Dehydroepiandrosterone, Over-studied but Under-used in the Treatment of Vascular Remodeling Diseases

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Abstract

Vascular remodeling is characterized by a narrowing of the lumen of the vessels, resulting in decreased blood flow, increased pressure and heart failure. This process is found in diseases like atherosclerosis, restenosis after angioplasty, transplants coronary disease, systemic and pulmonary hypertensive vascular disease, and is stimulated by elevated levels of cholesterol, inflammation, oxidative stress, excess of vasodilating molecules and growth factors. Efficient treatments able to fix or prevent the progression of this process are still missing. The hormone dehydroepiandrosterone (DHEA), which levels decrease with aging while cardiovascular risks increase, was hypothesized to have a role in the pathophysiology of vascular diseases. Despite the fact that numerous properties such as fat-reducing, anti-oxidant, vasodilating, anti-inflammatory and anti-proliferative have emerged from two decade of studies, DHEA remain clinically underused in the treatment of vascular remodeling diseases. The lack of understanding of the exact mechanism of action and some controversial epidemiological studies are not foreign to the fact that DHEA is shunned. Nonetheless, we believe that DHEA cannot be ignored since promising results were obtained pre-clinically and clinically in the treatment of vascular remodeling diseases. We are probably close to understand the function of this molecule, especially by its action as a peroxisome proliferator, and it will be a shame to deprive patient of a way to improve their quality of life, or worst a way to extend their survival.

Introduction

Inward inappropriate vascular remodeling is a common feature of several diseases like atherosclerosis, restenosis after angioplasty, transplants coronary disease, systemic and pulmonary hypertensive vascular disease [1] causing a narrowing of the lumen and decreasing maximal flow rates. The arterial wall is composed of three independent layers: a monolayer of endothelial cells (ECs) called intima, a main layer composed by vascular smooth muscle cells (VSMCs), the media, and a network of connective tissue, the adventitia. Under physiological conditions, VSMCs are quiescent, contractile and non-migratory. Remodeling occurs in response to various stimuli that disrupt the usually ordered multilayered structure of the wall by activating VSMCs. Elevated cholesterol levels, inflammation, oxidative stress, excess of vasodilating molecules and growth factor are potent stimuli that are found in these diseases. Most of these molecules bind receptors and enhance cascades of signal transduction resulting in a pro-proliferative, survival, constricted, migratory and invasive phenotype of the VSMCs. This abnormal VSMC’s phenotype plays a critical role in the thickening of vessel wall, the rearrangements of cellular and non-cellular elements and/or the formation of neointima or atherosclerotic plaque.

Dehydroepiandrosterone (DHEA) is an adrenal steroid circulating abundantly as a sulfate conjugated form DHEA-S [2]. DHEA-S reaches a maximal plasma level between 15 and 25 years old and the following decline in DHEA-S [3-5] has been related to aging-associated diseases development [6-10]. DHEA is a potent uncompetitive inhibitor of the first enzyme in the pentose phosphate pathway (PPP), the mammalian glucose-6-phosphate dehydrogenase (G6PDH). Studies performed on Sardinian males bearing a Mediterranean variant of G6PDH deficiency, support the hypothesis that reduced G6PDH activity has a beneficial affect on age-related disease development. Indeed, these individuals harbor reduced mortality rates from cerebrovascular and cardiovascular diseases and seems to be more likely to achieve centenarian [11]. Since almost a century, numerous hypothesis have emerged on the possible role of DHEA(-S) in the pathophysiology of vascular diseases, especially coronary heart diseases, atherosclerosis, carotid stenosis and Pulmonary Hypertension. Number of studies using DHEA as therapy exploded at the end of the eighties. These studies, while showing an efficient impact of DHEA in the reduction of remodeling processes [12-14], failed to demonstrate the exact mechanism by which the molecule act. Hormone replacement therapy using DHEA and DHEA-S in elderly has even been discussed [10,15-17] without concretization. The original enthusiasm has been replaced by sober skepticism, as many questions remain unanswered. Moreover epidemiologic studies were controversial concerning the hypothesis of an inverse correlation between the diseases manifestation and the serum level of DHEA(S), and showed dramatic differences according to sex and diseases end-point for example [18-21]. Close to two decades after, without clarification of the exact mechanism of action of the molecule, several properties of DHEA such as fat-reducing, anti-oxidant, vasodilating, anti-inflammatory and anti-proliferative properties have emerged, increasing again the interest for the treatment of cardiovascular diseases. We propose in this review to make an overview of the findings clarifying of the exact mechanism of action of the molecule, several end-point for example [18-21]. Close to two decades after, without clarification of the exact mechanism of action of the molecule, several properties of DHEA such as fat-reducing, anti-oxidant, vasodilating, anti-inflammatory and anti-proliferative properties have emerged, increasing again the interest for the treatment of cardiovascular diseases. We propose in this review to make an overview of the findings supporting the fact that DHEA could be an important therapeutic strategy in the treatment of vascular diseases, explaining how DHEA can works and to discuss why DHEA remain clinically underused as therapy.

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DHEA Cholesterol/Fat Reducing Properties

Low-density lipoproteins (LDL), also called bad cholesterol, are known to promote cardiovascular diseases and particularly atherosclerosis. This syndrome begins by damage to the endothelium leading to a chronic inflammatory response in the walls of arteries by expression of various adhesion molecules and cytokines, which promote the migration of circulating leukocytes, such as monocytes, T lymphocytes and dendrites into the sub-endothelial space of the artery [22]. Oxidized-LDL are implicated in the initiation of inflammatory processes [23] as migrating mononuclear leukocytes incorporate oxidized-LDL to become foam cells, which accumulate in the sub-endothelial space due to an impaired emigration. Foam cells secrete oxygen-free radicals as well as various cytokines that further accelerate inflammation [24-26]. VSMCs migrate into the neointima and secrete matrix proteins to stabilize the plaque [27-29]. Instability in the cap may lead to rupture and subsequent thrombus formation.

In humans and rodents, DHEA administration has been described to result in a substantial decrease in body fat mass, fat accumulation and decreased body weight [30-34]. As a G6PDH inhibitor, DHEA inhibits the production of NADP [35]. NADPH is involved in numerous metabolic pathways such as fatty acid, phospholipid, cholesterol and steroid synthesis and its reduced production lead to decreased fatty acid production and subsequent reduction of LDL production. In these conditions, less LDL can be oxidized and fewer atheromas would be formed [36]. Indeed, DHEA has been found to have an inhibitory effect on cholesterol ester accumulation induced by AcLDL in cultured macrophage cells (5774-I cells) [37], but the mechanism was poorly understood.

DHEA is known as a peroxisome proliferator able to induce many genes through peroxisome proliferator-activated receptors (PPAR) [38]. Once activated, the isoform PPARα represses activation of enzymes involved in fat synthesis [39,40]. DHEA can be implicated in lowering triglycerides production and in less fat deposition through its effect on PPARα. In adipose tissue the predominant isoform of PPAR is PPARγ, a nuclear hormone receptor and a ligand-activated transcription factor that binds specifically to PPAR response elements in the promoter regions of target genes and regulates the transcription of many adipocyte-specific genes [41,42]. DHEA has been shown to induce PPARγ expression by over 2.5-fold in adipose tissue of rats. DHEA-induced PPARγ activation may lead to an increase in lipolysis rate, increased flux of fatty acids through the β-oxidation pathway and a decrease in de novo lipogenesis rate in adipose tissue, accompanied by an increase in energy expenditure [43].

DHEA Anti-oxidant and Anti-inflammatory Properties

Another recent study hypothesized that DHEA may affect the oxidized LDL-induced inflammatory response. Indeed, DHEA administration was shown to modulate the expression of inflammatory molecules in human umbilical vein endothelial cells (HUVECs) injured by oxidized LDL, like up-regulating nitric oxide production and down-regulating malondialdehyde, adhesion molecules VCAM-1, ICAM and E-selectin. This was attributed in part to a DHEA-dependent inhibition of NF-κB and a subsequent attenuation of inflammation [44]. Indeed, multiple genes involved in monocyte/endothelial interaction such as vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemotactic protein-1 (MCP-1) contain in their promoters NF-κB binding sites [45]. DHEA-dependent inhibition of NF-κB is not surprising considering the fact that PPARα has been shown to antagonize NF-κB signaling pathway involved in the vascular inflammation of atherosclerosis [46,47]. This hypothesis was formulated by Altman et al. who showed that DHEA(-S)-dependent VCAM-1 decreased expression could be partially restored by using the PPARα inhibitor MK866 [48]. These findings furnish important clues on DHEA mechanism of actions and demonstrate a significant role for DHEA(-S) in the prevention of inflammatory processes in the endothelium.

DHEA Vasodilating Properties

A constricted state of VSMCs in wall arteries is also a factor increasing the inward narrowing of the vessels. In pulmonary arterial hypertension (PAH), distal arteries are particularly constricted and this phenomenon plays a critical role in the global rise of pressure observed in the pulmonary vasculature. Several mechanisms are implicated in this abnormal constricted state. First, an imbalance between vasoconstricting and vasodilating factors levels have been measured in the serum of PAH patients [49-51], with an abnormal downregulation of vasodilating molecules like nitric oxide and an overexpression of vasoconstricting molecules like endothelin-1 [52-54]. There are also evidences showing a decrease in gene expression and function of K+ channels [55] as well as a decrease in BKγ protein expression [56] resulting in membrane depolarization and enhanced contraction.

Ratios of cellular reducing factor, such as NADPH/NADPH and GSH/GSSG are known to open Kv and BKγ channels and hyperpolarize plasma membrane [57-59]. Following this principle, again as an inhibitor of the PPP and able to modify these ratio (Figure 1), DHEA was hypothesized to have vasodilating properties. DHEA was found to efficiently inhibit hypoxic pulmonary vasoconstriction, at least in part by opening BKγ channels in pulmonary VSMCs [60-62]. Western Blot analysis of arterial pulmonary extract showed that the BKγ subunit expression is upregulated after DHEA treatment compared to chronic hypoxia rats [63]. By using specific K+ channel inhibitors, it was identified that only Kγ1 channels are positively implicated in DHEA-dependent relaxation of VSMCs. DHEA also prevents and reverses chronic hypoxia induced pulmonary hypertension in rats by BKγ opening.

Vascular tone is also controlled by cyclic guanosine 3',5'-monophosphate (cGMP), a factor generated in the vasculature via two main guanylate cyclase: cytosolic soluble guanylate cyclase (sGC) and membrane-bound particulate guanylate cyclase (pGC) [64]. sGC serves as a receptor for biologically active gas nitric oxide (NO) [65,66] and GMP is generated by sGC following this interaction. DHEA has been reported to increase sGC protein expression and activity and by improving pulmonary artery vasodilator responsiveness to NO [67]. DHEA effects on sGC may not be direct but again, secondary to PPP inhibition and increased levels H2O2 production that have been reported to stimulate sGC and increase cGMP in vasculature [68,69]. Finally, activation of the RhoA/ROCK signaling pathway contributes to vasoconstriction in VSMCs, a pathway that plays an important role in the pathogenesis of PAH. Chronic DHEA treatments in PAH rat model were described to decrease RhoA/ROCK signaling pathway activity by multiple mechanisms, including preservation of sGC expression and inhibition of ROCK cleavage [70].

DHEA Anti-proliferative Properties

In diseases like restenosis and PAH, the proliferative phenotype of VSMCs is critical in the inward narrowing of the vessel. Some enzymes, essential for cell cycle progression like multifunctional Ca2+/CaM-...
DHEA-dependant G6PDH inhibition could also be beneficial in the treatment of vascular remodeling diseases. Through PPAR factors, evidence suggests that DHEA is a peroxisome proliferator. Through PPAR factors, it appears to be beneficial in the treatment of vascular remodeling diseases.

We have recently demonstrated the critical role of the Src/STAT3 (Signal transducer and activator of transcription 3) axis in PAH, that enhance NFAT (Nuclear Factor of Activated T-cells) expression and activation through a Pim (Provirus integration site for Moloney murine leukemia virus) dependant mechanism [77]. STAT3 has also been showed as a regulator of the Bone morphogenetic protein receptor 2 (BMPR2) [78], which is recognized as a hallmark of PAH [79,80]. An association between DHEA treatment and decreased STAT3 activation in regenerative rat liver [81] has been previously described and make us hypothesized that DHEA could also reverse PAH by STAT3 inhibition. Indeed, we demonstrated in vitro and in vivo that DHEA treatments decrease Src/STAT3 activation in PAH and restore several PAH downstream targets aberrantly expressed in PAH, such as BMPR2, Survivin, PimI and NFATc2 [82]. Nonetheless, the mechanism by which DHEA decreases STAT3 activation remains unknown. Once again, the PPAR family of proteins could be implicated in this mechanism as it has been demonstrated that activation of PPARγ by a decrease of vascular remodeling in the rat model of balloon-injured carotid treated with DHEA, showing the potential of DHEA as therapeutic for restenosis. It was demonstrated that PDGF-induced proliferation is inhibited by DHEA through a GSH/GRX1 mechanism [75], GRX1 playing an important role in PDGF signal regulation by a downregulation of tyrosine phosphorylation of the PDGF receptor [76]. This is in agreement with previous findings showing that GRX1 and γ-Glutamylcysteine synthetase (γ-GCS) display a PPAR response element in their promoter and are up-regulated at the transcriptional level by PPARα.

**Discussion**

Whereas several studies have strong evidences in vitro and in vivo showing that DHEA have several beneficial effects for the treatment of vascular remodeling, DHEA is still clinically poorly used. The first reason that can explain this skepticism is in part due to controversial epidemiologic studies. Nonetheless, these studies are often performed by measurement of endogenous DHEAS, and never on DHEA by measurement of endogenous DHEAS, and never on DHEA. It is the circulatory form of DHEA, more stable and no representative/
epidemiologic studies. Nonetheless, these studies are often performed on DHEA.

**Figure 1:** Vascular remodeling diseases are characterized by an inappropriate inward narrowing of the vessels that obstruct the lumen and decrease the flow. In atherosclerosis, there is an important role of "bad cholesterol" low-density lipoprotein (LDL) that once oxidized, is incorporated by leucocytes (monocytes, lymphocytes…) to form foam cells that and accumulate in the sub-endothelial space due to an impaired migration. Vascular smooth muscle cells (VSMCs) migrate into the neointima and secrete matrix proteins to stabilize the plaque. Instability in the cap may lead to rupture and subsequent thrombus formation. In hyperplasia and pulmonary arterial hypertension, the neointima is due to increased VSMCs constriction, proliferation and survival, fulfilling the internal space. Pro-inflammatory molecules, vasoconstrictors and growth factors play a critical role in the enhancement of this inappropriate VSMCs phenotype. Dehydroepiandrosterone (DHEA), that has been described to have anti-cholesterol, anti-proliferative, anti-inflammatory and vasodilating properties appear to be beneficial in the treatment of vascular remodeling diseases. Nonetheless, the exact mechanism by which DHEA acts is still unclear. Several evidences suggest that DHEA is a peroxisome proliferator. Through PPAR factors activation, several genes implicated in lipid metabolism are expressed, decreasing LDL accumulation. PPARα is also implicated in inhibition of inflammation by antagonize NF-κB. Moreover PPAR factors are able to enhance the expression of genes like glutaredoxin (GRX1), playing an important role in the downregulation of tyrosine phosphorylation, like for the PDGF receptor, and glutathionylation, a post transcriptional modification that could be implicated in DHEA-dependant inhibition of signalling factors such as Akt, STAT3 and NF-κB. Originally, DHEA was described as an inhibitor of the glucose 6-phosphate deshydrogenase (G6PDH), whose role in vascular remodeling processes is unknown. However, G6PDH inhibition is known to change NADPH ratio, whose reduced levels lead to decreased fatty acid production and subsequent reduction of LDL production; GSH ratio, which is also implicated in protein glutathionylation; and reactive oxygen species (ROS) production implicated in enhanced vasodilatation. Thus, DHEA-dependant G6PDH inhibition could also be beneficial in the treatment of vascular remodeling diseases.

Dependent protein kinase, calcineurin and spindle pole body protein are Ca²⁺/CaM-dependent, inactive in absence of Ca²⁺/CaM [71]. Ca²⁺ is also able to act directly on transcription factors (such as DREAM) or indirectly through protein phosphatase (calcineurin/NFAT) or kinases (CaM kinases/CREB, PKC/NFkB) to induce the activation of numerous target genes. Thus, the ability of DHEA to induce dilatation and to release cytosolic Ca²⁺ may also play important roles in cell proliferation. Nonetheless, DHEA is also recognized for anti-proliferative properties through its actions on pro-proliferative factors. DHEA treatment of human aortic SMC inhibits PDGF-induced MAPK activation [72]. In human internal mammary artery, DHEA significantly decreases PDGF-induced ERK1 kinase activity in a dose-dependent manner [73]. We also showed recently, in human carotid VSMC, that DHEA could inhibit PDGF-induced-Akt activation [74]. These results were confirmed in vivo by a decrease of vascular remodeling in the rat model of balloon-injured carotid treated with DHEA, showing the potential of DHEA as therapeutic for restenosis. It was demonstrated that PDGF-induced proliferation is inhibited by DHEA through a GSH/GRX1 mechanism [75], GRX1 playing an important role in PDGF signal regulation by a downregulation of tyrosine phosphorylation of the PDGF receptor [76]. This is in agreement with previous findings showing that GRX1 and γ-Glutamylcysteine synthetase (γ-GCS) display a PPAR response element in their promoter and are up-regulated at the transcriptional level by PPARα.

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**Discussion**

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the DHEA one [91]. These parameters should be considered in the future in order to avoid mis-conclusion about the inverse correlation between DHEA levels and vascular remodeling diseases frequency.

Another reason is the lack of knowledge regarding the exact mechanism of action of the molecule. I think that DHEA has lost credibility by the fact that it has been considered as a "miracle drug". Moreover, the scientific community is more and more dedicated to avoid side effect of treatments, and successfully accomplish this step is easier when the implicated molecular and signaling mechanisms are well known. The skepticism was thus replaced by fear of a long-term tragic side effect. Close to 30 years after the first studies, no specific toxicity has been described for DHEA, and we are close to define the exact action of DHEA. Known as a G6PDH inhibitor, it is believe that DHEA major effects are independent of this property. DHEA synthetic analogues 8354 and 8356, are 37-fold and 144-fold stronger inhibitors of G6PDH respectively than natural DHEA. However, they have less effect for example on CE accumulation, compare to natural DHEA [37]. Moreover, the role of G6PDH in vascular remodeling diseases is unclear. Some report described that G6PDH is implicated in VSMCs contractility [92-94] but it is not clearly established that this pathway is aberrantly expressed in vascular remodeling diseases. Thus, DHEA effects may not actually be related to the inhibition/rescue of G6PDH and associated pathways.

As described above, a lot of the DHEA effects can be associated to PPAR activation. PPARα has been shown to decrease fat accumulation, by enhancing enzyme involved in fat synthesis [39,40], regulates the transcription of lipolytic genes [41,42]. PPARα is also implicated in inhibition of inflammation by antagonize NF-κB [44-48]. And finally, by enhancing the transcription of multiple genes like GRX1, PPARα seems to play an important role the downregulation of tyrosine phosphorylation, like for the PDGF receptor [76]. We are now in rights to ask the tantalize question: Does this mechanism of reduced tyrosine phosphorylation can be implicated as well in the inhibition of Akt, STAT3, NF-κB and other transcription factor?

STAT3 is in part regulated by glutathionylation, a reversible and redox-sensitive post-translational modification occurring under oxidative stress. Glutathionylation of STAT3 decreases its affinity as a substrate for enzymatic phosphorylation and abrogates STAT3-specific DNA binding [95]. Glutathionylation depends on Glutaredoxin (GRX) and thioredoxin levels (deglutathionylation enzymes) and on the increase in the cellular GSH/GSSG ratio, which also exert a reversible action on protein S-glutathionylation. Interestingly Akt[96], NfκB [97], and other protein like eNOS or MEK1[98,99] are also subject to glutathionylation. This mechanism of regulation may be a masterpiece in the understanding of DHEA effect as a peroxysyme proliferator.

Concerning DHEA vasodilator properties, since Src and STAT3 is known as K+ channel inhibitors/Ca2+ channel opener [100-104] their inhibition by DHEA in PAH could explain how DHEA upregulates K+ and BK channels [63]. The large panel of DHEA action is probably secondary to the effect on a masterpiece like PPAR factors and repercussion of this signal downstream. Nonetheless, the implication of PPAR in all these processes is only speculative and has to be confirmed. It will be interesting that future studies dedicated to increase the knowledge on DHEA effect on vascular diseases take a look on PPAR implication.

DHEA is orally available, relatively cheap and without known side effects. Because DHEA is a naturally occurring substance, it belongs to the public domain and cannot be patented. Therefore, pharmaceutical companies are not rushing to invest millions of dollars on clinical trials to determine the effectiveness of DHEA. However, a wide range of small-scale studies has been conducted on DHEA for many years and for many diseases, and the findings show great promise for the value of DHEA. Interestingly, pharmaceutical firms have tested some synthetic forms of DHEA. With the development of the knowledge on DHEA properties, we will maybe see the development of interesting synthetic molecules that will reconcile DHEA and industry.

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