Review Article

Lead induced Oxidative Stress Mediated Myocardial Injury: A Review

Debasish Bandyopadhyay[1*#], Debosree Ghosh[1], Aindrila Chattopadhyay[2]
[1] Department of Physiology, University of Calcutta, University College of Science and Technology, 92, APC Road, Kolkata, India.
[2]Department of Physiology, Vidyasagar College, 39, Sankar Ghosh Lane, Kolkata, India.
#Principal Investigator, Centre with Potential for Excellence in a Particular Area (CPEPA), University of Calcutta, University College of Science and Technology, 92 APC Road, Kolkata, India.
***Corresponding author's E-mail:** debasish63@gmail.com

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ABSTRACT

Lead is a naturally occurring toxic element. It has several industrial uses and is highly toxic for living organisms if it enters and accumulates in body. Long term exposure to this heavy metal either environmentally or occupationally may cause various types of ailments among which myocardial injury and hepato-toxicity are worth mentioning. Lead induced myocardial injury occurs primarily through lead mediated oxidative damage of myocardial tissue. Lead stimulates generation of reactive oxygen species (ROS) which causes biochemical, cytological and physiological detrimental alterations of the cardiac tissue. Administration or supplementation of antioxidant rich aqueous curry leaves (a popular spice herb, *Murraya koenigii*) extract and melatonin, a natural indole, separately have the potentiality to provide protection against lead induced myocardial damage. Their combination can provide a stronger protection against myocardial damage brought about following exposure to lead and the protection is almost complete. Thus, we can think of designing a potent drug formulation with very low or no toxicity against lead induced oxidative stress mediated myocardial injury using aqueous curry leaves extract and melatonin in combination which may have future therapeutic relevance.

Keywords: Lead, Myocardial injury, toxic element.

INTRODUCTION

In spite of marked therapeutic advancement, cardiac ailments are still remaining to be one of the significant causes of death of millions around the globe[1]. Mortality due to cardiac failure is more in developed countries and the rate is increasing in the developing countries like India[2]. The causes underneath such cardiovascular pathogenesis have been recognised to be many. Involvement of insulin resistance and diabetic cardiomyopathy[3], altered lipid profile[5], obesity, altered life style, dietary habits [6] have been found to be the major contributors. Molecular genomic study reveals genetic predisposition for cardiac arrest and ailments [7]. Environmental toxin induced oxidative stress mediated cardiac disorders and ischemic changes has been extensively evaluated and established in various models [8, 9]. Our studies also revealed the involvement of heavy metal induced oxidative stress mediated damage in cardiac tissues of male Wistar rats[10-13].

Lead is an old environment pollutant and the history of lead poisoning is almost 2500 years old [14]. Lead exposure occurs either environmentally or occupationally or by both routes [15]. Children are more susceptible to lead toxicity [16]. Chronic lead poisoning has been found to be associated with hypertension, altered lipid profile, arteriosclerosis and cardiac ailments [17]. Lead once absorbed and if not excreted enters and gets accumulated mainly in three types of tissues i.e., blood, soft tissues (liver, kidneys, brain, heart) and mineralizing tissues (bones and teeth)[18]. We have found through atomic absorption spectrophotometric studies that lead accumulated in the heart tissues and, lead induced oxidative stress plays a significant role in ischemic changes in heart [10, 11] and other organs as well [19]. We have also evaluated *in vitro* the involvement of oxidative stress in lead induced damages in heart [20]. We observed marked alterations in the activities of antioxidant enzymes in cardiac tissues following lead exposure in both *in vitro* and *in vivo* models [10, 11, 20]. The level of lead in blood has been found to be associated with increased blood pressure [21]. Most of the blood lead is known to be accumulated inside red blood cells [22]. The level of lead in bones has also been evaluated and found to be related with hepertension in individuals [23]. We found altered lipid profile and changes in blood parameters with lead acetate treatment of rats for seven consecutive days [24]. Hypertension and changes in lipid profile are considered as precursors of myocardial injuries [21, 22, 23].

Myocardial injury

The myocardium is the muscular tissue of the heart. Myocardial injury can be of various types and may lead to various cardio-myopathic conditions i.e., arythmia, shock, necrosis, ischemia, infarction and failure[25]. The myocardium is supplied blood by the two major coronary arteries and their branches. Blockage of any of these blood vessels is accounted as one of the prime cause of myocardial infarction.

Occlusion or blockage of any of these coronary vessels may result as a cause of clotting of blood or due to deposition of cholesterol inside blood vessel which ultimately narrows the vessel, lessens its elasticity and leads to blood clotting inside vessel. Inadequate or

stoppage of blood supply to the cardio-myocytes causes ischemia which can be in a small area and is termed as "focal ischemia" or if a large area of the myocardium is deprived of blood supply then it leads to "global ischemia". Extended and undiagnosed ischemia leads to myocardial infarction. Damage of the cyto-architecture of the cardio-myocytes or the endothelial cells of the coronary vessels by any means may lead to functional inadequacy of the tissues (Fig.1) [26].

The most common type of heart disease in the developed countries is the coronary artery disease(CAD) [27] and men are more susceptible than women [27]. Studies reveal an increasing report of CAD in the developing countries these days [28].

Lead toxicity and myocardial injury: involvement of oxidative stress

Studies reveal incidence of myocardial injury due to occupational or environmental exposure to toxins like combustion particulates [29] and heavy metals [30]. Air pollution has been found to be associated with increased morbidity due to cardiovascular diseases and early mortality as well [29]. Histo-morphological studies revealed that particulate matter caused marked injury and inflammatory changes in myocardial tissue of experimental rats [29]. Heavy metals like lead, cadmium and arsenic have also been found to be associated with mayocardial injuries [10-13, 31]. We have also observed significant focal ischemia in heart tissues of male Wistar rats when exposed to lead acetate for seven consecutive days (Fig.1.) [10, 11].

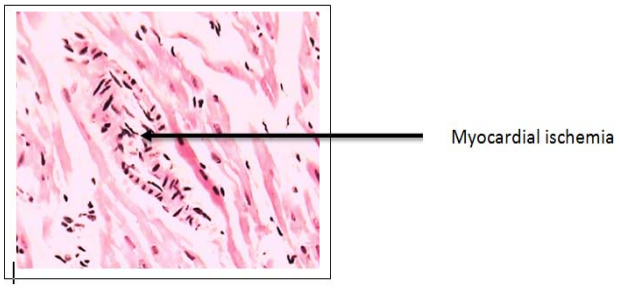

Figure 1: Section of rat heart stained with 'Eosin-Hematoxylin stain' (400 X,) showing lead induced myocardial ischemia due to exposure of the animals to lead acetate for seven consecutive days. Image captured using Magnus MLX DX 4B522434.

The mechanism of lead induced cardio-toxicity is considered multifaceted and multi-factorial [32]. After extensive research worldwide, it is inferred that lead mediated oxidative stress is a major contributor of lead toxicity [32]. Our studies showed that lead (administered to experimental rats in the form of lead acetate) increases the level of peroxidation of the membrane lipids of the cardio-myocytes and also increases the level of carbonylation of the proteins [10, 11]. This is brought about by lead induced generation of reactive oxygen species (ROS) which is evident from increase in the activity of the pro-oxidant enzymes i.e., xanthine oxidase and xanthine dehydrogenase in cardiac tissues [10, 11] of rats treated with lead acetate. Increased activity of the serum glutamate oxaloacetate transaminase (SGOT) is associated with lead toxicity which is a clinical marker of cardiac damage [10, 11]. We have also found that treatment of rats with lead acetate for seven consecutive days causes a decrease in size of the heart [10, 11]. Thus, lead has a tendency of inducing myocardial hypotrophy.

The ROS are recognised as potent inducers of DNA damage which leads to atherosclerotic changes in vessels and other deteriorative changes in cardio-myocytes . There is report of 'macro' DNA damage within atherosclerotic plaques[33]. The ROS induced mitochondrial DNA damage has been found to bear relationship with the extent of occurrence of atherosclerosis in human specimens [34]. The ROS has also been reported to cause mitochondrial DNA damage in aortas from ApoE(– / –) mice. Disruption of the antioxidant enzyme viz., manganese superoxide dismutase (Mn-SOD), a mitochondrial enzyme, indicates increased mitochondrial DNA damage and accelerated atherogenesis at arterial branch points [34]. Oxidative DNA damage increases with exposure to toxins [35]. We have found in our experimental models, marked damage of DNA isolated from heart of male Wistar rats, exposed to lead acetate for seven consecutive days. The ROS causes myocyte hypertrophy, apoptosis, and interstitial fibrosis by activating matrix metallo-proteinases. This event in the cardio-myocytes contributes significantly to development and progression of maladaptive cardiac remodeling and failure [36]. Lead exposure has also been reported to be related to clinical cardiovascular end points such as coronary heart disease, stroke, and peripheral arterial disease [37-39] and with other cardiovascular function abnormalities like left ventricular hypertrophy and changes in cardiac rhythm [40, 41]. A change in the lipid profile is considered a significant event in the pathogenesis and progression of atherosclerosis and cardiovascular diseases [42, 43]. We have also observed changes in total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, total cholesterol: HDL cholesterol, LDL cholesterol: HDL cholesterol in experimental rats when treated with lead acetate for seven consecutive days [24]. However, the mechanism underlying reduction of heart size in our experiments currently remains poorly understood and needs further exploration.

Lead has been known to cause inflammation by activating nuclear factor Kappa B (NFkB) via oxidative stress. The NFkB is a general transcription factor for various cytokines, chemokines and adhesion molecules. Thus, by activation of NFkB, oxidative stress can cause inflammation. Lead induced generation of ROS may trigger a cycle of oxidative stress and inflammation in the target tissues [22]. Studies showed increased level of plasma norepinephrine (NE) in lead exposed workers and thus, revealed stimulatory role of lead on the sympathetic nervous system and its contribution to the cardiovascular effects [44]. Lead has been reported to have effects on renin-angiotensin and kininergic systems. A marked

increase in the activity of angiotensin converting enzyme (ACE) in plasma and cardiac tissue has been reported following lead exposure at early age in experimental rats[45]. Thus, a correlation between activation of rennin angiotensin system at some point in the course of lead-induced hypertension (HTN) is well interpreted. An interrelationship of nitric oxide ($NO^{\bullet}$) and ROS is known to be a major contributor in lead induced hypertension [46]. Reduction in $NO^{\bullet}$ bioavailability by lead exposure is mediated by oxidative stress [47]. Effect of lead on prostaglandins, viz., endothelin (ET) and atrial natriuretic peptide (ANP) has also been studied [48, 49]. Lead exposure has been found to cause a significant increase of the metabolite of vaso-constrictive prostaglandin, thromboxane (TXB2), in urine of lead exposed workers [48]. *In vitro* studies showed that lead induces release of arachidonic acid by vascular smooth cells through activation of phospholipase A2 [49]. Lead has also been reported to cause an elevation in the content of endothelin in rat vascular tissue [50]. Lead-dependent effects on arachidonic acid accumulation and the proliferation of vascular smooth muscle has also been studied [51]. Atrial natriuretic peptide (ANP) is a vasodilator secreted by cardio-myocytes and is a natriuretic agent. Studies revealed that lead induces dysregulation of ANP which has been found to be a contributing factor of cardiovascular toxicity [52]. Lead has been found to cause vasoconstriction in isolated rabbit mesenteric artery [53]. Lead-calcium interaction in vascular tissue has also been observed [54]. Lead has been reported to be a potential competitor of Ca^{2+} and competes for the transport by channels and pumps across the cell membrane and between cytoplasm, endoplasmic reticulum and mitochondria [54, 55]. Besides, lead has been recognised to be acting as a substitute for calcium in Ca^{2+}-dependent signalling pathways and it interacts with calmodulin, PKC and calcium-dependent potassium channels [55]. These interactions of lead with cellular Ca^{2+} in the vascular cells may be considered to be responsible for alterations of vascular resistance and cardiovascular disorders (Fig.2).

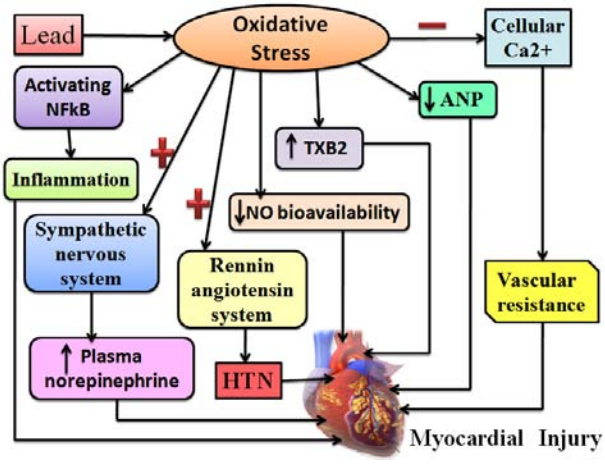

Figure 2: Scheme showing how lead induced oxidative stress mediates myocardial injury.
NFkB = nuclear factor Kappa B; HTN = hypertension; TXB2 = thromboxane; ANP = Atrial ntriuretic protein; Ca2+ = calcium ion;

Concluding remarks

Unavoidable exposure to lead environmentally or occupationally can cause generation of ROS *in vivo* and damages the myocardium leading to myocardial ischemic changes and infarction. Protection against myocardial injury has been investigated for years and researchers have come up with therapeutic solutions to the problem among which reperfusion therapy has been widely accepted and practised widely in spite of reported side effects i.e., reperfusion injury. Sudden perfusion of ischemic cardiac tissue during reperfusion therapy stimulates generation of myriads of ROS which causes further damage of the tissue [56].

We investigated protective measures against lead induced myocardial injury and found that aqueous curry leaves extract and melatonin, a small molecular weight indole with proven antioxidant efficacy, possess excellent protective action against lead induced oxidative stress mediated myocardial injury when tested separately [10, 11]. We have further examined that whether a combination of melatonin and aqueous curry leaves extract act together in a better manner to ameliorate lead induced myocardial injury. We have found that the combination complement the antioxidant potential of each other and act synergistically to protect against lead induced oxidative stress mediated hepatic and cardiac damage and antioxidant mechanisms are associated with such protection [57].

Both melatonin and aqueous curry leaves extract have no reported cyto-toxicity and have minimal or no side effects. The combination appears to be a better and safer option to prevent as well as protect against lead induced myocardial injury in humans expose to lead occupationally or environmentally although further studies in human situations are needed.

Antioxidant supplementation has already been recently adapted by cardiologists to optimise the conditions of various myocardial injuries. The future use of aqueous extract of curry leaves and melatonin individually or in combination may be an important step toward development of an important therapeutic strategy to fight against lead induced myocardial injury. Aqueous curry leaves extract and melatonin both appears to be ideal for using against lead induced oxidative damage of myocardium as both of them have been widely evaluated separately and have been found to possess very strong and all round protective action against lead induced oxidative stress mediated myocardial injury and in other human as well as animal situations.

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