

\*

/ / : / / :

## Effect of amlodipine on kidney tissue concentration of endothelin in rabbits receiving atherogenic diet

Mohammadi M. , Mirzaei F., Aslanabadi N.

Drug Applied Research Center, Tabriz University of Medical Sciences

Received: 2007/1/11 , Accepted: 2007/9/10

**Objectives:** Different factors are involved in inducing and progressing of atherosclerosis. One of these factors is endothelin-1. Since in atherosclerotic vessels obvious and certain changes with abnormality in transferring of calcium ions are seen, some researchers suggested that calcium channel blockers can slowdown the process of atherosclerosis. **Methods:** 36 male Newland white rabbits were divided into four groups: The normal control group, normal group receiving amlodipine, high-cholesterol diet group and high-cholesterol diet with amlodipine group. After 8 weeks all animals anesthetized and blood and tissues samples were collected. **Results:** The levels of cholesterol and triglyceride in groups of high-cholesterol diet comparison to control group increased significantly ( $p < 0.01$ ). Amlodipine consumption in eight weeks reduced significantly ( $p < 0/01$ ) plasma endothelin-1 levels in both of high-cholesterol diet plus amlodipine and amlodipine groups. Amlodipine consumption caused significant reduction ( $p < 0/01$ ) in the level of endothelin-1 in heart tissue of high-cholesterol diet plus amlodipine group but did no effect on reduction of heart tissue endothelin-1 in amlodipine group. **Conclusion:** High-cholesterol diet caused enhancing of plasma and renal tissue endothelin-1 and amlodipine reduced plasma and tissue endothelin-1 levels in high-cholesterol diet group. In conclusion amlodipine treatment could have positive effects in pathology of atherosclerotic renal arteries.

**Key Words:** amlodipine, Endothelin-1, atherosclerotic rabbits

( $P < /$  )

+

+

( $p < /$  )

( $p < /$  )

\*Corresponding Author: Dr Mustafa Mohammadi, Associate Professor, Drug Applied Research Center, Tabriz University of Medical Sciences, Tel: 0411-: 3364664; Fax: 0411-3364664; E-mail: M.Mohammadin@yahoo.com

.( )

(CCBs)

.( )

CCBs .( )

.( )

.( )

.( )

Masaki) (

Yanagisawa)

.( )

(Et-1)

.( )

ET

ET-1 .

ET-1 .

± /

/

ET-1

.( )

Big ET-1

.( )

ET-1

( )

.( )

%

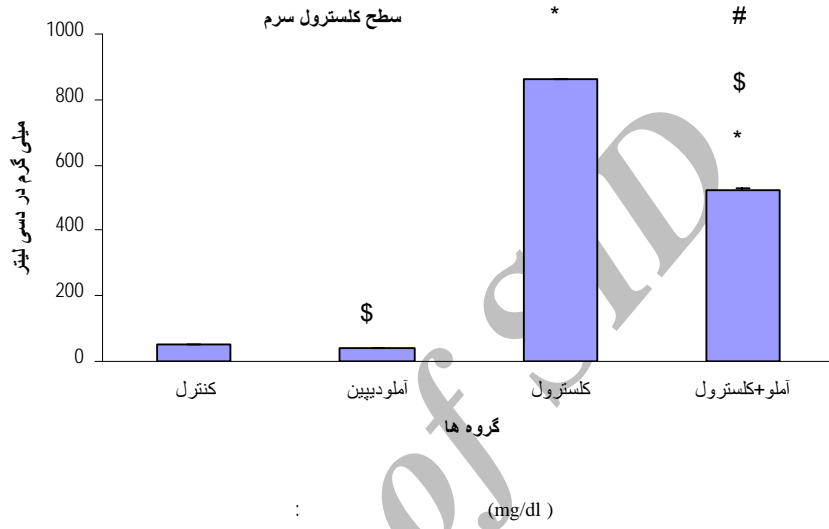
( )  
 mg/kg/day  
 (P< / )  
 mg/kg mg/kg  
 + ) ( )  
 ( ) (P< / )  
 + :  
 (P < / )  
 (P< / ) ( mmol/l )  
 (1mol/l - (HOMO 4/R MIT)  
 (P< / ))  
 (Christ Alpha1-4 )  
 (Titer Zyme ® EIA kit - No:03080625 )  
 ( ) ( )  
 (p< / )  
 (Tukey)  
 (p< / )  
 + SPSS Excel  
 p< /  
 +  
 (p< / )  
 ( )  
 ( )  
 (p< / )

3 -Merk  
 4- One Way ANOVA  
 5 Post Hoc Multiple Comparison  
 6 Mean ± SEM

+

( )

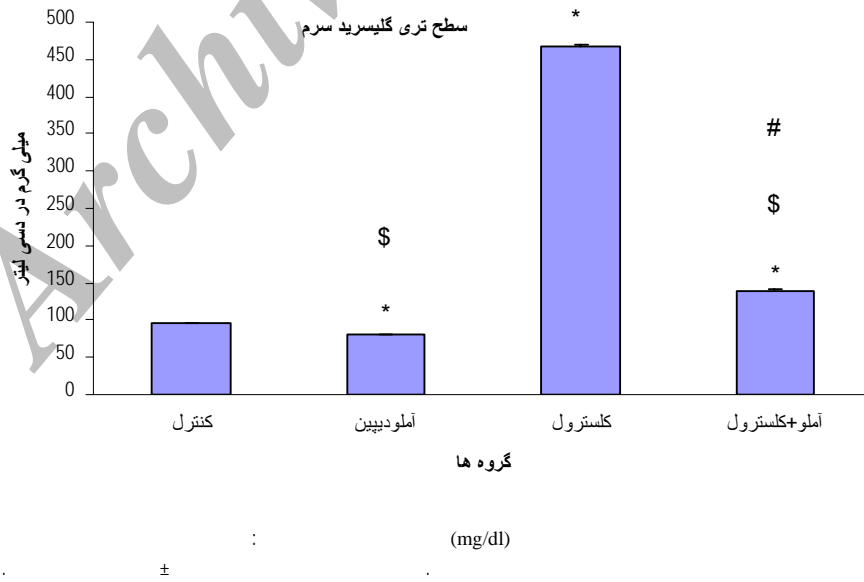
(p < / )



±

(p < / )  
(p < / )  
(p < / )

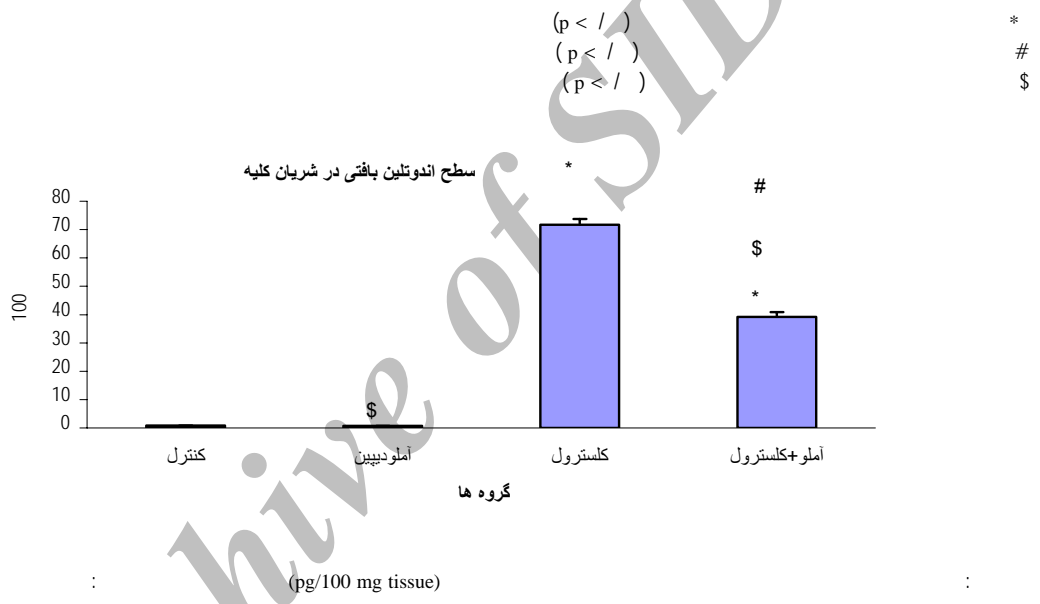
\*  
\$  
#



±

(p < / )  
(p < / )  
(p < / )

\*  
\$  
#



(LDL,VLDL)

( )

( )

( )

( )

ET-1

Foam

( )

invitro ,invivo

( )

( )

( )

SOD

( )

CCBs

( )

CCBs

AGE

( )

AGE

( )

+

(p< / )

( )

( )

ET-1

( )

( )

( )

CCBs

mg/kg/day

7 Foam

8 Superoxid Dismutase

9 Advanced Glycation End Product

## 6- References

- 1- Ross R. The Pathogenesis of atherosclerosis. *Nature*, 1993, 302, 801-9.
- 2- Shamma N.W. Epidemiology, classification, and modifiable risk factors of peripheral arterial disease. *Vasc Health Risk Manag*, 2007, 3(2), 229-34
- 3- Yanagisawa M.A. novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature*, 1998, 332, 411-415.
- 4- Masaki T. Historical review : Endothelin. *TERND in oharmacol Sci*, 2004, 25(4), 119-224.
- 5- Dashwood M.R., Tsui C.S. Endothelin -1 and atherosclerosis :potential complication associated with endothelin receptor blockade. *Atherosclerosis* , 2002, 160, 297-304.
- 6- Wagner O.F, Christ G., Wojta J., Vierhapper H., Parzer S., Nowotny P.J., Schneider B., Waldhausl W., Binder B.R. Polar Secretion of Endothelin-I by cultured endothelial cells .*J Bio Chem*, 1992, 267(23) ,16066-16068.
- 7- K.edzierski R.M. and Yanaisawa M.: Endothelin system: The Double-Edged Sword in Health and Disease. *Annu. Rev. Pharmacol. Toxicol*, 2001, 41, 851-76,
- 8- Douglas S.A., Ohlstein EH. Vascular and cardiac effect of endothelin .In: Warner TD: Endothelin and its Inhibitors, 2001, Spring, 401-451.
- 9- Henry P.D. Atherosclerosis , calcium and calcium antagonists. *Circulation* , 1995, 72, 456-459.
- 10- Borhani N.O., Mercury M., Buckalew V.M. Final outcome result of the multicenter isradipine diuretic atherosclerosis study . *J Am Med Assoc*, 1996, 276, 758-791.
- 11- Biswas T.K. Endothelium, atherosclerosis and calcium channel blockers. *J Indian Med Assoc*, 2003, 101(7), 428-31
- 12- Yakubu M.A., Leffler C.W. L-type voltage-dependent Ca<sup>2+</sup> channels in cerebral microvascular endothelial cells and ET-1 biosynthesis. *Am J Physiol Cell Physiol*, 2002, 283 (6), 687-95.
- 13- Lerman L.O., Chade A.R. Atherosclerotic process, renovascular disease and outcomes from bench to bedside. *Curr Opin Nephrol Hypertens*, 2006, 15(6), 583-7
- 14- Fava C., Minuz P., Patrignani P., Morganti A. Renal artery stenosis and accelerated atherosclerosis: which comes first? *J Hypertens* 2006, 24(9), 1687-96.
- 15- Lulis AJ. Atherosclerosis .*Nature*, 2000, 407, 233-241.
- 16- Akira K., Amano M., Okajima F., Hashimoto T., Oikawa S. Inhibitory effects of amlodipine and fluvastatin on the deposition of advanced glycation end products in aortic wall of cholesterol and fructose-fed rabbits. *Biol Pharm Bull*, 2006, 29(1), 75-81.
- 17- Barry M.W., Myron S., Peter F. M. Localization of Et-1 Like Immunoreactivity in human Placenta. *The journal of Histochemistry and Cytochemistry*, 1993, Vol 41, No 4, 535-541
- 18- Kedzierski R.M. and Yanaisawa M.: Endothelin system: The Double-Edged Sword in Health and Disease. *Annu. Rev. Pharmacol. Toxicol*, 2001, 41, 851-76
- 19- Boulanger C.M., Tanner F.C., Bea M.L., Hahn A.W., Werner A., Luscher T.F. Oxidized low density lipoproteins induce mRNA expression and release of endothelin from human and porcine endothelium . *Circ Res*, 1992, 70, 1191-1192.
- 20- Horio T., Kohno M., Yasonari K., Murakawa K., Yokokawa K., Ikeda M., et al. Stimulation of endothelin -1 release by low density lipoproteins and very low density lipoproteins in cultured human endothelial cells. *Atherosclerosis*, 1993, 101, 185-190.
- 21- Haug C., Schmid Kotsas A., Zorn U., Schaeff S., Gross H.J., Gruenert A., et al. Endothelin -1 synthesis and endothelin B receptor expression in human coronary artery smooth muscles cells and monocyte derived macrophages is up regulated by low density lipoproteins. *J Mol cell Cardiol*, 2001, 33 ,1701-1712.
- 22- Trion A., de Maat M., Jukema W., Mass A., Offerman E., Havekes L., et al. Anti atherosclerotic effect of amlodipine, alone and in combination with atorvastatin, in APOE-3 Leiden CRP transgenic mice. *J cardiovasc.Pharmacol*, 2006, 47(1) ,89-95.
- 23- Dense J.A., Desmet W.J., Coussement P.C., Sheerder I. K. De. Long term effects of nisoldipine on the progression of coronary atherosclerosis and the occurrence of clinical events. *Heart*, 2003, 89(8), 887-892.
- 24- Zhang X., Hintze T.H.. Amlodipine release nitric oxide from canine coronary microvessels: an unexpected mechanism of action of a calcium channel blocking agent. *J Cardiovasc Pharmacol*, 1998, 20, s54-56.
- 25- Mason P.R., Walter M.F., Trumbore M.W., Olmstead E.G., Mason P.E. Membrane antioxidant effect of the charged dihydropyridine calcium antagonist amlodipine. *J Mol Cardiol*, 2001, 31, 275-281.
- 26- Akira K., Amano M., Okajima F., Hashimoto T., Oikawa S. Inhibitory effects of amlodipine and fluvastatin on the deposition of advanced glycation end products in aortic wall of cholesterol and fructose-fed rabbits. *Biol Pharm Bull*, 2006, 29(1), 75-81.
- 27- Naylor W.C. Review of preclinical data of calcium channel blockers and atherosclerosis. *J Cardiovasc Pharmacol* , 1999, 33 (2) , 7 – 11.
- 28- Byington P.R., Craven T.E., Furberg C.D., Pahor M. Isradipine ,raised glycosylated haemoglobin, and risk of cardiovascular events. *Lancet*, 1997, 350, 1075-1076.
- 29- Chen L., Haight W.H., Yang B., Saldeen T.G., parathasarathy S., Metha J.L . Preservative of endogenous antioxidant activity and inhibition of lipid peroxidation as common mechanisms of antiatherosclerotic effects of vitamin E , lovastatin and amlodipine. *J AM COLL Cardiol* ,1997, 30, 569 – 75
- 30- Henry P.D. Anti-atherosclerotic effects of calcium antagonists: abrief review. *Clin Invest Med*, 1987, 10(6), 601-5.
- 31- Chou T.C., Yang S.P., Pei D. Amlodipine inhibits pro-inflammatory cytokines and free radical production and inducible nitric oxide synthase expression in lipopolysaccharide/interferon-

- 
- gamma-stimulated cultured vascular smooth muscle cells. *Jpn J Pharmacol*, 2002, 89 (2),157-63.
- 30-Turgan N., Habif S., Kabaroglu C.G., MutafI, Ozmen D., Bayindir O. Effects of the calcium Channel blocker amlodipine on serum and aortic cholesterol, lipid peroxidation, antioxidant status and aortic histology in cholesterol-fed rabbits. *J Biomed Sci*, 2003, 10(1) , 65-72.
- 31-Akira K., Amano M., Okajima F., Hashimoto T., Oikawa S. Inhibitory effects of amlodipine and fluvastatin on the deposition of advanced glycation end products in aortic wall of cholesterol and fructose-fed rabbits. *Biol Pharm Bull*, 2006, 29(1) , 75-81.
- 32- Chou T.C., Yang S.P., Pei D. Amlodipine inhibits pro-inflammatory cytokines and free radical production and inducible nitric oxide synthase expression in lipopolysaccharide/interferon-gamma-stimulated cultured vascular smooth muscle cells. *Jpn J Pharmacol*, 2002, 89(2) ,157-63.

Archive of SID