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Review

Biomolecular basis of the role of chronic psychological stress in the development and progression of Atherosclerosis

Bipradas Roy* and Mahbub E Sobhani

Biotechnology and Genetic Engineering Khulna University, Khulna-9208, Bangladesh

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Psychological stress has extreme adverse consequences on health. However, the molecular mechanisms that mediate and accelerate the process of atherosclerosis due to stress hormone are not well defined. This review has focused on diverse molecular paths that come out in response to chronic psychological stress via the release of excessive glucocorticoids (GCs), involved in the progression of atherosclerosis. GCs acts as a pathological agent of insulin resistance (IR), inhibition of NO and prostacyclin synthesis, over synthesis of reactive oxygen species (ROS) and Angiotensin-II (AT-II). All these processes may induce changes in blood pressure through different mechanisms. In one side high blood pressure may disrupts the arterial endothelial cells and on the other side IR triggers the increased production of very low density lipoprotein (LDL). LDL penetrates through the disrupted endothelial linings into the sub-endothelial space and converts into oxidized LDL (Ox-LDL).Ox-LDL binds to the arterial endothelial cells and signals for the expression of vascular cell adhesion molecules and other peptides. Circulatory monocytes bind to the vascular cell adhesion molecules and penetrate through the endothelial layer and convert into macrophage within the sub endothelial space. Macrophages and some vascular smooth muscle cells (VSMC) in the medial layer engulf the Ox-LDL and convert into foam cells. VSMC also migrate from the medial layer and arrange around the dead necrotic core of the foam cells to form a fibrous cap as well as atherosclerotic plaque.

Key words: Chronic psychological stress, Glucocorticoid, Insulin Resistance, LDL,AG-II, VSMC, Atherosclerosis.

Introduction

Atherosclerosis is a disease that causes medium-sized and larger blood vessels in the body to harden and narrow. Atherosclerosis is the ultimate cause of most of the coronary heart diseases like stroke, heart attack, myocardial infarction, paralysis and so on. On the other hand, chronic psychological stress can be defined as a factor resulting from a long term exposure of stimulus that triggers a series of events activating physiologic responses which is generally non-adaptive in the body". Stress can be a threat to homeostasis provoked by a variety of stressor, such as environmental, psychological or physiological factors. In recent decades, there has been increasing interest in exploring the relationship between psychological stress and various health conditions. An enlarging body of evidence suggests the presence of interactions between the immune system, the central nervous system (CNS) and the endocrine system, where these systems can be influenced by psychological and social factors (Roger CM Ho, 2010). Extensive studies support that behavioral and psychological factors contribute significantly to the development and prevention of atherosclerosis. Psychological factors, specifically depression, anxiety, personality factors, social isolation, and chronic and sub-acute life stress, are known to be related to the risk of heart disease (Ick-Mo Chung 2005). This spurred on the relentless effort to explore how behavior and biological systems could interact in the endeavor to uncover more mysteries of the human body (Roger CM Ho, 2010). This review addresses the biomolecular mechanism of understanding the role of acute and chronic psychological

*Corresponding Author. E-mail:biplobbge06ku@gmail.com
Tel: +8801737260794

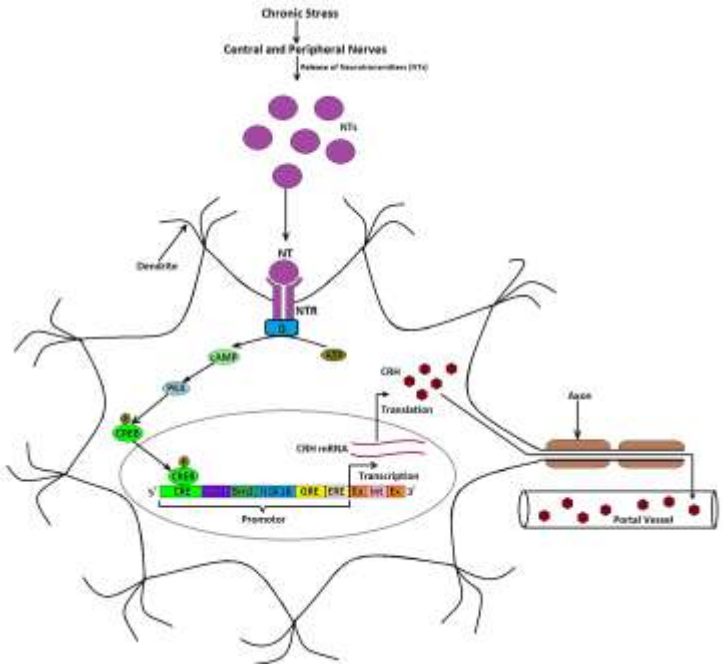

Figure 1. Chronic stress induced synthesis of CRH by CRHergic neurons. Psychological chronic stress stimulates the central & peripheral nervous system to secret monoaminergic NTs. These NTs binds to its receptor on CRHergic neurons of the PVN that trigger intracellular cascade. In this cascade cAMP is a second messenger that activates Protein Kinase A (PKA), PKA further activates cAPM Response Element Binding Protein (CREBP) through phosphorylating it. Phosphorylated CREB act as a transcription factor that bind to the cAMP response element (CRE) of the promoter sequence and triggers the transcription of CRH gene.

stressors on the immune system and development of atherosclerosis as well as established the relationship between the chronic psychological stress and the atherosclerosis.

Chronic stress and the HPA axis

A key component of this stress system is the hypothalamic-pituitary-adrenal (HPA) axis. Chronic stress can overcome negative feedback regulation of the HPA axis, leading to a substantial increase in cortisol production. Parvocellular PVN CRH/AVP neurons are the motor neurons of the stress response which is located in the HPA axis (Seasholtz 2000; E. Ron de Kloet 2005; Saebom Lee, 2010). In response to a stressful stimulus, neural signals(neurotransmitters) from the central and peripheral nervous system converge on the paraventricular nucleus (PVN) in the hypothalamus and signal for increased synthesis and release of corticotrophin releasing hormone (CRH) through cAMP-PKA mediated pathway (Herman 2002; E. Ron de Kloet 2005; Patricia Joseph-Bravo 2006; Kazunori 2009) (Figure 1).

CRH and pituitary

This peptide (CRH) are released into the hypophyseal portal vessel blood and carried to the adenohypophysis of anterior pituitary, where it binds to CRH receptor on the hormone secreting cell. As with other Gs protein–coupled membrane receptors, CRH receptors stimulate production of the intracellular second messenger cAMP. Activation of this pathway induces the increased production of propiomelanocortin (POMC) and adrenocorticotropic hormone (ACTH). CRH also stimulates the locus coeruleus to secrete norepinephrine (NE) at sympathetic nerve endings (Ick-Mo Chung, 2005).

ACTH and adrenal gland

The mechanism of ACTH action follows the classical peptide hormone rules. Indeed, ACTH binds to its receptor located on adrenal cell membrane activating a Gs-protein resulting in an increase of intracellular cyclic adenosine monophosphate (cAMP). cAMP activates protein kinase A (PKA). This PKA is the central activator of ACTH function (Simpson ER 1983; BISCHOF 1997; Li 2008). PKA stimulates cortisol synthesis and secretion by affecting several steps in the steroidogenesis pathway: **(a)** PKA increases the number of low-density lipoprotein (LDL) receptors resulting in increased cholesterol uptake, the precursor for the biosynthesis of all steroid hormones. **(b)** In the LDL, cholesterol esterified with other

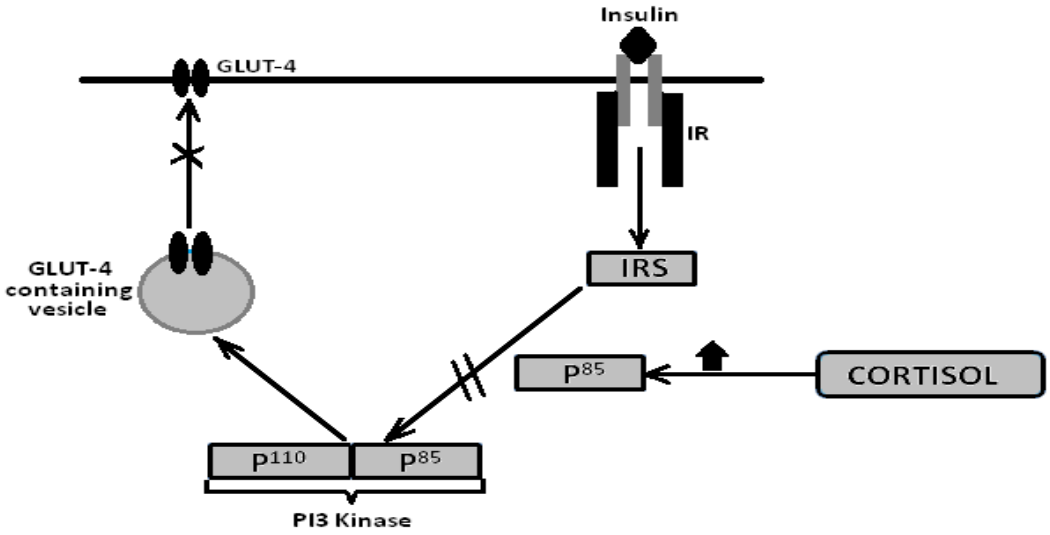

Figure 2. Inhibition of insulin action by cortisol. Excess cortisol induce the over expression of p85 genes. This excess p85 subunit then compete with the p85-p110 heterodimeric protein for the same binding site of IRS. This imbalance decrease the activity of PI3 kinase and ultimately this inability of PI3 kinase led to the decrese in GLUT-4 activity.

substances. Cholesterol Ester Hydroxylase (CEH) is an enzyme which is used for the separation of free cholesterol from its esterified form. PKA stimulates the transcription of CEH gene. **(c)**Free cholesterol side chains are removed and converted to pregnenolone by the enzyme Cyt P450s. P450c17 hydroxylates pregnenolone to give to 17-OH-pregnenolone,which then travels to the endoplasmic reticulum for conversion to 11-deoxycortisol by the enzyme P450c21. 11-deoxycortisol moves back to mitochondria where another hydroxylation takes place at position 21 to produce the final product, cortisol by the enzyme P45011β. PKA stimulates the synthesis of all the P450 family enzymes by regulating the respective genes. Cortisol is not stored in the adrenal cortex but is promptly secreted (Gill 1972; Li 2008).

Glucocorticoid and insulin resistance

There are many experimental evidence that glucocorticoid induce insulin resistance (D Dardevet 1999; Hollingdal, Juhl et al., 2002). Normally binding of insulin to its receptor activates a series of mediator that ultimately causes the translocation of glucose transporter-4 (GLUT4)-containing vesicles to the cell surface. This action of insulin promotes blood glucose uptake and storage under anabolic conditions. This insulin-triggered signalling cascade can be attenuated or 'turned down' by Cortisol (Newgard 2008; Draznin 2006). PI3-kinase is a heterodimeric protein, consisting of a regulatory subunit (p85) which is tightly associated with a catalytic subunit, (p110). The regulatory subunit p85 is encoded by at least three genes that generate highly homologous products. Two isoforms are termed p85α and p85β. Three splice variants of p85α have been reported, including p85α itself, p55α, and p50α. The third gene product is p55γ. p85α, however, appears to be the most abundant isoform. Normally, the regulatory subunit (p85) exists in stoichiometric excess to the catalytic one (p110), resulting in a pool of free p85 monomers not associated with the p110 catalytic subunit. Thus, there exists a balance between the free p85 monomer and the p85-p110 heterodimer, with the latter being responsible for the PI 3-kinase activity. Increased or decreased expression of p85 shifts this balance in favor of either free p85 or p85-p110 complexes. Because the p85 monomer and the p85-p110 heterodimer compete for the same binding sites on the tyrosine-phosphorylated IRS proteins (Draznin 2006). This imbalance could cause the decrease of PI3-kinase activity as well as the subsequent activities like glucose transport, cell growth & differentiation, gene expression and so on **(**Figure 2**).**

Insulin resistance and lipoprotein lipase (LPL) activity

The tissue expression profile of LPL is regulated during a number of physiological states, with reciprocal changes often being seen that help to direct fatty acid utilization according to the specific metabolic demands. Such changes in LPL expression are mediated predominantly through the action of hormones, such as insulin, glucocorticoid, and adrenaline during the diseased condition like atherosclerosis, diabetes, cachexia & infection (Ramji 2002). Potential sites for regulation of cardiac LPL include: **(a)** nucleus (transcriptional control), (**b)** rough endoplasmic reticulum (maturation of LPL by

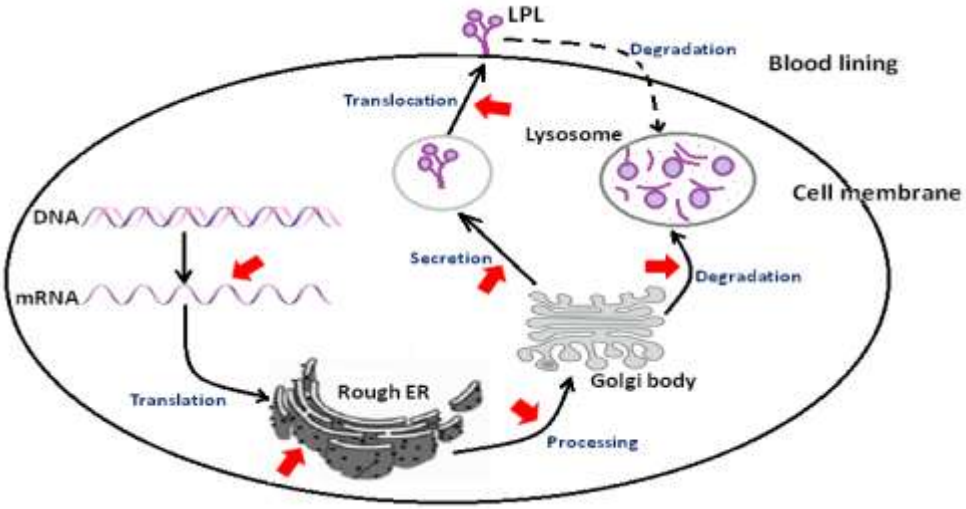

Figure 3. Regulation of LPL synthesis by insulin. Following synthesis in the ER, LPL is exported to the Golgi body for further processing. Then the processed LPL either undergo liposomal degradation or translocate on the site of activation. The red arrows indicating the effects of insulin.

glycosylation), **(c)** Golgi network (vesicular transport and secretion of LPL), **(d)** plasma membrane (LPL binding to the cell surface), and **(e)** vascular endothelial cell surface (vectorial transfer and recycling of the enzyme). Of these sites, the majority of studies have focused on enzyme regulation at the transcriptional and translational levels. The unique characteristic of LPL is that in some tissues like adipose and heart, changes in activity can occur independent of alterations in LPL mRNA. Such changes would be desirable given that during conditions like insulin resistance wherein insulin levels are altered, and FA utilization is augmented, rapid increase in LPL activity may not match the slow turnover of LPL mRNA (Ramji 2002; Thomas Pulinilkunnil 2006). Insulin mediated control of LPL occurs post transcriptionally. Such post-transcriptional regulation can potentially be mediated at a number of steps, including mRNA stability, translation, protein degradation, processing, secretion, translocation to the site of action, and competitive inhibition by products (Figure 3).

Glucocorticoid and hypertension

Binding of glucocorticoid with glucocorticoid receptor (GR) reduce the activity of vasodilator systems. There are four possible regulatory pathways through which glucocorticoid induce elevated blood pressure by regulating vasodilator system.

(a) Regulation on the nitric oxide (NO) production

The nitric oxide (NO) pathway plays a major role in regulation of blood pressure by inducing vasodilation and it is also very essential for maintaining the vascular tone**.** NO is generated by nitric oxide synthase from L-arginine and oxygen. In addition to regulating NOS expression, glucocorticoid also decreases **(1)** the availability of L-arginine through repression of L-arginine transporters; **(2)** the production of tetrahydropterin, a necessary cofactor for NOS, By repressing the rate-limiting enzyme of tetrahydropterin synthesis from GTP; and **(3)** the regeneration of L-arginine via repression of argininosuccinate synthase **(**Figure 4**).** All these effects lead to reduced NO and subsequently elevated blood pressure (Whitworth, Schyvens et al. 2002; Xiao Hu 2006).

(b) Regulation by the production of reactive oxygen species (ROS)

Another related pathway that also contributes to blood pressure regulation by glucocorticoid is the reactive oxygen species (ROS) mediated pathway. Increased oxidative stress in vasculature is known to cause hypertension (Paravicini and Touyz 2006; Xiao Hu 2006). ROS interacts with NO to form highly reactive peroxynitrite. The deleterious effect of peroxynitrite is twofold. **Firstly,** it reduces the NO availability and NO-dependent vasodilation. **Secondly**, peroxynitrite causes vascular damage through nitration of proteins (Alvarez, Rubbo et al. 1996; Xiao Hu 2006)**.** ROS can be generated by numerous enzymes. The most relevant sources of ROS with respect to hypertension are NADPH oxidase, xanthine oxidase, uncoupled eNOS, and mitochondrial electron transport chain. In addition to promoting ROS production, glucocorticoid also regulates antioxidant enzymes such as superoxide dismutase

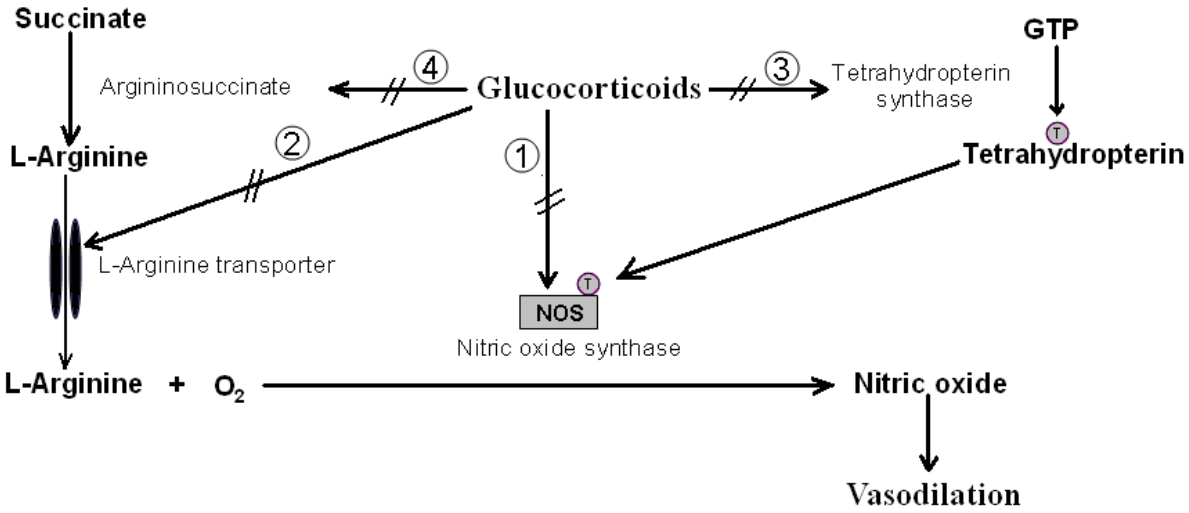

Figure 4: Four possible mechanisms in the regulation of endothelial nitric oxide production by glucocorticoids. (1) Glucocorticoid directly repress the expression of endothelial nitric oxide synthase(NOS) production. **(2)** Glucocorticoid decrese L-arginine availability through repress the expression of L-arginine transporter. **(3)** Tetrahydropterin is an essential cofactor for NOS activation and is synthesized from GTP by the action of tetrahydropterin synthase. Glucocorticoid decreases the production of tetrahydropterin by repressing tetrahydropterin synthase**. (4)** Regeneration of L-arginine from succinate is occoured by the enzyme arginosuccinate. Glucocorticoid inhibit the regeneration of L-arginine by repressing the expression of argininosuccinate.

(SOD).The specific effect of glucocorticoid on the expression of these antioxidant enzymes seems to be tissue-dependent (Pereira B 1999; Xiao Hu 2006).

(c) Regulation on the prostacyclin synthesis

Another mechanism by which glucocorticoid regulates vasodilation involves the inhibition of prostacyclin synthesis. Prostacyclin is an effective vasodilator and inflammation mediator. Glucorticoid represses the expression of a number of enzymes involved in prostacyclin synthesis, including the cycloxygenases (COX-1 and COX-2). COX-1 is considered the rate-limiting enzyme in prostacyclin synthesis. The inhibition of COX-1 expression by glucocorticoid in endothelial cells seems highly context dependent (Crutchley, Ryan et al. 1985; Xiao Hu 2006; Jun SS. 1999.).

(d) Regulation on the Angiotensin-II production

Besides the inhibition of vasodilation, glucocorticoid also regulates vascular tone by potentiating vasoconstriction through regulation of AT-II levels (Li 1996; L. Morgan 1996; Ullian 1999). Stress induced Angiiotensinogen is mainly produced in the liver cells (Hepatocyte) by the regulation of glucocorticoid**.** This angiotensinogen is converted to angiotensin-I by the action of rennin, and finally converted into angiotensin-II by the action of angiotensin converting enzyme (ACE) (Li 1996). Angiotensin-II also has direct effects on the adrenal gland by stimulating aldosterone and catecholamine secretion and indirect effect on the HPA axis through the activation of CRH (Ick-Mo Chung, 2005).

Low density lipoprotein penetration into the intima

Low density lipoprotein (LDL) in the plasma originates from very-Low Density Lipoprotein (vLDL) produced by the liver. vLDL is converted to LDL by the action of Lipoprotein Lipase (LPL), an enzyme that hydrolyzes triglycerides into vLDL, removing them from the vLDL particle and releasing free fatty acids. The removal of triglycerides from vLDL by LPL leaves a greater proportion of Cholesterol, increasing the density of the particle and changing it to LDL. One of the first steps in the development of Atherosclerosis is the passage of LDL out of the Arterial lumen into the Arterial wall.LDL is considered to be the main atherogenic class of lipoprotein, and elevated levels of LDL represent one of the most important risk factors for atherosclerosis and cardiovascular morbidity (Martin 1986; Gouni-Berthold 2002). It has been proposed that due to hypertension and vascular damage most of the circulating LDL is transported through the vascular endothelium by transcytosis (classic LDL receptor independent pathway) via plasmalemma vesicles that deliver about 85% LDL to other cells of the vascular wall (Vasile 1983; Gouni-Berthold 2002). Elevated blood pressure & increased levels of circulating LDL increase transport of the circulating LDL into the subendothelial space (Daly 1972; Fry 1987; Curmi 1990; Lusis 2000; Gouni-Berthold 2002)

or prolongs the retention of low density lipoprotein cholesterol (LDL-C) in the intima (Williams 1995; Bihari-Varga 1988; Gouni-Berthold 2002).

Retention of low density lipoprotein into the intima

LDL retention into the vessel wall seems to involve interactions between the LDL constituent apolipoprotein B-100 (apoB-100) and matrix proteoglycans. In addition to LDL, Proteoglycans contain long carbohydrate side-chains of glycosaminoglycans, which are covalently attached to a core protein by a glycosidic linkage. The glycosaminoglycans consist of repeating disaccharide units, all bearing negatively charged groups, usually sulfate or carbohydrate groups. In vitro, LDL binds with high affinity to many proteoglycans found in the artery wall, including dermatan sulfate proteoglycans (for example, biglycans) and chondroitin sulfate proteoglycans (for example, versican), which are produced by smooth muscle cells. The interaction between LDL and proteoglycans apparently involves clusters of basic amino acids in apo-B100, the protein moiety of LDL, that interact with the negatively charged glycosaminoglycan proteoglycans or by bridging molecules, such as apo-E or lipoprotein lipase (Jan Borén 1998; Lusis 2000; Roland Stocker and John F. Keaney 2004).Thus these data support an important role for proteoglycan binding in the retention of apolipoprotein B-containing lipoproteins in the early stages of atherosclerosis. In addition to proteoglycan binding, lipolytic and lysosomal enzymes in the extracellular matrix also appear to play a role. For example, lipoprotein lipase enhances the adherence of LDL in vitro and this effect is independent of enzymatic activity (Roland Stocker and John F. Keaney 2004).

Modification of LDL into the intima

Native LDL is not taken up by macrophages rapidly enough to generate foam cells, and so it was proposed that LDL is somehow ‘modified’ in the vessel wall. It has subsequently been shown that trapped LDL does indeed undergo modification, including oxidation, lipolysis, proteolysis and aggregation, and such modifications contribute to inflammation as well as to foam-cell formation. One of the modifications most significant for early lesion formation is lipid oxidation as a result of exposure to the oxidative waste of vascular cells (Lusis, 2000). The modification mainly occurs in the apolipoprotein part of LDL so a configurational change take place on LDL. During this process, LDL is subject to oxidation and, as a consequence, apolipoprotein B-100 lysine groups are modified so that the net negative charge of the lipoprotein particle increases. This modification of apolipoprotein B-100 renders LDL susceptible to macrophage uptake via a number of scavenger receptor mediated pathways producing cholesterol ester-laden foam cells (Roland Stocker and John F. Keaney 2004).

The process of LDL oxidation is associated with a number of other potentially proatherogenic events. For example, during the initial stages of in vitro LDL oxidation, modification of LDL lipids can occur in the absence of any changes to apolipoprotein B-100. Such modified LDL has been termed "minimally modified LDL"and shown in vitro to induce the synthesis of monocyte chemotactic protein-1 in both smooth muscle and endothelial cells (Cushing, Berliner et al. 1990; Rajavashisth TB 1990; Roland Stocker and John F. Keaney 2004) resulting in the recruitment of inflammatory cells (Navab M 1991).This particular step appears critical as mice lacking the receptor for monocyte chemotactic protein-1 are resistant to atherosclerosis (Boring L 1998; Gosling J 1999; Roland Stocker and John F. Keaney 2004). More heavily in vitro oxidized LDL (ox-LDL)," is chemotactic for Monocytes (Quinn MT 1987) and T lymphocytes (McMurray HF 1993; Roland Stocker and John F. Keaney 2004), perhaps as the result of lysophosphatidylcholine formed during oxidation (Steinbrecher UP 1984). Oxidized LDL has also been shown to stimulate the proliferation of smooth muscle cells (Stiko-Rahm A 1992) and to be immunogenic by eliciting the production of auto-antibodies (Parums DV 1990; Salonen JT 1992; Roland Stocker and John F. Keaney 2004) and the formation of immune complexes that can also facilitate macrophage internalization of LDL (Roland Stocker and John F. Keaney 2004).

Oxidized LDL induced expression of adhesion molecules and other factors

Ox-LDL is a potent inducer of inflammatory molecules. It stimulates inflammatory signaling by Endothelial cells, releasing chemotactic proteins such as Monocyte Chemotactic Protein-1 (MCP1) and growth factors such as Monocyte Colony Stimulating Factor (mCSF), which favor the recruitment of Monocytes into the Arterial wall (Catapano, Maggi et al. 2000). Ox-LDLs also promote the differentiation of Monocytes into Macrophages that take-up the oxidized LDL and subsequently converted into Foam cells, the hallmark cells of Atherosclerosis. Apart from that, Ox-LDLs also have other effects, such as inhibiting the production of Nitric Oxide (NO), an important mediator of vasodilation and the expression of endothelial leukocyte adhesion molecules. All these functions are performed by Lecti like ox-LDL Receptor-1 (LOX-1) mediated signal transduction pathway (Toru Kita * 1999; Jawahar L. Mehta a 2006; Xiu-Ping Chen 2007) (Figure 5).In addition to LOX-1, nuclear factor- kB (NF-kB) (a crucial transcription factor) is also an important mediator of this pathway which controls the transcription

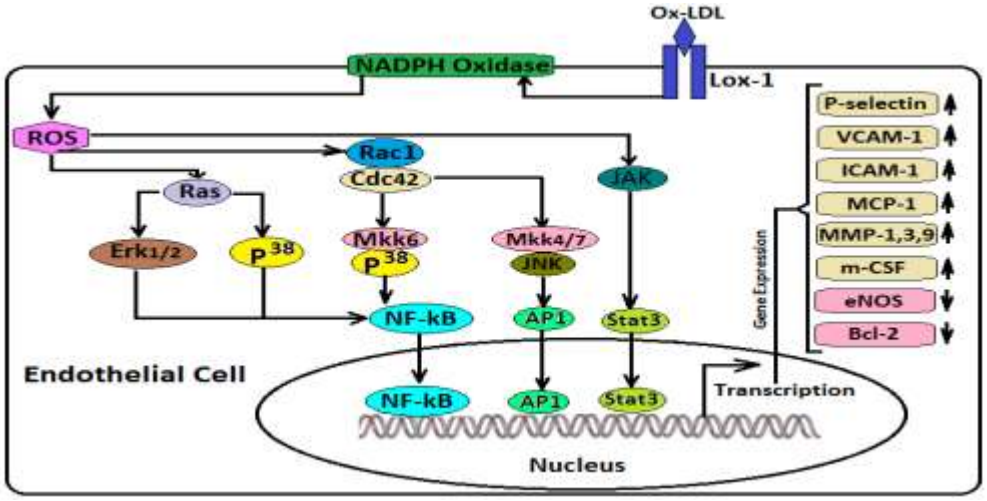

Figure 5. Ox-LDL induced signal transduction pathways. Binding of ox-LDL to LOX-1 activates the NADPH oxidase on the cell membrane through some unknown mechanisms that results in the quick increase of intracellular ROS. The elevated level of ROS then in turn activates NF-kB, AP-1 and Stat3 through activation of different intermediate signaling proteins including Ras, Rac1, Cdc42, Erk1/2, P^{38}, Mkks, JNK and JAK. This NF-kB not only induce the over expression of P-selectin, VCAM-1, ICAM-1, MCP-, MMPs, mCSF which are responsible for the attachment and migration of monocyte to the endothelium but also repress the expression of eNOS & Bcl-2. Cdc42, cell division cycle 42; Erk1/2, extracellular signal-regulated kinase 1/2; JAK, Janus kinase; JNK, c-jun N-terminal kinase; MKK, mitogen-activated kinase kinase; NF-κB, nuclear factor kappa B; Rac1, Ras-related C3 botulinum toxin substrate 1; ROS, reactive oxygen species; Stat3, signal transducer and activator of transcription.

of the genes of cytokines, chemokines, adhesion molecules, acute phase proteins, regulators of apoptosis, and cell proliferation (Menno P.J. de Winther 2005; Xiu-Ping Chen 2007).

Entry of monocyte to the artery wall (intima)

The entry of particular type of leukocytes into the artery wall is mediated by adhesion molecules and chemotactic factors. Vascular cell adhesion molecule-1(VCAM-1) binds particularly those classes of leukocytes found in nascent atheroma: the monocyte and the T lymphocyte(Libby, 2002).In addition to VCAM-1, P- and E-selectin also seem to contribute to leukocyte recruitment**.** The nonrandom attraction of mononuclear cells to specific tissue targets is governed by sequential steps in the interaction with the vessel wall, namely rolling mediated by selectin-carbohydrate interactions, integrin-dependent arrest, and transendothelial diapedesis triggered by chemokines. (Lusis 2000; Christian Weber 2004; Zernecke 2004; R.L. Tiwari 2008).

Differentiation of monocytes into macrophage in the arterial intima

Once trapped in the arterial wall, monocytes undergo differentiation. In the arterial intima, monocytes that differentiate into macrophages are characterized by a continuously increasing volume of the cytoplasm containing vesicles, vacuoles, primary and secondary lysosomes. The differentiation of monocytes into macrophages is accompanied by macrophage colony stimulating factor (M-CSF). There are evidence that macrophage express different types of scavenger receptors like Class A, ClassB & classes(D-E) on their surface in atherosclerotic lesion. Out of all the scavenger receptors, type A and CD-36 scavenger receptors are more important(Lusis 2000; R.L. Tiwari 2008). All these receptors are expressed by Ras- MAPKs mediated pathway induced by M-CSF **(**Figure 6**)**. There are some evidence that in addition to M-CSF, Ox-LDL also induce the expression of Scavenger Receptor A(SR-A) by macrophage as well as smooth muscle cells (SMCs) in the atherosclerotic lesion (Michele Mietus-Snyder 2000; Amanda C. Doran 2008)**.**

Mechanisms of foam cell formation

In the arterial wall, macrophages react to the plaque microenvironment by internalizing and metabolising a variety of subendothelial components (Skalen 2002; Itabe 2003; Williams 2005; Bobryshev 2006). Some lipoprotein aggregates are internalised by macrophages through a scavenger receptor mediated pathway (Figure 7)**.** Scavenger receptors are characterised by different structures and can bind and internalise a wide range of polyanionic ligands, including modified forms of LDL like Acetylated LDL (Ac-LDL) and Ox-LDL (Skalen 2002; Itabe 2003; Williams 2005; Bobryshev 2006; R.L. Tiwari

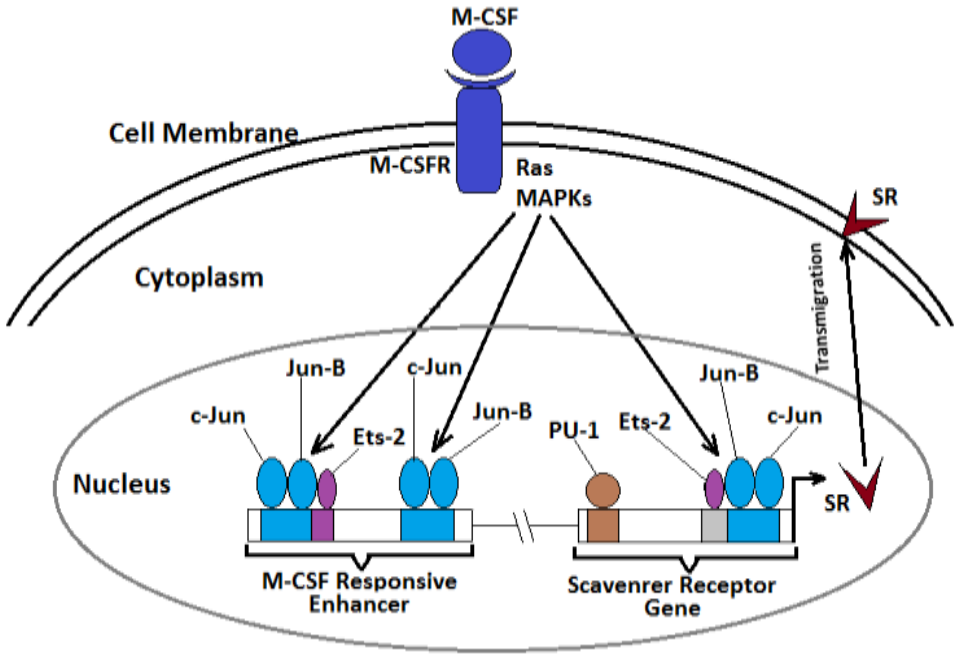

Figure 6. Mechanism of M-CSF induced transcriptional control of scavenger receptor (SR). Transcriptional activation of the SR-A gene by M-CSF is mediated by a Ras-dependent signal transduction cascade that stimulates the expression and activities of AP-1 and Ets (E-twenty six) domain transcription factors (Not shown in the figure). MAPK induced transcription factors c-Jun, JunB (members of AP-1 family of transcription factors), and Ets2 (member of Ets family of transcription factors) bind to regulatory elements in the M-CSF-dependent enhancer and act synergistically to stimulate transcription. Activation of the SR gene by M-CSF is mediated by a M-CSF-dependent enhancer.These transcription factors are downstream targets of a Ras-dependent mitogen-activated protein kinase (MAP-K) cascade that controls both their levels of expression and their transcriptional activities.

2008). Uptake of Ox-LDL by scavenger receptors-A (SR-A) and CD36 constitute the major pathways for foam cell formation in vivo and that lipid uptake by either receptor is a pro-atherosclerotic event. There is evidence that macrophages transforming into foam cells through the retention of modified lipoproteins in nondegraded or minimally degraded forms (Bobryshev 2006).

Although the majority of foam cells in the atherosclerotic lesion are thought to be derived from macrophages, SMCs also give rise to a significant number of lipid laden cells (Michele Mietus-Snyder 2000; Amanda C. Doran 2008).

Foam cells and the formation of necrotic cores

Fibrous plaques are characterized by a growing mass of extracellular lipid, mostly cholesterol and its ester, and by the accumulation of SMCs and SMC-derived extracellular matrix (Lusis 2000). Formation of a distinct fibrous cap over a large lipid core occurs only as a late consequence of atherosclerosis. The lipid core arises because macrophages die by apoptosis and spill their lipid contents. The plaque cap could form by migration of typical, contractile VSMC from the media, which would account for the frequent medial wasting observed at the base of atherosclerotic plaques (NEWBY 2005). Intimal thickening constitutes the generation of new tissue at least in part using VSMC derived from the media. MMPs could catalyze removal of the basement membrane around VSMC and facilitate contacts with the interstitial matrix. This could promote a change from quiescent, contractile VSMC to cells capable of migrating and proliferating to mediate repair (NEWBY, 2005).

Discussion

During stressful condition the central and peripheral nervous system converge their signals (neurotransmitters) to the paraventricular nucleus (PVN) located in the HPA axis (E. Ron de Kloet 2005). These neurotransmitters activate the gene of CRH through corresponding mechanisms. Then in turn CRH secreted on the portal system and carried to the adenohypophysis region in the anterior pituitary gland to activate the gene of ACTH via specific mechanisms (Ick-Mo Chung, 2005). This ACTH in turn induces adrenal cortex to secret glucocorticoids and catecholamines (Simpson ER 1983; BISCHOF 1997; Li 2008). These steroid hormones

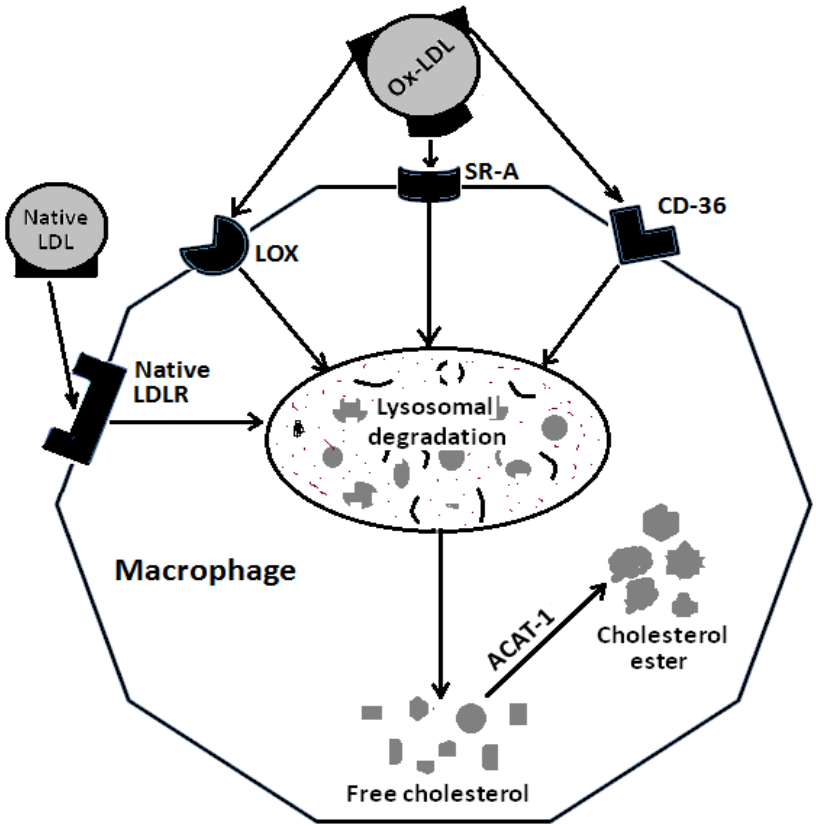

Figure 7: Convertion of macrophage to foam cell. Ox-LDL is taken up by SR-A,CD-36, and oxidized LDLR. These receptors are upregulated and accumulate LDL in a faster way than the native receptor.Native LDL is also taken up by macrophages through a process termed as pinocytosis.Free cholesterol is generated inside the macrophage via lysosomal degradation and is converted into cholesterol esters by the enzyme ACAT-1.These esters give macrophage a foamy appearance and hence the name macrophage foam cell.

induce the immune system in such a way that it could challenge the stressful condition through different mechanisms depending on the type of stress. This total process is called the “Fight and Flight response” and this happen in the case of acute stress. But in the chronic stress condition the steroid hormones (mainly glucocorticoids and catecholamines) secreted from the adrenal gland suppress the immune system and induce the progression and development of atherosclerosis. **(**Figure 8**).**

In this review we have found that LDL and arterial endothelium cells are the major two factors which are susceptible to stress and ultimately responsible for the progression and development of atherosclerosis. Psychological chronic stress induce these two factors indirectly through different complex mechanisms.

We have found that glucocorticoid is the basic hormone, secreted during the chronic stress which mainly triggers the excessive production of LDL and induce the damage of endothelium through a broad range of mechanisms. Macrophage plays a major role in atherogenesis. Macrophages express different types of scavenger receptors. Ox-LDL binds to these receptors and engulfed by the macrophage and then converts into foam cells (Itabe 2003; Williams 2005; Bobryshev 2006; R.L. Tiwari 2008).

VSMC also plays a crucial role in atherogenesis. VSMC itself express different types of scavenger receptors. They uptake Ox-LDL by these receptors and converted into foam cells (Michele Mietus-Snyder 2000; Amanda C. Doran 2008). Some VSMC also migrate to the sub-endothelial space and arrange around the dead foam cells to form a fibrous cap.

Conclusion

The physiological response of body to acute stress is helpful for the adaption of stressful situation. But chronic psychological stress is destructive for life. Beside psychological problems it also cause severe physiological problem. It is not only the root of many diseases but also

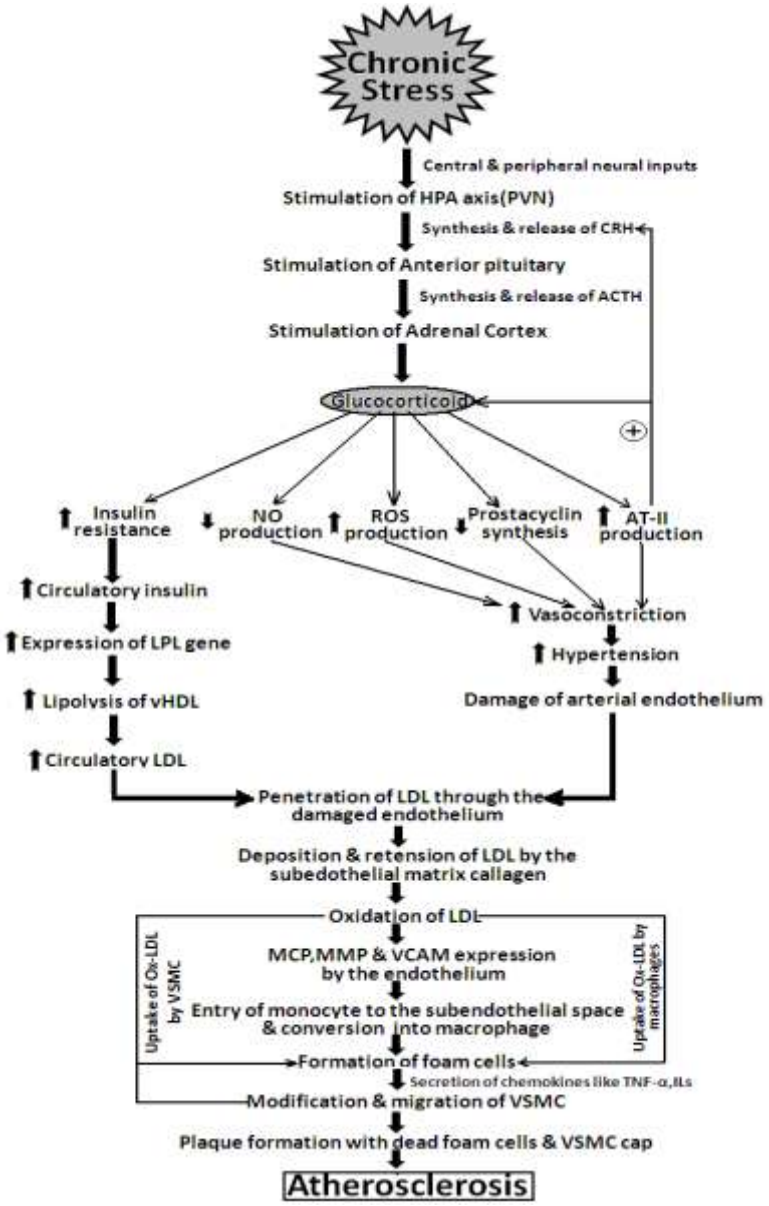

Figure 8. An overview of the chronic psychological stress induced atherosclerosis.

makes the body vulnerable and susceptible to diseases like stroke, diabetes mellitus, cancer, multiple sclerosis, autoimmune disease and so on. So it is not desirable and one can follow religious practice, mediation, exercise and other practices to be free from psychological stress.

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