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Mini Review

Role of statin as inducer of Hmox-1 system in treatment of preeclampsia

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Abstract: Preeclampsia is the major cause of both maternal and neonatal morbidity and mortality. Its insidence remains high and the management has not been established yet because its etiology and pathophysiological are still poorly understood. Theories regarding etiopathogenesis and management of preeclampsia have been postulated yet it remains controversial. Placental ischemic and angiogenic imbalance are suggested to be predisposing factors of preeclampsia. It is thereby targeted in prevention of preeclampsia. Unfortunately, both primary and secondary prevention using various supplements and drugs fails to exhibit good outcome. Overall, these efforts are considered useless. In recent years, researchers have been using statin derivative in management of preclampsia. It has been reported that statin provides protective effect in endothelial cells by inducing expression of Hmox-1 and inihibiting release of sFlt-1 as well as potent antioxidant properties. Thus, statin has been proposed as promising agent to significantly reduce anti-angiogenic in preeclamptic patients which is overviewed in this review based on recent studies.

Key words: Hmox-1; Preeclampsia; Statin.

Introduction

Preeclampsia is known to contribute to 5% pregnancy and major cause in maternal mortality (24%) after hemorrhage (28%). Preeclampsia also increase perniata morbidity and mortality. However, its underlying mechanism remains elusive, hence it is called as the disease of the theories. Recent studies suggest that endothelial dysfunction plays role in preeclampsia. Endothelial dysfunction is associated with nitrit oxide pathway that naturally undergo damage and reduced nitrite oxide. There area several factors involved such as inadequate placental remodelling, ischemia, oxidative stress, hemmorhage, angiogenics imbalance and loss of endogenous regulator (1-4).

Placental ischemia and angiogenics imbalance has been investigated as major cause in preeclampsia. Ischemia occurs due to erytrocite destruction that results in hemoglobin or heme and Fe release in big amount into circulation. This further generates induction in ferritin system. Ferritin ia a protein as main Fe storgae found in lymph, liver, bone narrow, mucosa of small intestinal placenta, kidney, testis, skeletal muscle and plasma (4-6).

Angiogenic imbalance comprise of sFlt-1 (soluble fms-like tyrosine kinase-1), VEGF (vascular endothelial growth factor) and PlGF (plasenta growth factor). Elevated sFlt-1 generates endothelial damage and inhibits angiogenesis by binding of has a antagonist role toward VEGF and P1GF, increase oxidatove stress and inflammation, whilst elevated sEng (soluble Endoglin) in preeclampsia limits signal transduction of TGFβ1 (transforming growth factor β1) and eNOS (endothelial nitric oxide synthase) that later facilitate blood vessels damage and angiogenesis inhibition (2,4,7).

Endothelial dysfunction is believed to underly preeclamspsia and associated with altered angiogenics and antiangiogenics, placental metabolism, inflammatory mediators, alteredd very low density lipoprotein (VLDL). Integrity of endothelial cells is established by balance of proangiogenic and antioangiogenic; in which its alteration in preeclampsia is indicated by overproduction of antiangiogenics, sFlt-1. Presence of sFlt-1 has been frequently studied to diagnose preeclampsia on laboratory scale long before symptoms such as hypertension and proteinuria emerged. Endothelial changes is documented in preeclamptic patients due to elevated sFlt-1 (2,7-10).

On the other hand, Heme oxygenase (Hmox) is an enzyme in catabolism of heme in endoplasmic reticulum to produce biliverdin, free iron (Fe) and carbon monoxide (CO). Carbon monoxide is a strong vasolidator that maintains angiogenic balance by inhibiting sFlt-1 and sEng, as well as increasing P1GF and VEGF. Biliverdin will be reduced to form bilirubin facilitated by biliverdin reductase. Bilirubin is a potent antioxidant. Angiogenic imbalance in preeclampsia caused by elevated sFlt-1 and sEng that results in decreased PlGF and VEGF, affects Hmox-1 level in regulating biological process in human. This event indicates down regulation of antioxidant Hmox-1 which is correlated to pathogenesis of preeclampsia in placenta (11-14)

Many treatments to prevent preeclampsia primarily and secondarily using various suplements and drugs,

has failed. MgSO4 is only used to take care of spactic and as antihypertension to patients with chronic hypertension without reducing risk of preeclampsia. Supplements containing fish oil, calsium or vitamin C and E, has not shown significant results either. Low dose aspirin has been also reported to prevent preeclampsia, yet it has some adverse effetcs. Low dose aspirin can only be used before 16 weeks of gestational age. Overall, prevention of preeclampsia has not provided good result (15,16).

Hmox System

Heme is a protein responsible in many physiology process including oxygen, mitochondrial respiration and signal transduction. It is mostly found in hemoglobin and the rest is present in myoglobin, mitochondria, cytochrome microsomal and various catalytic enzyme such as nitric-oxide synthase, catalase, and burst respiratory oxidase. Formation of free radicals and lipid peroxide give toxicitiy to free heme. (11,12,17)

There are three forms (isoform) of heme oxygenase (Hmox), Hmox-1, Hmox-2 dan Hmox-3. Hmox-3 is a pseudogene originate from Hmox-2 transcription and Hmox-2 plays role in regulating cell physiology, whilst Hmox-1 is inducedd as response toward tissue damage (11,17).

Heme oxygenase is a responsible enzyme of Heme catabolism (Figure 1). Heme is degraded by heme oxygenase into carbon monoxide, Fe and biliverdin. Biliverdin is further reduced into bilirubin via bilirubin reductase. Hmox-1 is 32 kDa and expressed in lymph and other tissues that takes place in red blood cell degradation such as reticuloendothelial cells in liver and bone narrow. Hmox-1 is an essential cytoprotective mechanism in terms of its activation during inflammation, ischemia, hypoxia, hyperoxia, hyperthermia or radition. (12,17).

Several studies show Hmox-1 expressed in vasculature provides protection toward vascular inflammation and it might play role as immunomodulatory in which antioxidant protecction of Hmox-1 is a defence mechanism toward vascular inflammation on antigen-independent ischemia reperfusion injury (IRI) thar reintroduce oxygen after ischemia and generation of reactive oxygen species (ROS) as the main pathogenesis (17,18)

Hmox-1 system has been recently noted as its important role in placental vascular physiology. Induction of Hmox-1 has been investigated as antihypertension agent in several trials. Although its underlying mechanism requires further studies, it is suggested that Hmox-1 mechanism is associated with action of potential vasolidator CO, sFlt-1 inhibitor and bilirubin antioxidant. Stimulation of oxidative stress such as peroxinitrite, modified lipids, hypoxia, hyperoxia, ischemia/ reperfusion, hyperthermia and endotoxic shock are regulated by Hmox-1 expression. Hmox-related products has advantages in regulation of biological process such as oxidative stress, inflammation, apoptosis and angiogenesis in various condition (12,17-20)

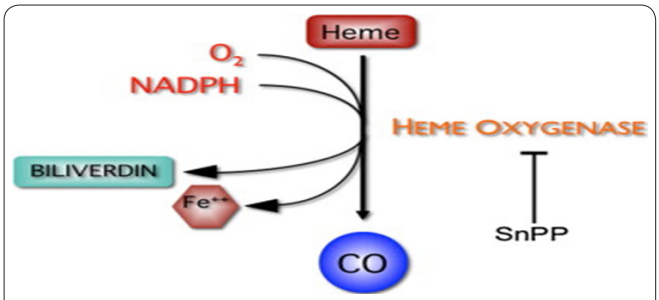

Figure 1. Pathway of Hmox-1 and its related product (17). Heme is degraded by heme oxygenase into carbon monoxide, Fe and biliverdin. Biliverdin is further reduced into bilirubin via bilirubin reductase.

Deficiency of Hmox-1 in human is usually linked to pregnancy abnormalities such as recurrent miscarriages, intrauterine growth retardation (IUGR) and preeclampsia. This has been shown in previous studies where Hmox-1 on mRNA and protein level were expressed in rat and human placenta. During development, expression of Hmox-1 mRNA in placenta increase along with gestational age. Hmox system has protective effects during pregnancy toward physiological threat (17,18)

Wikstrom et al., conducted a study on effects of cigarette toward preeclampsia in Swedia. Women who continue smoking from middle to end of pregnancy has 50% lower risk of preecclampsia than women who did not consume tobacco. Tobacco burning-procuts contain CO which is responsible in reducing preeclampsia onset in the population. Further study observed effect of Hmox-1 induction on RUPP of placental ischemia-induced hypertension rat. Hmox-1 induction by Cobalt Protoporphyrin shows reduction to 50% of RUPP-induced hypertension at 19 days of gestational age, as well as increasing angiogenic balance in placenta and increasing free VEGF in maternal circulation. Induction of Hmox-1 also significantly affects placental oxidative stress and characteristics of preeclamptic patients and RUPP rats due to overproduction of bilirubin (21,22).

Hmox-1 has been reported to be expressed in mRNA and protein level. Study done by Farina et al., shows Hmox-1 mRNA level in chorionic villi at 11 weeks of gestational age in preeclamptic women was lower than that in normal pregnancy. This indicate down regulation of antioxidant, Hmox-1, which can be associated with pathogenesis of preeclampsia in placenta. These findings are also supported by Sekizawa et al. that report on Hmox-1 mRNA level in blood of preeclamptic women was lower than that in normal preganancy at 15-20 weeks of gestational age (23,24)

Angiogenic imbalance in preeclampsia is caused by increased sFlt-1 and sEng and decreased P1GF that affects level of Hmox-1 in regulating biological process. Therefore, angiogenic imbalance repair is a important step which can potentially cure preeclampsia (12,17)

Correlation between Statin, Hmox-1, sFlt-1, and PlGF in preeclampsia

The main cause of preeclampsia has not been established. Recently, endothelial damage, placental ischemia and angiogenic imbalance are suggested as presdisposing factors of preeclampsia. Placental ischemia occurs due to red blood cell damage in placenta area that results in exessive release of heme and Fe into circulation. It further induces ferritin system, resulting in high level of ferritin in blood.

On the other hand, angiogenic imbalance increase

sFlt-1 and sEng, decrease PlGF level (2-4). Repairment of angiogenic imbalance is therefore important in preeclampsia treatment. Recent study exhibits pharmocological role of Hmox-1 and its related products that recover angiogenic balance and reduce oxidative stress in placental ischemia. Heme oxygenase is degrading enzyme of heme to form biliverdin, free Fe and CO. Biliverdin generates bilirubin antioxidant facilitated by biliverdin reductase that reduce red blood cell damage as major part in ischemia. Meanwhile, CO is a strong vasolidator to inhibit sFlt-1 and sEng release, as well as to increase P1GF. sFlt-1, sEng and P1GF affects angiogenic imbalance as one of predisposing factors of preeclampsia (4,2,7).

Expression of Hmox-1 can be induced by several compounds including drugs clinically used in cardiovascular disease such as statin, rapamycin, erytrhropoetin, and prabucol. Increse Hmox-1 by statin can be observed in smooth muscle of blood vessels and macrofag. Statin affects angiogenesis with two approaches, as proangiogenic (nanomolar) and antiangiogenic (17,18,20)

Role of Statin in Preeclampsia

It has been confirmed that reduced sFlt-1 below threshold is an important key of preeclampsia treatment, as well as protection of Hmox. Hence, an agent to compensate deficiency or to induce activity of Hmox which ultimately reduce sFlt-1 and sEng is one of potential strategy in preeclampsia treatment. Many researches has been performed to prevent and cure preeclampsia. To date, statin derivatives are still used in preeclampsia treatment. Statin has been usually used in hypercholesterolemia by inhibiting HMG-CoA reductase in liver that further decrease cholesterol LDL. Moreover, statin has protective effect in endothelial cells (Figure 2). Most importantly, statin induce Hmox-1 expression and inhibits sFlt-1 release mediated by cytokines in placental culture.(12,17,23).

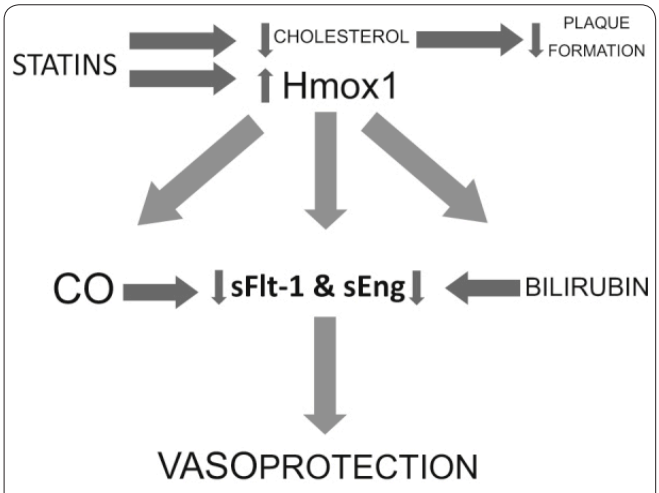

Figure 2. Role of statin and Hmox-1(17). Statin, usually used to reduce cholesterol, increases Hmox-1 production which is responsible in Heme degradation resulting in end product: biliverdin, free Fe and CO. Biliverdin generates bilirubin antioxidant facilitated by biliverdin reductase that reduce red blood cell damage as major part in ischemia. Meanwhile, CO is a strong vasolidator in angiogenesis in which it reduces levels of sFlt-1 and sEng and increase levels of P1GF. sFlt-1, sEng and P1GF.

In other study, rats treated with statin exhibits increase Hmox activity as indicated by increase CO release in tissue, along with increase antioxidant plasma. Exposure of Hmox inhibitor and statin, shows failure in increasing antioxidant level in rats, that might be due to regulation of Hmox pathway statin. Thus, statin has been an interest to significantly reduce circulation of anti-angiogenic factors in preeclamptic women (17,19,23).

However, statin remain controversial due to lack of information regarding its use during pregnancy. It is suggested that there is teratogenic effects to fetus, although it has not been fully proved. Other studies confirm that statin has no teratogenic effects in fetus at the beginning of pregnancy.(24-26) To minimize the negative outcome, hospitable statin derivatives such as pravastatin can be an alternative which is the most polar one and hydrophilic among others. This makes pravastatin unable to pass through placenta except to be a potential sterol inhibitor (19,26).

Pravastatin is a competitive inhibitor of HMG-CoA reductase that catalyze rate-limiting in synthesis of cholesterol. In some trials conducted on animal model of preeclampsia with over-expressing sFlt, pravastatin shows reduced oxidative stress and blood pressure. Moreover, pravastatin significantly reduces sFlt-1 level and increases P1GF level in same rat. This shows ability of pravastatin to increase P1GF and neutralize effects of sFlt-1 that promote preeclampsia. In summary, pravastatin can be a candicate in preeclampsia treatment by balancing angiogenic and antiangiogenic (17,19).

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