Journal of Obesity & Weight Loss Therapy

Jarrar and El-Shafey et al., J Obes Weight Loss Ther 2018, 8:1
DOI: 10.4172/2165-7904.1000363

Review Article Open Access

The Paradox of Ectopic Melanin Synthesis in Adipose: Potential Mechanism, Benefits and Perspectives in Abating Obesity Complications

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Received date: January 16, 2018; **Accepted date:** January 22, 2018; **Published date:** January 25, 2018

Abstract

Obesity and related non-communicable diseases (NCDs) are global health challenges prevalent worldwide. Intervention became imperative for creative natural measures to minimize NCDs. The chronic state of inflammation and oxidative stress are the land mark signatures for obesity driven NCDs. In this description study, we try to decipher and rationalize the new puzzle of ectopic melanin synthesis in adipose by formulating analytical view from extensive literature review. Oxidative stressed adipose triggers structural homeostasis program to initiate renovation of adipose tissue for self-healing. These processes are induced by rewiring interactions of signalling pathways for promoting adipocytes survival or replenishing them from their precursors. We postulate that melanogenesis and adipogenesis are co-driven by sharing interactive molecular signalling mechanisms. Cross-talk between melanogenesis and adipogenesis occurs through Wnt/β-catenin pathway and its interaction with Sox signalling molecules; through PPAR-γ and C/EBP-α. Activating these signalling pathways stimulate adipogenesis to relief the oxidative stress induced cell damages. Ectopic melanin synthesis and adipogenesis concurrently occur as adaptative response to hypertrophic induced oxidative stress and ROS as second messengers. Therefore, the activation of melanin synthesis probably is a natural preventive measure to slow down or minimizes hyperplasia and ameliorates consequent obesity complications. In conclusion; before we recommend using analogs of melanin inducers as therapeutic strategy, we advocate the use of the melanin intermediates as antioxidants or anti-inflammatory agents in obesity research and therapy. This descriptive study is based on very limited amount of preliminary data and at times several levels of assumptions are made. The hypothesis of melanin production in adipose tissue having a role to prevent complications of obesity is unconventional and challenges current dogma.

Keywords: Adipose tissue; Obesity; Adipogenesis; Melanin; Antioxidant

Introduction

Melanogenesis is a biological process, active in specialized cells called melanocytes. "With the coordination of keratinocytes, they form 'melanin producing units." Melanogenesis produces polymeric phenolic pigment called melanin in skin, hair, eyes, inner ear, bones, heart, and brain. The UV light absorption properties of melanin principally contribute in photo protection [1,2] thermoregulation and coloring [3]. Melanin is a strong cation chelator, anti-oxidant and free radical scavenger [4-6].

The Biochemical synthesis of melanin starts by oxidation of amino acid tyrosine catalyzed by tyrosinase and results in forming a black-brown eumelanin and red-yellow pheomelanin [7]. The quantity and the quality of the melanin are controlled by a collection of enzymes mainly tyrosinase (TYR), tyrosine related protein 1 (TYRP 1) and tyrosine-related protein 2 (TYRP 2) [8,9]. The activity of these enzymes is controlled by complex signalling pathways. The main pathway is through cyclic adenosine monophosphate (cAMP) and microphthalmia-associated transcription factor (MITF) which is triggered by the action of α-MSH agonist on melanocortin 1 receptor (MC1R) in the membrane of melanocytes [10]. Genetic elements, hormonal and environmental factors interact intricately affecting over all the melanogenesis process.

Even though melanin can be present in all tissues of human body, it has been thought its synthesis is restricted to melanocytes and that MITF is a lineage specific marker. Interestingly, ectopic expression of MITF can convert 3T3 fibroblasts into cells with characteristics of melanocytes and some of these cells expressed melanogenic marker proteins [11]. Lately, ectopic melanin synthesis has been newly discovered in adipocytes of adipose tissue [12]. A significant overexpression of melanogenesis related genes in visceral fat of obese individuals was also reported [12,13]. However, among studied obese subjects, there was no significant correlation in melanogenic activity and the degree of obesity [13]. Page suggested that melanin could be used to halt oxidative stress and inflammation through its capability to scavenge reactive oxygen species (ROS) in adipose of obese tissue [13].

Page and Randhawa provided inadequate scientific explanations to many questions related to ectopic melanin synthesis [13]. Examples, what are the possible molecular mechanisms that initiates or activates melanogenesis in adipocytes, how could melanin abrogate or stop reactive oxygen species in adipose? When does oxidative stress and inflammation induce ectopic melanogenesis?

This is a description study that tries to illustrate the inflammatory and oxidative nature of adipose status in obesity and seeks to link inflammation and oxidative stress nature in obese adipose with biological mechanisms that could explain ectopic melanogenesis. Furthermore, in this review we intend to discuss the probable functions of ectopic melanin in obesity and critically evaluate the

possible physiological role of ectopic melanin and its intermediates in ameliorating obesity complications.

Oxidative stress and inflammation are complementary and interconnected drivers of obesity complications.

Obesity and its related complications such as insulin resistance, cardiovascular disease and non-alcoholic fatty liver disease (NAFLD) are prevalent worldwide and became a global health challenge. As a matter of fact, intervention became imperative but for new creative and scientific measures to minimize these non-communicable diseases (NCDs). The pathogenesis mechanisms of NCDs that stem from obesity are complex. However, the chronic state of inflammation and oxidative stress are interconnected but interdependent signatures for most obesity driven complications.

Redox state balance is intricate process but vital for the health of adipocytes and adipose tissues. Redox state imbalance leads to plethora of consequences that lay the ground for the final health status of the cell. Unrestrained oxidative stress mainly results from excess of reactive oxygen species (ROS). Oxidative stress usually is the end result of the dominance of endogenous and external pro-oxidant molecules over their counterpart antioxidants in the adipocyte cells in adipose tissue [14].

The plasma membrane, mitochondria, endoplasmic reticulum and peroxisomes are the primary natural sources of endogenous ROS production. Most of these ROS molecules are a result of biochemical reactions such as oxidative phosphorylation that is catalysed by enzymes such as NADPH oxidase, aldehyde oxidase, xanthine oxidase, and glucose oxidase. These enzymes are more active in people with obesity [15].

High activity of NADPH oxidase in hypertrophic adipocytes and infiltrated macrophages produces most of ROS in obese tissue [15]. Many antioxidant defences are higher in the normal weight subjects and their levels inversely correlate with central adiposity [16]. For example, gene expressions of antioxidant enzymes superoxide dismutase (SOD), glutathione peroxidase *(GPX)*, and catalase, are lower in white adipose tissue in obese mice [16].

Obese subjects with insulin resistant have reduction in the expression of antioxidant enzyme glutathione S-transferase alpha 4 *(GST-A4)* [17]. Even though adipose tissue is a favoured storage site for lipid-soluble endogenous antioxidants such as vitamins and carotenoids [18], it is probable that the food quality consumed by obese subjects is poor in antioxidants. Nevertheless, excess fat in adipose can also act as a sequester basin for vitamins and some antioxidants in adipocyte lipid droplets, therefore, limiting their bioavailability [19,20].

Oxidative stress can initiate obesity and drives its complications, but also can be an end result [21]. Excess of ROS in adipose tissue will lead to many damages starting by lipids peroxidation, DNA adducts formation, proteins carbonylation, inflammation of cells and tissues and even death. For example, excess of fat in adipocytes leads to increase of ROS in the hypertrophic adipocytes and ends up in pyroptosis and a proinflammatory programmed cell death [22,23]. Some of the hypertrophic adipocytes also undergo necrotic-like death and spill out many of their inflammatory molecules into the adipose extracellular spaces feeding the vicious cycle of oxidative stress.

Some of the most common oxidative stress biomarkers are end-products of ROS and pro-oxidants mediated lipid peroxidation. Free radicals attack the methylene group next to the double bonds in polyunsaturated fatty acids (PUFAs) in lipids of the cell and the products of this process are aldehyde derivatives. The main two reactive products are malondialdehyde (MDA) and 4-hydroxy-2-nonenal (4-HNE) [24-26].

Both are important signalling molecules in stimulating some gene's expression for cell survival. But they also have cytotoxic role in inhibiting other gene's expression and promoting cell death (Figure 1).

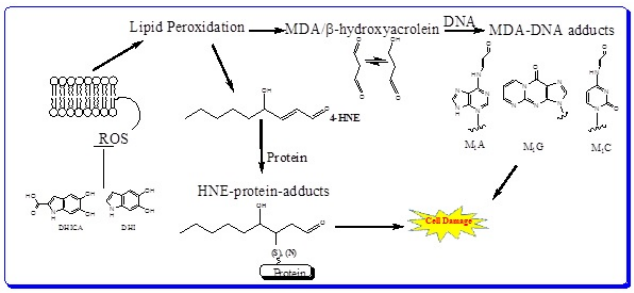

Figure 1: Cell damage induced by ROS and lipid peroxidation. The mitochondria could be considered the main source of the production of reactive oxygen species (ROS). ROS in excessive concentrations can cause cellular damage to DNA, lipid membranes, proteins and other macromolecules. ROS attack polyunsaturated fatty acids (PFUAs) as an oxidation target. The free radicals of oxygen (O_2) especially hydroxyl radical (HO) and superoxide anion (O_2) are strong generators of lipid peroxidation. The end products of lipid peroxidation in PFUAs include malondialdehyde (MDA) and 4-hydroxyl-2-nonenol (4-HNE) which reacts with DNA and proteins to form adducts which lead to cell damage and death.

MDA appears to be the most mutagenic product of lipid peroxidation, whereas 4-HNE is the most toxic [27]. Lipids peroxidation of omega-6 fatty acids causes an increase of 4-HNE [28] which is more common complication in obese subjects than lean ones.

HNE leads to carbonylation of many proteins and enzymes such that involved in lipids and carbohydrates metabolism [29]. The rate of lipids peroxidation correlates with the amount of HNE produced and so with the degree of obesity [29]. HNE formation can lead to insulin resistance in adipocytes as it binds to insulin receptor substrate 1 and 2 (IRS-1/-2) generating HNE-IRS adducts impairing IRS function and favour their degradation [30]. For example, stressing adipose cells by exposing them to high concentration of glucose oxidase induces formation of lipid markers as 4-HNE and MDA [31].

This process caused a decrease in adiponectin secretion and an increase in lactate production; both are intermediate markers for progression to insulin resistance [31]. In addition, 4-HNE also stimulated cyclooxygenase-2 (COX-2) expression which directly linked to inflammation [30]. Adipocytes exposed to ROS increased gene expression of proinflammatory cytokines as plasminogen activator inhibitor-1 (PAI-1), Interleukin-6 (IL-6) and macrophage chemo attractive molecule (MCP-1) [16,32]. Increases of such molecules usually promote infiltration of adipose by pro-inflammatory macrophages.

In contrast, obese mice treated with antioxidants corrected and improve diabetes, hyperlipemia, and adipocytokine dysregulation [16].

Moreover, it has been shown that fatty aldehyde dehydrogenase (*FALDH*), antioxidant enzyme; improved insulin resistance resulted in 3T3-L1 adipocyte that is driven by HNE exposure. In the same study, rosiglitazone showed to have an antioxidant effect by increasing *FALDH* gene expression which in turn blocks the poisonous effect of HNE on IRS-1 [33].

Prospects of boasting natural antioxidant defines compounds such as glutathione, melatonin, carotenoids, natural flavonoids, and vitamins, has been an appealing preventive strategies for obesity and minimizing its complications. From therapeutic perspective, we think that directly interfering with production of ROS in adipose is appealing but an intricate process. Because ROS are produced from many different sources in the body with different levels, and the type and quantity vary through obesity progression [34]. However, in this review we focus our discussion and analysis on using ectopic melanin synthesis in intervention and abating the oxidative stress and toxic effects in adipose tissue.

The significant over-expression of melanogenesis-related genes in visceral fat and in variant concentrations in obese subjects is puzzling in many ways. What trigger and activate melanogenesis in adipocytes may also influence adipogenesis, indicating that both processes share interactive molecular signalling mechanisms. ROS act as second messengers in adaptive responses to oxidative stress. Consequently melanin synthesis is also an adaptive response to this oxidative stress especially after hypertrophy of adipocytes. As melanogenesis development in the skin evolved as adaptive selection to counter the detrimental effect of UV radiations [35], ectopic melanin synthesis evolved as adaptive response to counter the effect of oxidative stress in adipose tissue.

Cross talk between melanogenesis and adipogenesis in adipose tissue

Both melanocytes and adipose cell; in addition to others; are generated upon development from neural crest cells (NCCs). It is probable that they share some of the signals that regulate their morphogenetic induction, migration, and fate determination. Some of their precursors' stem-like cells reside in their specific tissues for regeneration at times of stress and insult for healing and regeneration. For example, adipocytes proliferating progenitors has been found to be residing in the mural cell compartment of the adipose vasculature [36] and melanoblasts in the neural crest.

It has been demonstrated that the expansion of adipose tissue in obesity is mainly characterized by hypertrophy, accompanied by oxidative stress and inflammatory environment influenced by disturbances in energy and lipids storage [37,38]. ROS produced from mitochondrial oxidative stress play an important role in regulating adipocyte differentiation of mesenchymal stem cells (MSCs) [39]. We believe that ROS induced adipocyte differentiation is an adaptative responses to hypertrophy stress. To relief hypertrophy and associated oxidative stress, adipose tissue attempt to reinstate metabolic homeostasis.

Adipose triggers structural homeostasis program to initiate renovation of adipose tissue for self-healing. Restructured homeostasis involves interaction of signalling pathways for promoting adipocytes survival or replenishing them from their precursors either from neural crest cells or from proliferating progenitors in the mural cell compartment of the adipose vasculature [40].

Another alternative is trans differentiation of MSCs and redirecting them from becoming neurogenic and/or chondrogenic to become adipogenic. Trans differentiation of MSCs could be accomplished by enrichment of a specific cocktail of transcription factors that are considered as key cell fate modulators. Another promising strategy comes from the plasticity potential of adipocytes which is reflected by its capability of dedifferentiation to adipo fibroblasts *in vitro* [41]. This characteristic gives adipofiroblast's proliferation and multi potent capacities of the potential to repair many organs and tissues.

All mentioned processes, involve selectively activating many signalling pathways and molecules to stimulate adipogenesis to relief the oxidative stress induced cell damages. However, some of these signalling pathways and molecules also influence melanogenesis process in adipose. The activation of Wnt/β-catenin signalling is one of the first molecular responses to hypertrophy, cellular damage, and inflammation [37].

Wnt/β-catenin signalling and low-density lipoprotein (LDL) receptor-related proteins are modulators of inflammatory mechanisms [42,43]. As some researchers suggested we support that melanogenesis and adipogenesis triggered and intertwined by an increase in shared or common signalling molecules.

Wnt signalling could be anti-adipogenic and pro-melanogenic in the same cell or in different cell types. Inhibition of WNT signalling is required to induce mesenchymal stem cells to undergo adipogenesis and differentiation [44,45]. WNT molecules play role in the pathogenesis of human obesity and type 2 diabetes [46]. Wnt3a inhibit the adipogenic differentiation of porcine adipose-derived mesenchymal stem cells *in vitro* culture [47], while Wnt3a acts on melanoblasts to maintain MITF expression and promote melanoblast differentiation into melanocytes [48].

Wnt10b promotes differentiation of mouse hair follicle melanocytes [49], while expression of Wnt10b is elevated in 3T3-L1 pre-adipocytes and declines upon induction of differentiation. Moreover, ectopic expression of Wnt10b activates the Wnt signalling pathway and potently blocks differentiation [50,51].

Furthermore, over expression of Wnt5a increases adipose tissue inflammation [52] and on the other side, Wnt5A has been promoted to be a therapeutic target for melanoma metastasis [53]. WNT pathway can be an attractive drug-development target to combat obesity-associated metabolic complications [44]. SRY-related HMG-box (SOX) proteins and signalling pathway also interact with Wnt signalling path way in many processes. SOX-Wnt interactions adjust the activity of cAMP response element binding protein (CREB) and its action on MITF activation.

A new research by Leow and his colleagues shed light on the vital role of sox transcription factors in melanogenesis (Figure 2). *SOX5* hinders melanogenesis and *SOX6* involved in the developmental origins of obesity by promoting adipogenesis [54]. Overexpressing of *SOX6* increased cellular triglyceride content and promote adipogenesis through stimulating PPAR-γ and C/EBP-α and inhibition of WNT/β-catenin signaling [54].

Other recent studies have provided evidence that limiting *SOX9* through the up regulating prefadipocyte factor-1 (Pref-1) is necessary for differentiation of pre adipocyte to adipocytes [55] but *SOX9* induces the expression of *SOX10* which in turn controls the transcription of MITF and melanogenesis proteins [56,57]. Such findings suggest that the main cross talk between melanogenesis and

adipogenesis processes occurs through Wnt/β-catenin pathway and its interaction with *SOX* signaling molecules.

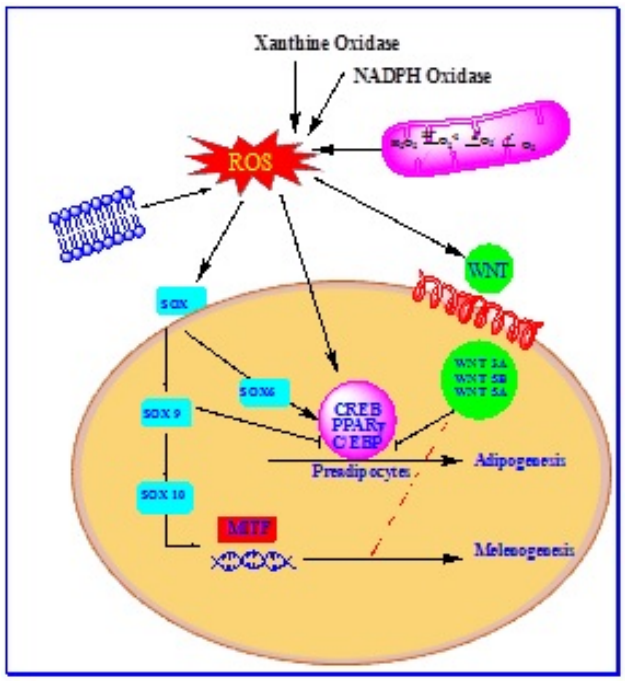

Figure 2: Role of WNT and SOX signaling on adipogenesis and melanogenesis. Melanogenesis and adipogenesis processes are under complex regulatory control by numerous shared signaling molecules. For instance, *SOX9* inhibits adipogenesis through PPAR-γ and C/EBP, while it promotes the expression of *SOX10* which in turn positively controls the transcription of MITF and melanogenesis. Over expressing of *SOX6* activate adipogenesis through stimulating PPAR-γ and C/EBP. Similarly, WNT 3A, 5B, 5A abrogate adipogenesis through PPAR-γ and C/EBP, and simultaneously promote melanogenesis.

Furthermore, there is growing evidence that the inflammatory molecules and ROS's stimulate both melanogenesis and adipogenesis. Many studies established that post-inflammation released cytokines such as interleukin 1 (IL-1), interleukin 1 (IL-6), tumour necrosis factor (TNF-α) stimulate melanin synthesis in the epidermis [58-60]. ROS also promotes adipocyte differentiation from MSCs by activating peroxisome proliferator-activated receptor gamma (PPARγ), and the antioxidant N-acetyl-L-cysteine inhibits adipocyte differentiation through ROS [39]. The cross talk mediator of melanogenesis and adipogenesis apparently occur through PPAR-γ and C/EBP-α [31-36]. PPAR-γ regulates both MITF and some inflammatory molecules. PPAR-γ down regulates the *MITF* gene expression and so tyrosinase-related proteins [61,62]. Activation of PPAR γ negatively influences the production and localization of TNF-α, IL-6, and IL-1beta by macrophages [63,64]. Macrophages and lymphocytes infiltrating adipose also contribute to the signalling circuits of linking melanogenesis and adipogenesis. Lysosomal stress in adipose tissue macrophages (ATM) in adipose induces glycoprotein non metastatic melanoma protein B (Gpnmb) expression and both positively correlate with obesity and insulin resistance [65]. Gpnmb identified as a novel marker for obesity-induced ATM infiltration. Interestingly, Gpnmb influence nuclear MITF localization and activity [65].

Moreover, a nuclear protein that is expressed in lymphocytes called lymphoid enhancing factor (LEF-1) is a mediator of Wnt signalling. LEF-1 and MITF interact and regulate dopachrome tautomerase, a key protein in melanin synthesis [66]. MITF, the main marker of melanocytes, is a transcription factor and regulator of many other genes. Activation of melanogenesis through MITF not only activates melanocytes related proteins, but also may have a role in lipids metabolism. For example, MITF recognizes and binds promoter of phospholipase A1 and apolipoprotein l domain containing 1 *(APOLD1)* genes [67]. MITF is also found that it controls attractin gene *(ATRN). ATRN* in human is ortholog to mahogunin gene in mice produced by some white blood cells in human. It affects melanogenesis through *MC1R* signaling by a cAMP-independent pathway [68]. Attractin contributes to the skin color of Europeans and East Asians through convergent evolution [69]. In connection, a membrane-bound isoform of attractin has been found to promote obesity. Mutation in mahoguim gene *(ATRN)* keep mice lean even after fed with high amounts of fat rich diet [68]; attractin expression also was higher in circulating monocytes in people with obesity [69-71]. While other isoform secreted by t-lymphocytes influences inflammatory responses and immune cells interactions [72].

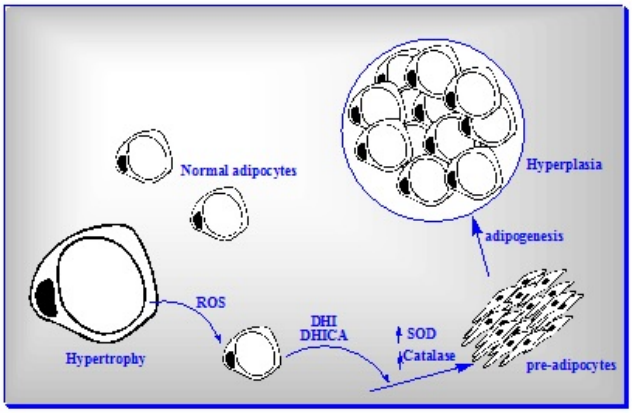

Figure 3: Effects of reactive oxygen species on differentiation of adipocytes. Hypertrophy in obesity is marked by inflammation and oxidative stress. Melanin and its precursors (DHI and DHICA), a pigment known by its antioxidant and anti-inflammatory properties, may decrease the oxidative stress and inflammatory molecules in the adipose tissue by acting as antioxidants or increasing some antioxidants activity as for superoxide dismutase and catalase. Consequently, the high level of such antioxidants will promote pre-adipocytes differentiation.

Like hypertrophy in obesity is marked by inflammation and oxidative stress, also melanogenesis process itself produces ROS and is influenced by some inflammatory molecules. Even though, the melanin's anti-oxidative and scavenging power for ROS much more than the ROSs produced through the melanogenesis process. We think that if the oxidative stress and inflammation accompanied or consequent to hypertrophy in obese exceeds to ROS's that result from melanogenesis process in adipocytes, the melanogenesis is rewired and activated. The indirect effect of melanogenesis could be through dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid

(DHICA) melanin precursors which further stimulate expression of antioxidants genes [73]. High level of antioxidants genes has been shown to be promoting pre-adipocytes differentiation [74,75]. In this mechanism, we can assume that melanogenesis can co-drive adipogenesis to relief hypertrophy (Figure 3).

Subsequently adipocytes undergone hypertrophy probably rather melanin production as it will slow down or stop the momentum of oxidative stress and inflammatory environment in obesity. This may explain why melanogenesis rate varies in people with obesity but is not correlated with obesity level; and why ectopic melanin is much less in lean subjects compared to people with obesity.

Therapeutic potential of melanin and intermediates in ameliorating NCDs

Melanin protective characteristic against UV harmful effects is sound and solid. Although melanogenesis is an oxygen dependent process, it has both antioxidant and ROS-dependent cytotoxic properties [76]. Melanin synthesis process itself generates ROS as superoxide anion (O_2) and hydrogen peroxide (H_2O_2), which could subject other cells in tissues to oxidative stress [77,78].

However, there is still uncertainty about whether the melanin or the melanin intermediates can be used as antioxidants and/or anti-inflammatory agent especially in obesity research and therapy. Melanin has antimicrobial properties as it can neutralize their enzymes and toxins [7]. Natural human melanin is insoluble in water and so non-diffusible. However, treatment of 3T3-L1 adipocytes with water-soluble melanin complex extracted from some fungi showed significant increase in insulin-stimulated glucose uptake and adiponectin gene expression [79]. Same treatment improved insulin sensitivity and reduced adiposity in high fat fed obese mice [79]. The soluble and diffusible melanin intermediates such as DHI and DHICA could have better anti-inflammatory and anti-oxidant capabilities [80,81].

L-dopa, one of the melanin intermediates, can thwart production of the inflammatory cytokines from T lymphocytes and monocytes [8,81]. DHI has scavenging character for free radicals [82]. It has been demonstrated that DHI and DHICA substantially decreased malondialdehyde (MDA) formation from lipid peroxidation in rat brain cortex homogenates [83]. DHICA increased the activity and expression of antioxidant enzymes such as SOD and catalase and protect cells from UVA harm and apoptosis [73]. Authors even stipulated that "DHICA is a messenger in the cross-talk among epidermal cells". Also few researchers showed that some melanin precursors may has pro-oxidant characteristic based on results from *in vitro* experiments on cell cultures [84,85].

Nevertheless, great caution must be taken in extrapolating on such conclusions due to the innate nature of the oxidative stress and ROS that are often produced from chemical reactions in the culture media [86]. It is also important to take into consideration the insoluble nature of melanin and its confinement in melanosomes could undermine the significance of some of their conclusions. Also, the same researchers neglected or underestimated of possible secondary role of melanin or its intermediates, which can stimulate anti-oxidative enzymes such as SOD and catalases in other cells in paracrine fashion [73]. What's more is that the concentration of the used melanin or its intermediates may have different effect on the cell viability and type.

For example, (DHI) protected retinal cells in cultures from UVA-damage but only at low concentrations [87]. Therefore, evaluation of the melanogenesis process as a whole is more central than focusing on partial components alone as its end product or specific intermediates. The multi-biological effect of melanogenesis depends on the relative type of melanin, the levels of melanin intermediates, the concentrations of reactive metals within the melanosome microenvironment and its influence on anti-oxidative enzymes.

Baranova has advocated that melanocortins especially α-melanocyte stimulating hormone (α-MSH) or its synthetic analogues could have therapeutic potential by stimulating ectopic melanogenesis and so ameliorating or minimizing obesity complications [88]. The author cited many supporting research. Mainly, certain concentrations of α-MSH and analogs have been used for reducing body weight or preventing body weight gains in mice [89]. Also in one human trial, by using intranasal administration of α-MSH, showed it is effective in reducing weight of lean subjects but not that of people with obesity [90,91].

It is also true that much research has shown that α- MSH and other melanocortins suppresses the expression or secretion of many pro-inflammatory cytokines. So α- MSH can be used in treatments of inflammatory diseases and bacterial infections. For example, it has been demonstrated that α-MSH can inhibit nuclear factor-κB (NF-κB) that regulates the expression of genes of pro-inflammatory cytokines linking mediator of the melanocortin system with inflammatory responses [92]. As Baranova deduced, "α-MSH may prevent or delay the onset of the secondary complications of obesity" and mentioned that still there is no solid proof of correlation of serum levels of α-MSH and obesity level. So, there is no one reliable bioassay that can be used to link α-MSH and the relief of obesity complications collectively.

However, the risks associated in using α-MSH and the uncertainties in its therapeutics dose effect on different people with obesity individuals are still worrying. α-MSH analogues might increase blood pressure [93]. Also, α-MSH analogues promoting of melanogenesis and melanocytes proliferation might cause melanoma [94]. In addition, melanotan, especially II, raises some concerns of its usage especially on long terms and in high dosages. MTII causes rapidly growing of moles in a male with a malignant melanoma [95] and concerns of higher risk of cussing new melanomas [96,97]. Not to forget the possible secondary disturbing endocrinological consequences.

Brennan in 2004 suggested in part of his patent; the idea of combination of α-MSH and leptin may have better effect in treatment of obesity and reducing body weight [89]. Though the authors ignored the leptin' resistance implication in obesity development as the main issue to fix rather than the serum level of leptin.

In addition, α-MSH itself may increases leptin release from adipocytes and so serum levels [98]. From our point of view, we advocate and encourage animal trials to use α-MSH in combination with adiponectin instead of leptin. Adiponectin and its serum level is a better reliable marker negatively correlates with obesity and its complications. Adiponectin also tightly linked to adipogenesis and cell differentiation which can relief the stress of hyperplasia by inducing more adipocytes. More importantly, adiponectin helps in ameliorating secondary complication of obesity in other tissues as liver by preventing LPS-induced ROS production [99].

Nevertheless, the right magic formula and combinations of molecules as adiponectin to be used in human trial need more study. Moreover, whether the ultimate and final effect of such suggested treatment would have anti-inflammatory effect, anti-oxidative effect or

both; still need to be examined. Also it needs to be clarified that if the treatment leads to fine tuning of the metabolic process in systematic or localized way; or whether can it be excreted on adipose or fat cells only. All such inquiries need further studies.

Conclusions

We may postulate that the activation of melanin synthesis is a natural preventive measure or adaptive response to oxidative stress to slow down or minimizes hyperplasia and ameliorate consequent obesity complications. Oxidative stress in hypertrophy drives melanogenesis and adipogenesis by sharing interactive molecular signalling mechanisms. Cross-talk between melanogenesis and adipogenesis occur through Wnt/β-catenin pathway and its interaction with *SOX* signaling molecules; through PPAR-γ and C/EBP-α.

Solid research quiet still needed to explain why melanogenesis process in adipose happen in various levels in different levels of obesity but not correlated. This can be checked based on the idea that the momentum of melanogenesis may be is related to the stage and time of hypertrophy. Moreover, *in vivo* and *in vitro* studies are still necessary to determine whether melanin or the melanin intermediate metabolites are better anti-oxidants and scavengers for ROS in adipose tissue to be used as therapeutic potential molecules.

More research still needed on different animals to strengthen the ectopic melanin finding in adipose and more animal trials to determine the right doses, mode of administration and possible side effects when using α-MSH alone or in combination with other molecules preferably with adiponectin. Such proposed explanatory studies are based on very limited amount of preliminary data and at times several levels of assumptions are made.

The assessments of melanin regulation of ROS production and inflammatory mediators (cytokines and macrophages) in adipose cell models are relevant and may generate novel pharmacological concepts, especially that pharmacological tool are already available. Melanin itself as well as available melanocortin receptor agonists can be tested *in vitro* and also *in vivo* in mice. It is also possible that such compounds could be used for human proof-of-principle studies in the future.

Limitations of such proposed studies also exist. The hypothesis challenges previous research findings in adipose tissue biology and the current support is fairly weak. Thus, there is some likelihood that it is proven wrong, which nonetheless will be important knowledge.

The high levels of the polymorphism in human genes regulating melanin biosynthesis provide a basis for the highly individual melanogenic response of adipocytes that may account for the differences in an individual's propensity to develop secondary complications of obesity. Accordingly, one of the pitfalls for induction of ectopic melanogenesis by using the melanocortin analogues, in animal models or even on cellular level, makes the translation of the results of such project to the clinical practice is a little challenging for the need of tailored application. In addition, unclear consequences of possible global induction of melanogenesis in animal models could undermine the values of systematic ectopic melanogenesis value.

The hypothesis of melanin production in adipose tissue having a role to prevent complications of obesity is unique and challenges current dogma. Although, the current evidences supporting such local melanin effects are rather scarce.

Conflict of Interests

The authors do not have any potential conflict of interest.

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