modulators of BAT physiology. Binding of ANP and BNP to natriuretic peptide receptor-A (NPR-A) activates cyclic guanosine monophosphate (cGMP) signalling and **protein kinase G (PKG).** This pathway stimulates lipolysis, mitochondrial biogenesis, and UCP1 expression independently of β_3-adrenergic signalling. The natriuretic peptide pathway provides an alternative mechanism through which cardiovascular function can influence thermogenic activity, particularly during conditions associated with increased cardiac workload.

4.18. Leptin and Adiponectin

Adipose-derived hormones also influence BAT regulation.

Leptin, secreted primarily by white adipose tissue, acts centrally within the hypothalamus to enhance sympathetic outflow toward BAT. Through this mechanism, leptin indirectly promotes BAT activation, increases UCP1 expression, and stimulates energy expenditure.

Adiponectin, another adipokine, improves insulin sensitivity and enhances fatty acid oxidation. Although its direct effects on BAT remain incompletely understood, adiponectin appears to support mitochondrial function and metabolic flexibility within brown adipocytes.

4.19. Integrated Endocrine Regulation

The activation of brown adipose tissue after cold exposure is ultimately regulated by the integration of various hormonal signals rather than by a singular endocrine mechanism.

Thyroid hormones regulate the basal thermogenic capability of brown adipose tissue via modulating mitochondrial activity and the expression of UCP1. Catecholamines serve as the immediate trigger for thermogenesis via β_3-adrenergic signalling. Insulin guarantees sufficient glucose availability, whilst FGF21 and irisin facilitate sustained thermogenic adaptation and the browning of white adipose tissue. Natriuretic peptides offer supplementary signalling pathways that augment mitochondrial function, while chronically high glucocorticoids impose inhibitory effects. The interplay of these hormones enables brown adipose tissue to consistently modulate its metabolic function in response to external temperature, dietary status, physical activity, and overall physiological condition. This exceptional endocrine integration allows brown adipose tissue to act as an active regulator of energy expenditure and thermal homeostasis, rather than merely a passive heat-generating organ.

4.20. Summary

Hormonal control is a vital aspect of brown adipose tissue physiology, enhancing thermogenic efficiency with sympathetic nervous system activation. Thyroid hormones, insulin, catecholamines, FGF21, irisin, natriuretic peptides, leptin, adiponectin, and glucocorticoids collaboratively modulate brown adipose tissue (BAT) via integrating neuronal and endocrine signals to govern mitochondrial metabolism, substrate utilisation, and adaptive thermogenesis. These endocrine systems guarantee that heat production is accurately aligned with environmental and metabolic requirements, establishing the foundation for the extensive physiological and environmental regulation of BAT addressed in the subsequent paragraph.

4.21. Environmental and Physiological Modulators of Brown Adipose Tissue Activation

Although sympathetic and endocrine signalling serve as the primary mechanisms for the activation of brown adipose tissue (BAT), the extent and efficacy of thermogenesis differ significantly among individuals. This variability signifies the impact of several environmental and physiological factors that govern BAT quantity, activity, and adaptive potential. Age, sex, genetic predisposition, seasonal variations, circadian rhythms, dietary

condition, physical activity, and prolonged cold acclimatisation all influence the thermogenic capacity of brown adipose tissue (BAT). These modulators affect both the immediate reaction to cold exposure and the long-term structural remodelling of brown adipocytes, therefore determining the overall role of BAT in human thermoregulation.

4.22. Age-Related Changes in Brown Adipose Tissue

Age is one of the strongest physiological determinants of BAT activity. Human newborns possess relatively large amounts of BAT, accounting for approximately 2–5% of total body mass. During the neonatal period, BAT is essential for maintaining body temperature because infants have a high

surface area-to-volume ratio, limited skeletal muscle mass, and an underdeveloped shivering response. Consequently, non-shivering thermogenesis is the primary mechanism by which newborns defend against hypothermia. Although BAT persists throughout adulthood, both its quantity and functional activity decline progressively with advancing age. Imaging studies using **^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT)** consistently demonstrate that younger adults exhibit greater BAT volume, higher glucose uptake, and stronger thermogenic responses to cold compared with older individuals. Several mechanisms contribute to this age-related decline, including:

- Reduced sympathetic nervous system responsiveness.
- Decreased β_3-adrenergic receptor expression.
- Impaired mitochondrial biogenesis.
- Lower UCP1 expression.
- Increased mitochondrial dysfunction.
- Accumulation of oxidative damage.
- Reduced vascularisation and capillary density.
- Diminished progenitor cell differentiation into brown adipocytes.

These age-associated changes collectively reduce the capacity for adaptive thermogenesis and contribute to the decline in resting energy expenditure observed in older adults.

4.23. Sex Differences in BAT Activity

Sex-related differences also influence BAT physiology. Numerous human studies have demonstrated that women generally possess greater BAT activity than men under comparable cold exposure conditions.

Several factors contribute to these differences. Women typically exhibit the following:

- Higher BAT glucose uptake.
- Greater BAT volume.
- Increased expression of thermogenic genes.
- Enhanced cold tolerance.
- Higher mitochondrial density.

The mechanisms underlying these observations are multifactorial. **Oestrogen** enhances mitochondrial biogenesis, improves sympathetic responsiveness, and promotes expression of UCP1 and PGC-1α. Experimental studies indicate that oestrogen receptors within BAT influence lipid metabolism and mitochondrial function, thereby increasing thermogenic efficiency. Conversely, **androgens** appear to exert more variable effects on BAT. Although testosterone contributes to overall metabolic regulation and muscle mass, excessive androgen signalling may suppress certain thermogenic pathways. However, the precise physiological role of sex hormones in adult human BAT remains incompletely understood and continues to be an active area of investigation.

4.24. Seasonal Variation

Environmental temperature profoundly influences BAT activity throughout the year. Human studies consistently demonstrate significantly greater BAT activation during winter than during summer.

Repeated exposure to colder ambient temperatures during winter induces a process known as 'cold acclimatisation', characterised by:

- Increased BAT volume.
- Enhanced UCP1 expression.
- Greater mitochondrial density.
- Increased capillary formation.
- Improved fatty acid oxidation.
- Enhanced glucose uptake.
- Greater sympathetic innervation.

In contrast, prolonged exposure to warm environments reduces sympathetic stimulation, resulting in decreased BAT metabolic activity and partial regression of thermogenic adaptations. Seasonal fluctuations illustrate the remarkable plasticity of BAT and emphasise that thermogenic capacity is dynamically regulated according to environmental conditions rather than remaining constant throughout the year.

4.25. Circadian Regulation

Thermogenesis is also influenced by the body's **circadian clock**, which synchronises physiological processes with the 24-hour light–dark cycle. The **suprachiasmatic nucleus (SCN)** of the hypothalamus serves as the master circadian pacemaker and regulates sympathetic nervous system activity directed toward BAT. Circadian clock genes, including C**LOCK, BMAL1, PER,** and **CRY**, are expressed within brown adipocytes and influence mitochondrial metabolism, lipid utilisation, and UCP1 expression. Experimental studies suggest that BAT thermogenic activity follows daily rhythmic fluctuations, with increased responsiveness occurring during periods corresponding to the organism's active phase. Disruption of circadian rhythms, such as through shift work, irregular sleep patterns, or chronic sleep deprivation, may impair BAT function by reducing sympathetic stimulation, altering hormone secretion, and disrupting metabolic homeostasis. Thus, circadian regulation ensures that thermogenic activity is coordinated with daily variations in energy expenditure and environmental exposure.

4.26. Nutritional Status

Nutrient availability significantly influences BAT activation and metabolic flexibility.

During fasting, sympathetic activity increases lipolysis, mobilising fatty acids that serve as the principal substrates for thermogenesis. However, prolonged caloric restriction may reduce BAT activity by suppressing thyroid hormone production, decreasing insulin secretion, and conserving energy. Following food intake, insulin enhances glucose uptake into BAT, while dietary lipids provide additional substrates for oxidation. Certain nutrients have also been shown to stimulate thermogenesis indirectly. For example:

- Capsaicin and capsinoids activate transient receptor potential vanilloid 1 (TRPV1) channels, increasing sympathetic outflow.
- Caffeine may enhance catecholamine release and modestly increase BAT activity.
- Dietary nitrates have been investigated for their potential

influence on mitochondrial function and thermogenic efficiency.

Although these nutritional factors contribute to BAT regulation, cold exposure remains the most potent physiological activator of thermogenesis.

4.27. Physical Activity

Exercise influences BAT through both direct and indirect mechanisms. During physical activity, skeletal muscle releases numerous signalling molecules known as myokines, including **irisin, interleukin-6 (IL-6),** and **meteorin-like protein (METRNL).** These molecules promote mitochondrial biogenesis and stimulate browning of white adipose tissue, thereby increasing whole-body thermogenic capacity. Exercise also improves insulin sensitivity, enhances mitochondrial function, increases oxidative capacity, and promotes metabolic flexibility, all of which support efficient BAT function. Although exercise-induced thermogenesis differs mechanistically from cold-induced thermogenesis, both processes share several common molecular regulators, particularly PGC-1α and AMPK.

4.28. Genetic Determinants

Genetic variability contributes substantially to interindividual differences in BAT abundance and thermogenic responsiveness.

Polymorphisms affecting genes involved in BAT biology include:

- **UCP1**
- **PPARGC1A (PGC-1α)**
- **PRDM16**
- **β_3-adrenergic receptor (ADRB3)**
- **DIO2**
- **FGF21**

These genetic variations influence mitochondrial function, sympathetic responsiveness, adipocyte differentiation, and substrate metabolism, partially explaining why individuals exhibit markedly different thermogenic responses despite experiencing similar environmental temperatures. Recent genome-wide association studies (GWAS) continue to identify additional loci involved in BAT development and adaptive thermogenesis, suggesting that BAT function is regulated by a highly polygenic network.

4.29. Environmental Pollutants and Lifestyle Factors

Emerging evidence suggests that chronic exposure to environmental pollutants may negatively influence BAT physiology.

Air pollution, cigarette smoking, endocrine-disrupting chemicals, and certain persistent organic pollutants have been associated with:

- Increased oxidative stress.
- Mitochondrial dysfunction.
- Chronic low-grade inflammation.
- Reduced sympathetic responsiveness.
- Impaired thermogenic gene expression.

Similarly, sedentary behaviour and prolonged exposure to thermoneutral indoor environments reduce physiological stimulation of BAT, potentially diminishing thermogenic capacity over time. Conversely, regular exposure to mildly cool environments may help preserve BAT activity through repeated activation and adaptive remodelling.

4.30. Integration of Environmental and Physiological Regulation

The activity of BAT reflects the combined influence of environmental exposure, endocrine regulation, neural signalling, and intrinsic physiological characteristics. Age, sex, seasonal temperature variation, circadian rhythms, nutritional status, physical activity, genetics, and lifestyle factors continuously interact with sympathetic and hormonal pathways to determine the overall thermogenic response. Importantly, these modulators influence not only the immediate activation of BAT but also its long-term structural adaptation, including mitochondrial biogenesis, angiogenesis, sympathetic innervation, and maintenance of brown adipocyte identity. Consequently, BAT should be viewed as a highly plastic tissue that continuously adapts to changing internal and external environments rather than as a static thermogenic organ.

5. Summary

Apart from acute cold exposure, several other physiological and environmental factors dramatically affect brown adipose tissue activation. Age, sex, seasonal adaptation, circadian rhythms, nutrition, exercise, genetic predisposition, and environmental factors all influence BAT quantity, metabolic activity, and thermogenic efficiency. The exceptional plasticity of BAT enables it to assimilate many regulatory inputs, ensuring that heat production is suitably aligned with both external temperature and the body's metabolic needs. Comprehending these modulators offers critical insight into the variability of BAT function in healthy individuals and lays the groundwork for the comprehensive physiological model of adaptive cold acclimation addressed in the subsequent part.

5.1. Integrated Regulation and Adaptive Cold Acclimation

The activation of brown adipose tissue (BAT) is regulated by a complex interplay of neuronal, endocrine, molecular, metabolic, and environmental cues rather than a singular physiological process. This coordinated regulation allows BAT to swiftly react to acute cold exposure while concurrently undergoing long-term structural and functional changes during repeated or sustained cold stress. Adaptive cold acclimation signifies the culmination of these integrated regulatory mechanisms, leading to augmented thermogenic efficiency, heightened metabolic flexibility, and enhanced maintenance of core body temperature. Comprehending the interaction of these varied signalling systems offers an extensive perspective on BAT physiology and demonstrates why thermogenesis is among the most intricate homeostatic mechanisms in human biology.

5.2. Integration of Neural and Endocrine Signalling

The physiological reaction to cold initiates with the activation of peripheral thermoreceptors and central thermoregulatory

pathways in the hypothalamus. Sympathetic stimulation prompts the release of norepinephrine (NE), which activates β_3-adrenergic receptors on brown adipocytes, thereby rapidly inducing lipolysis, mitochondrial respiration, and heat production mediated by uncoupling protein 1 (UCP1). Nonetheless, sympathetic activation alone is inadequate to maintain extended thermogenesis. Hormonal signals, such as thyroid hormones, insulin, fibroblast growth factor 21 (FGF21), irisin, natriuretic peptides, leptin, and adiponectin, perpetually influence brown adipose tissue (BAT) responsiveness by governing mitochondrial biogenesis, nutrient availability, substrate utilisation, and transcriptional activity. These endocrine variables enhance or calibrate sympathetic signalling based on the body's metabolic condition, ensuring that thermogenic activity is commensurate with environmental requirements and energy supply. The amalgamation of neuronal and endocrine pathways allows brown adipose tissue to sustain effective thermogenesis while averting excessive energy expendi ure that may jeopardise overall metabolic equilibrium.

5.3. Integration of Cellular Metabolism

Effective thermogenesis necessitates the precise coordination of numerous metabolic processes functioning concurrently inside brown adipocytes. Cold-induced β_3-adrenergic stimulation initiates intracellular lipolysis, swiftly converting triglycerides into free fatty acids (FFAs). These free fatty acids perform multiple roles by facilitating mitochondrial β-oxidation and directly activating uncoupling protein 1 (UCP1). Simultaneously, both insulin-dependent and insulin-independent pathways enhance glucose absorption via GLUT1 and GLUT4 transporters, providing glycolytic intermediates that facilitate mitochondrial metabolism and cellular biosynthesis. Supplementary substrates—such as circulating triglycerides, branched-chain amino acids (BCAAs), lactate, ketone bodies, and acetate—enhance mitochondrial respiration under extended cold exposure. The capacity of BAT to use various energy sources illustrates its exceptional metabolic flexibility, enabling continuous thermogenesis despite variations in dietary availability. The synchronised management of substrate absorption, oxidation, storage, and recycling guarantees ongoing heat generation while maintaining intracellular energy equilibrium.

5.4. Transcriptional and Structural Adaptations During Cold Acclimation

Repeated cold exposure induces profound transcriptional remodelling that extends far beyond acute activation of existing thermogenic proteins. Sustained sympathetic stimulation increases the expression and activity of transcriptional regulators, including:

- Peroxisome proliferator-activated receptor gamma (PPARγ)
- PR domain-containing protein 16 (PRDM16)
- Peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α)
- Nuclear respiratory factors (NRF-1 and NRF-2)
- Mitochondrial transcription factor A (TFAM)

Together, these regulators stimulate mitochondrial biogenesis, oxidative enzyme synthesis, fatty acid oxidation, angiogenesis, and UCP1 expression.

Structural remodelling accompanies these molecular adaptations. Chronic cold acclimation increases the following:

- Mitochondrial number.
- Mitochondrial cristae density.
- Capillary vascularisation.
- Sympathetic innervation.
- Brown adipocyte size and oxidative capacity.
- Expression of thermogenic enzymes.

These adaptations significantly enhance the efficiency and sustainability of non-shivering thermogenesis during repeated cold exposure.

5.5. Browning of White Adipose Tissue

An important component of adaptive cold acclimation is the recruitment of **beige (brite) adipocytes** within white adipose tissue (WAT). Under prolonged sympathetic stimulation, precursor cells residing within WAT differentiate into beige adipocytes that express UCP1, PGC-1α, PRDM16, and other thermogenic proteins. Although beige adipocytes differ developmentally from classical brown adipocytes, they acquire many functional characteristics of BAT, including mitochondrial uncoupling and increased oxidative metabolism. This process, commonly referred to as **browning**, expands the body's overall thermogenic capacity without requiring the formation of entirely new BAT depots. Browning illustrates the extraordinary plasticity of adipose tissue and its ability to adapt to persistent environmental challenges.

5.6. Brown Adipose Tissue as an Endocrine Organ

Current evidence increasingly supports the concept that BAT functions as an active endocrine organ rather than solely as a thermogenic tissue.

During cold exposure, activated BAT secretes numerous signalling molecules, collectively known as **batokines,** including:

- Fibroblast growth factor 21 (FGF21)
- Neuregulin 4 (NRG4)
- CXCL14
- Interleukin-6 (IL-6)
- Growth differentiation factor 15 (GDF15)

These molecules provide communication between brown adipose tissue and several organs, including the liver, skeletal muscle, pancreas, heart, immune system, and central nervous system. Through endocrine signalling, brown adipose tissue coordinates systemic modifications that enhance nutrition utilisation, glucose metabolism, lipid oxidation, and overall energy homeostasis during extended cold exposure. Consequently, BAT engages in comprehensive physiological control that transcends localised heat generation.

5.7. Physiological Adaptation to Repeated Cold Exposure

Repeated exposure to mild cold environments induces

cold acclimation, a process characterised by progressive improvements in thermogenic efficiency.

Human studies have demonstrated that several weeks of daily cold exposure result in:

- Increased BAT glucose uptake.
- Enhanced fatty acid oxidation.
- Greater mitochondrial respiratory capacity.
- Increased UCP1 expression.
- Expanded BAT volume.
- Reduced reliance on shivering thermogenesis.
- Improved maintenance of core body temperature.
- Increased resting energy expenditure during cold exposure.

These adaptations occur without major alterations in core body temperature, indicating that BAT becomes progressively more efficient at maintaining thermal homeostasis.

Importantly, cold acclimation illustrates that BAT remains highly adaptable throughout adult life, even though its abundance declines with ageing.

5.8. Limitations and Remaining Knowledge Gaps

Notwithstanding considerable progress in BAT research, some critical enquiries remain unanswered. Significant heterogeneity in BAT quantity and thermogenic responsiveness is observed among healthy adults, while the mechanisms underlying these variances remain inadequately understood. Genetic variables, developmental programming, environmental exposure, nutritional status, and epigenetic regulation presumably interact to affect BAT function; however, their respective contributions remain ambiguous. Moreover, numerous molecular pathways recognised in animal models remain inadequately verified in humans. The physiological importance of many newly identified batokines, mitochondrial signalling pathways, and epigenetic regulators necessitates additional research. Future research utilising single-cell transcriptomics, spatial metabolomics, improved molecular imaging, and integrated systems biology is anticipated to yield profound insights into the intricate regulation of human brown adipose tissue.

5.9. Overall Summary of BAT Regulation

The activation of brown adipose tissue in response to cold exposure exemplifies a highly coordinated physiological reaction in the human body. Peripheral thermoreceptors register changes in environmental temperature, which are processed by hypothalamic thermoregulatory centres, leading to sympathetic activation of brown adipose tissue (BAT). Intracellular β_3-adrenergic signalling promotes lipolysis, fatty acid oxidation, and UCP1-mediated mitochondrial uncoupling, while endocrine hormones, transcription factors, nutrient-sensing pathways, and mitochondrial quality-control mechanisms collectively enhance thermogenic efficiency. Repeated cold exposure triggers adaptive remodelling, defined by mitochondrial biogenesis, angiogenesis, browning of white adipose tissue, and improved endocrine communication via batokine production. These combined responses allow BAT to sustain thermal homeostasis and facilitate systemic metabolic regulation. Collectively, current evidence establishes BAT as a highly specialised thermogenic, metabolic, and endocrine organ whose activity reflects the continuous interaction of neural, hormonal, molecular, and environmental regulatory systems. This integrated physiological framework provides the foundation for understanding the broader significance of non-shivering thermogenesis in adult human adaptation to cold and leads naturally to the concluding section of this review.

5.10. Physiological Significance and Future Perspectives

Brown adipose tissue (BAT) has become a pivotal element of human thermoregulatory physiology, significantly transforming the conventional perspective that significant BAT activity is restricted to infancy. The identification of metabolically active brown adipose tissue in healthy individuals has shown that non-shivering thermogenesis is a crucial physiological process for maintaining core body temperature during cold exposure. In contrast to skeletal muscle shivering, which generates heat through repetitive muscle contractions and incurs significant energy expenditure, brown adipose tissue (BAT) produces heat by uncoupling oxidative phosphorylation via uncoupling protein 1 (UCP1), facilitating the efficient transformation of chemical energy into thermal energy while maintaining muscular function. This system allows individuals to sustain thermal homeostasis throughout mild and extended cold exposure with no disruption to voluntary movement or physical performance. The metabolic significance of brown adipose tissue transcends mere thermogenesis. This article highlights that brown adipose tissue (BAT) is among the most metabolically active tissues in the human body, adept in swiftly oxidising fatty acids, glucose, branched-chain amino acids, lactate, and various other metabolic substrates to support thermogenesis. During cold exposure, activated brown adipose tissue significantly elevates oxygen consumption and overall energy expenditure while concurrently aiding in the clearance of circulating glucose and triglycerides. These data suggest that BAT serves not only as a thermogenic organ but also as a crucial regulator of systemic substrate metabolism. The exceptional metabolic adaptability of brown adipocytes enables them to consistently adjust fuel utilisation based on substrate availability, ensuring effective heat generation while preserving cellular energy equilibrium.

The regulation of BAT illustrates the complexity of human physiological integration. Effective thermogenesis requires coordinated interactions among the central nervous system, sympathetic nervous system, endocrine pathways, intracellular signalling cascades, transcriptional regulators, and mitochondrial metabolic networks. Cold exposure initiates a cascade beginning with activation of peripheral thermoreceptors and hypothalamic thermoregulatory centres, followed by sympathetic release of norepinephrine and activation of β_3-adrenergic receptors on brown adipocytes. Intracellular signalling through cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), mitogen-activated protein kinase (MAPK), AMP-activated protein kinase (AMPK), and phosphatidylinositol 3-kinase (PI3K)-Akt pathways coordinates lipolysis, fatty acid oxidation, mitochondrial biogenesis, and UCP1 activation. At the

transcriptional level, regulators such as PPARγ, PRDM16, PGC-1α, NRFs, and TFAM maintain brown adipocyte identity and ensure sustained thermogenic capacity during prolonged cold acclimation. Another major physiological insight is the recognition of BAT as an endocrine organ. Activated BAT secretes numerous bioactive molecules, collectively known as **batokines,** including fibroblast growth factor 21 (FGF21), neuregulin 4 (NRG4), CXCL14, interleukin-6 (IL-6), and growth differentiation factor 15 (GDF15). These signalling molecules facilitate communication between BAT and distant organs such as the liver, skeletal muscle, pancreas, cardiovascular system, immune system, and central nervous system. This endocrine function demonstrates that BAT participates in whole-body metabolic coordination rather than acting solely as a localised heat-producing tissue. Consequently, BAT is increasingly recognised as an essential component of integrated physiological homeostasis.

The tremendous adaptability of BAT underscores its biological importance. Human brown adipose tissue has significant responsiveness to recurrent environmental stimuli, exhibiting both structural and functional remodelling during cold acclimatisation. Prolonged exposure to cold enhances mitochondrial density, vascularisation, sympathetic innervation, oxidative enzyme expression, and UCP1 levels, while concurrently facilitating the recruitment of beige adipocytes in white adipose tissue. These modifications enhance overall thermogenic capacity and demonstrate the dynamic characteristics of human adipose tissue. This plasticity enables the thermogenic system to adapt well to seasonal variations, ambient temperature changes, and metabolic demand fluctuations.

Notwithstanding significant advancements in BAT research over the last twenty years, some critical enquiries persist unresolved. Significant interindividual diversity in BAT quantity and activity is observed in healthy adults; however, the processes underlying these variances are not fully elucidated. Age, sex, genetic polymorphisms, developmental programming, environmental exposure, nutritional status, and epigenetic control seemingly affect BAT function; however, the precise contribution of each element remains undetermined. Moreover, whereas numerous molecular pathways governing brown adipose tissue (BAT) have been elucidated in experimental animal models, their exact physiological relevance in adult humans necessitates further exploration. Translating findings from rodents to humans is difficult due to species-specific variations in adipose tissue distribution, sympathetic innervation, metabolic rate, and thermogenic control. Subsequent study should concentrate on enhancing the comprehension of human brown adipose tissue biology using sophisticated molecular and physiological methodologies. Emerging technologies, including single-cell RNA sequencing, spatial transcriptomics, proteomics, metabolomics, epigenomic profiling, and high-resolution molecular imaging, provide an unparalleled opportunity to delineate the cellular heterogeneity and regulatory networks that govern brown adipose tissue activation. These approaches may reveal hitherto unrecognised thermogenic cell types, novel signalling pathways, and other endocrine mediators implicated in cold adaptation. Longitudinal studies investigating the impacts of recurrent cold acclimation, ageing, environmental exposure, and genetic diversity will elucidate the mechanisms underlying individual disparities in thermogenic capacity.

Another important direction for future investigation is the integration of BAT physiology with systems biology. Rather than studying BAT as an isolated tissue, future work should examine its interactions with the nervous, endocrine, immune, cardiovascular, hepatic, and skeletal muscle systems. Understanding these complex inter-organ communication networks will provide a more comprehensive view of how BAT contributes to whole-body physiological homeostasis during environmental stress.

In conclusion, brown adipose tissue represents a highly specialised thermogenic organ whose function depends on the coordinated interaction of neural, endocrine, molecular, metabolic, and environmental regulatory mechanisms. Cold-induced activation of BAT through sympathetic stimulation, mitochondrial uncoupling, transcriptional remodelling, and endocrine communication enables efficient non-shivering thermogenesis and maintenance of core body temperature in adult humans. Contemporary research has transformed BAT from a relatively obscure adipose depot into a dynamic metabolic and endocrine organ with broad physiological importance. Continued investigation into the molecular mechanisms governing BAT activation will not only deepen our understanding of human thermoregulation but also provide valuable insight into the adaptive capacity of human physiology in response to environmental challenges.

6. Conclusion

Brown adipose tissue (BAT) is now recognised as a highly specialised thermogenic organ that plays a fundamental role in maintaining thermal homeostasis in adult humans. Contrary to the traditional belief that BAT is functionally significant only during infancy, advances in molecular imaging and physiological research have confirmed the persistence of metabolically active BAT throughout adulthood. During cold exposure, BAT generates heat through **uncoupling protein 1 (UCP1)-mediated non-shivering thermogenesis,** a process that efficiently converts chemical energy into heat by uncoupling oxidative phosphorylation within mitochondria. This mechanism enables the maintenance of core body temperature while minimising reliance on energetically costly skeletal muscle shivering. The activation of BAT represents a highly coordinated physiological response involving the integration of neural, endocrine, molecular, and metabolic signalling pathways. Cold-induced stimulation of the sympathetic nervous system initiates β_3-adrenergic signalling, leading to lipolysis, fatty acid oxidation, mitochondrial uncoupling, and increased expression of thermogenic genes. These responses are further regulated by transcription factors and coactivators, including **PPARγ, PRDM16,** and **PGC-1α**, which preserve brown adipocyte identity and promote mitochondrial biogenesis during prolonged cold exposure. Endocrine factors such as thyroid

hormones, insulin, fibroblast growth factor 21 (FGF21), irisin, and natriuretic peptides further modulate BAT activity by coordinating substrate utilisation, energy metabolism, and adaptive thermogenesis.

In addition to generating heat, brown adipose tissue serves as a metabolically active endocrine organ that aids in systemic energy balance. Its capacity to oxidise glucose, fatty acids, and other metabolic substrates while releasing biologically active signalling chemicals, termed 'batokines', underscores its significance in inter-organ communication and physiological adaptation to environmental stress. Moreover, the exceptional plasticity of brown adipose tissue, encompassing mitochondrial remodelling and the recruitment of beige adipocytes during cold acclimation, illustrates the dynamic characteristics of human adipose tissue and its ability to adapt to fluctuating temperature settings.

Notwithstanding significant progress in comprehending BAT physiology, critical information deficiencies persist. Significant heterogeneity in BAT quantity and thermogenic response among adults exists, and the molecular mechanisms driving these variances remain inadequately understood. Subsequent research utilising modern technologies, including single-cell transcriptomics, spatial omics, metabolomics, and high-resolution molecular imaging, will be crucial for delineating the intricate regulatory networks that control brown adipose tissue activation and adaptability in humans. In conclusion, cold-induced activation of brown adipose tissue exemplifies a highly advanced physiological mechanism for regulating body temperature in adult humans. Brown adipose tissue (BAT) effectively produces heat and participates in overall metabolic regulation through the synchronised interaction of neuronal, endocrine, and intracellular signalling pathways. Ongoing investigation into the molecular underpinnings of non-shivering thermogenesis will deepen our comprehension of human thermoregulation and yield significant insights into the adaptive physiology of brown adipose tissue. Furthermore, investigating the therapeutic potential of BAT activation in obesity and metabolic illnesses may yield innovative treatment methods. Comprehending the complex mechanisms of cold-induced BAT activation may provide novel avenues for targeting metabolic pathways to enhance health outcomes. Furthermore, examining the function of brown adipose tissue in energy expenditure and glucose metabolism may facilitate the creation of novel treatments for metabolic disorders. Exploring the molecular processes of non-shivering thermogenesis could transform our treatment of energy balance and metabolic disorders.

Declarations

Ethics Approval and Consent to Participate

Not applicable. This review article is based exclusively on previously published literature and did not involve human participants, animals, or identifiable personal data.

Consent for Publication

Not applicable.

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The author solely conceived the review topic, performed the literature search, critically evaluated and synthesized the published evidence, drafted and revised the manuscript, and approved the final version for publication.

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Data Availability Statement

No datasets were generated or analyzed during the current study. All data discussed in this review are available in the cited published literature.

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