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MODULATION OF PAIN PERCEPTION BY RAMIPRIL AND LOSARTAN IN HUMAN VOLUNTEERS

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Abstract : The angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are a well known entity and have been used in therapeutics for various indications like hypertension, myocardial infarction and CHF. However, there is a renewed interest in these compounds in terms of their effects on pain perception in animals as well as in human beings. They have yielded contradictory results, showing hyperalgesia in some studies but analgesia in others. Hence this study was undertaken to evaluate the effect of Ramipril (an ACE-I) and Losartan (an ARB) on pain perception in human volunteers using cola caps and handcuff of sphygmomanometer. A total of 30 healthy, normotensive individuals with no previous history of intake of analgesics during or 4 weeks prior to the study were selected after an informed consent. The first group received a single dose of placebo, the second group received Ramipril (2.5 mg) & the third group received Losartan (50 mg). Pain perception threshold (the point at which an individual first experiences pain) and the maximum tolerated pain were assessed using the above method. The control group showed no significant changes in pain threshold, but the group receiving either Ramipril or Losartan showed a decline in threshold for maximum tolerated pain. Only Ramipril and not Losartan decreased the pain perception threshold. Our study revealed that single dose treatment of healthy volunteers with Ramipril and Losartan may cause algesia as early as after ingestion of the first dose and further studies are needed to study their long term effects on pain perception.

Key words : angiotensin receptor blockers pain ACE inhibitors

INTRODUCTION

Pain is a very subjective phenomenon, difficult to quantify in human beings but at the same time can be an incapacitating experience if left untreated. It may be a defensive mechanism in our body, protecting us from harmful stimuli in day today life or an early warning symptom for life threatening situations like MI, hypertension or an underlying inflammatory condition (1, 2, 3, 4). Renin angiotensin system has recently been evaluated for its varied effects on pain and its modulation has carved a

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definite niche in therapeutics with angiotensin receptor blockers (ARBs) and Angiotensin converting enzyme inhibitors (ACEIs) being used treatment various pathological states like hypertension, congestive heart failure etc. (5, 6, 7). The ACEIs, but not the ARBs inhibit the enzyme dipeptidyl carboxypeptidase which is involved in the conversion of Angiotensin I to Angiotensin II and in the degradation of kinins (like substance P and Bradykinin and various other peptides). The ACEIs thus increase the level of pain producing peptides like the Bradykinin, substances P etc (8). These kinins are capable of inducing inflammatory changes like pain, vasodilatation, and increased vascular permeability, dry cough, swelling of lips, itching and urticaria. However, some recent-studies have shown that ACEIs and ARBs play a role in modifying pain perception (9) and the results have ranged from hyperaglesia to analgesia.

MATERIAL AND METHODS

Inspired by earlier findings of RAS modulation and its effects in pain perception, this study was conducted in our department after taking a written informed consent from volunteers.

Inclusion Criteria :

The subjects included were :

1. Normotensive healthy adults aged between 25–30 years with an average weight between 50–70 kg.
2. No history of hypertension, renal disease, peripheral neuropathy or recent use of analgesics were selected for the study.

Exclusion Criteria

1. Obese individuals
2. History of recent use (within 4 weeks of study) of analgesics, ACE inhibitors, ARBs or any other long term treatment.
3. Pregnant females.
4. Individuals with gout, arthritis.
5. Extremes of age (children and elderly were not included).

Material :

Tablets of Losartan (25 mg), Ramipril (2.5 mg) and a multivitamin (placebo), were obtained from a local commercial outlet.

Method :

A double blind randomized placebo controlled trial was done in 30 human volunteers. Based on above inclusion and exclusion criteria, the volunteers were divided into 3 groups of 10 each and allotted numbers between 1 to 30.

The pain perception threshold was assessed using blood pressure instrument (the sphygmomanometer) and a cola cap (26). Though each individual acted as its own control at 0 h, but in order to exclude the placebo effect of consuming a tablet on pain perception over a period of time i.e., at 0 h, 2 h and 4 h, we included the third group which received the multivitamin tablet in our study. The multivitamin tablet acted as the positive control. The tablets were packed in similar packets (same size and colour) which were coded as A, B and C. The volunteers were asked to pick up a packet, tell us the code and the number allotted to

him/her. The number allotted to each volunteer and their respective code was noted and the corresponding readings were tabulated against their codes at 0 h, 2 h and 4 h.

A cola-cap with smooth serrated edges was placed on the ventral aspect of the left forearm and the blood pressure cuff was wrapped around it and inflated. The point at which an individual first perceived the pain (i.e. the pain perception threshold) and the point of maximum tolerated pain, were noted in terms of mm of mercury. The pain perception threshold and threshold for maximum tolerated pain was recorded for each individual at 0 h (i.e. before giving drug) 2 h and 4 h.

Statistical analysis

All the data were expressed as mean ± SE and were analysed using paired t–test. P values < 0.05 were considered significant.

RESULTS

1. In the Ramipril group, there was a significant reduction (P<0.05) in pain perception threshold at 4 h but not at 2 h when compared to 0 h values. However in the Losartan group, there were no significant change in pain perception threshold either at 2 h or 4 h when compared to baseline value at 0 h (Table I).

2. The maximum tolerated pain threshold reduced significantly in the Losartan as well as Ramipril group at 4 h when compared with 0 h values. However no significant reduction was found at 2 h when compared with 0 h values (Table II).

3. In the Placebo treated group, no significant change in pain perception

TABLE I: Effect of Losartan and Ramipril on pain perception threshold values at 0 hour, 2 hour and 4 hour after giving the drugs as evaluated by Sphygmomanometer (B.P. Cuff) and Cola Cap method.

	Mean ± S.E.		
Time in hours	*0 hour (mmHg)*	*2 hour (mmHg)*	*4 hour (mmHg)*
Control	118.2±10.20	125.6±8.78	121.6±9.49
Losartan	120.6±7.26	109.6±6.26	103.2±8.94
Ramipril	116.2±6.29	105.0±4.84	93.60±3.42*

Significant values *P value < 0.05.

TABLE II: Effect of Losartan and Ramipril on maximum pain threshold values at 0 hour, 2 hour and 4 hour after giving the drugs as evaluated by Sphygmomanometer (B.P. Cuff) and Cola Cap method.

	Mean ± S.E.		
Time in hours	*0 hour (mmHg)*	*2 hour (mmHg)*	*4 hour (mmHg)*
Control	187.40±9.84	202.2±12.27	184.8±10.95
Losartan	223.8±13.72	219.00±10.75*	195±10.23*
Ramipril	213.0±12.49	198.60±13.4*	186.8±9.79*

Significant values *P value < 0.05.

threshold or maximum tolerated pain threshold occurred at 0 h, 2 h or 4 h (Table I and II).

DISCUSSION

The present study indicates that Ramipril but not Losartan lowered the threshold for pain perception at 4 h, while both losartan and ramipril lowered the threshold for maximum tolerated pain at 4 h.

The role of renin angiotensin system in pain perception has been reported in earlier studies (9). However, pain perception is in itself a complex phenomenon which has central and peripheral components and the two have been historically found to be linked differently in their sensitivity to pain in response to renin, renin substrates (21) and angiotensin. This inspired us to study the effect of single dose administration of Losartan and Ramipril on pain perception in human beings. It has been reported earlier that hypertension is associated with reduced pain sensitivity in men and this can be antagonized by ACEIs and ARBs (11, 12, 13). The facilitation of algesic peptides, bradykinin, substance P etc. by ACEIs was the presumed etiology in these patients because kinins are known to stimulate nerve endings and produce burning pain via bradykinin type 2 i.e. B_2 receptors (15). In our study, however, losartan which does not facilitate the algesic peptides also led to hyperalgesia which has been attributed to the unopposed action of angiotensin II on AT_2 receptors, AT_1 being blocked by ARBs. Not only Angiotensin II but for the first time a study has shown that renin substrates like angiotensin I, II, III have a well defined role in periaqueductal grey matter (PAG) region (21), the region which has been earlier identified to produce antinociception in response to the RAS peptides injected here and this antinociceptive response was blocked by saralsin (23). These observations point towards complex pain mechanisms which not only involve neurotransmitters like serotonin, but also the endogenous opioidsystem, prostaglandins, substance P, bradykinin (10). The extent of involvement of these neurotransmitters in our study, however, could not be evaluated because it remains to be determined whether the central mechanisms are activated on single dose administration of losartan and ramipril or not. Various anatomical regions of brain like area postrema and nucleus tractus solitarius (8) have been involved in pain pathways and are modulated differently by RAS, and both AT1 and AT2 receptors were immunolocalized in neuronal cell bodies and in the ventrolateral PAG (22). Similar reasons could have been the contributory factors in our study where both the losartan and ramipril treated groups showed hyperaglesia. It has been postulated that bradykinin B_2 receptors and AT_1 receptors heterodimerise and this process enhances angiotensin II sensitivity in pre-eclampsia patients (16). Though the functional role of AT_2 receptors in pain has been documented earlier but whether such heterodimerization of B_2 receptors also occurs with AT_2 receptors is not known. In our study, increased pain sensitivity to pain can be attributed to preferential activation of AT_2 by losartan and subsequent heterodimerization with B_2 (bradykinin 2) receptors or by other unexplored mechanisms.

A recent study suggests that AT_1 receptor blockers can cause endogenous bradykinin induced hypotension via AT_2 mediated

increase in bradykinin and NO production and losartan has been shown to increase bradykinin concentration in hypertensives (18, 19, 20). A similar increase in algesic peptides even after a single dose of losartan and ramipril seems to be the probable cause of algesia in our study with both ramipril and losartan. However, more studies with single dose of ACEIs and ARBs are needed to confirm whether hyperalgesia occurs on a single dose only or also after chronic administration of these drugs.

A further enigmatic finding associated with RAS manipulation is the difference in terms of peripheral and central stimulation of RAS. Peripheral as well as central RAS stimulation can lead to either algesia or analgesia (23).

The role of renin angiotensin system if further explored can open an entirely new field of research and perhaps and alternative way of stimulating the endogenous opiod system without the risk of addiction or exposing an individual to pinpricks of the conventional accupuncture therapy of the Chinese origin. Both long and short term studies are needed at various stages of use of both ACEIs and ARBs. The production of algesia in an early phase of treatment can be rather beneficial in diabetics with previous history of angina or cardiovascular risk, where warning signs of an impending MI may save a patients life by converting a painless silent MI into a painful one (24, 25). Algesic effect, however, may warrant a cautious use of ACEIs in painful conditions which may worsen in presence of increased algesic peptides like in patients with cancer pain, herpes zoster and bone secondaries.

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REFERENCES

1. Fields HL. Neurophysiology of pain and pain modulation. *Am J Med* 1984; 72: 2–8.
2. Maixner W. Interaction between cardiovascular and pain modulatory systems: physiological and pathophysiological implications. *J Cardiovasc Electrophysiol* 1991; 2 (suppl): S3–S12.
3. Aicher SA, Randich A. Antinociception and cardiovascular responses produced by electrical stimulation in the nucleus tractus solitarius, nucleus reticularis ventralis, and the caudal medulla. *Pain* 1990; 42: 103–119.
4. Randich A, Ren K, Gebhard GF. Electrical stimulation of cervical vagal afferents, II: central relays for behavioural antinociception and arterial blood pressure decrease. *J Neurophysiol* 1990; 64: 1115–1124.
5. Davie AP. Dargie HJ, McMurray JJV. Role of bradykinin in vasodilator effects of Losartan and enalapril in patients with heart failure. *Circulation* 1999; 100: 268–273.
6. Carey RM, Howell NL, Jin XH and Siragy HM. Angiotensin type 2 receptor mediated hypotension in angiotensin type 1 receptor blocked rats. *Hypertension* 2001; 38: 1272–1277.
7. Jackson EK. Renin and Angiotensin. In: Hardman JG, Limbird LE, Oilman AG, eds. Goodman and Oilman's. The Pharmacological basis of therapeutics. 10th edition. New York. *McGraw Hill*, 2001: 809–821.
8. Haulica I, Neamtu C, Stratone A, Petrescu OH, Branisreanu D, Rosca B, Slarineanu S. Evidence for involvement of Cerebral rennin angiotensin system (RAS) in stress analgesia. *Pain* 1986; 27: 237–245.
9. Guasti, Luigina, Zanotta, Danilo, Diolisi, Alessio, Garganico, Deborah, Simoni, Cinzia, Gaudio,,

Giovanni, Grandi, Anna M, Venco Achille. Changes in pain perception during treatment with angiotensin converting enzyme-inhibitors and angiotensin II type 1 receptor blockage. *J Hypertens* 2002; 20(3): 485–491.

10. Guasti L, Grimoldi P, Diolisi A, Petrozzino MR, Gaudio G, Grandi AM, Rossi MG, Venco A. Treatment with Enalapril modifies the pain perception pattern in hypertensive patients. *Hypertension* 1998; 31: 1146–1150.
11. Ghione S, Rosa C, Mezzasalma L, Panattoni E. Arterial hypertension is associated with hypalgesia in humans. *Hypertension* 1988; 12: 491–497.
12. Guasti L, Merlo B, Verga R, Cattaneo R, Gaudio G, Bianchi L, Zanzi P, Grandi AM, Bossi PM, Venco A. Effects of arithmetic mental stress test on hypertension-related hypalgesia. *J Hypertens* 1995; 13: 1631–1635.
13. Guasti L, Cattaneo R, Daneri A, Bianchi L, Gaudio G, Regazzi MB, Grandi AM, Bertolini A, Restelli E, Venco A. Endogenous betaendorphins in hypertension. Correlation with 24- hour ambulatory blood pressure. *J Am Coll Cardiol* 1996; 28: 1243–1248.
14. Sakamoto K, Sugiomoto K, Fujimura A. Different potentiating effects of imidapril and enalapril on kaolin-induced writhing reaction in mice. *Life Sci* 2001; 8(21): 2415–2421.
15. Abd alla S, Lolher H, Abdel Tawal AM and Quitterer U. The angiotensin II AT_2 receptor is an AT, receptor antagonist. *J Biol Chem* 2001; 276: 3974–3926.
16. Irvine RJ, White JM, Head RJ. The renin and angiotensin system and nocioception in spontaneously hypertensive rats. *Life Sci* 1995; 56: 1073–1078.
17. Gohlke P, Pees C, and Urger T. AT_2 receptor stimulation increases aortic cyclic GMP in SHRSP by a kinm-dependent mechanism. *Hypertension* 1998; 31: 349–355.
18. Gohlke P, Pees C, and Urger T. AT_2 receptor stimulation increases aortic cyclic GMP in SHRSP by a kinm-dependent mechanism. *Hypertension* 1998; 31: 349–355.
19. Campbell DJ, Krum H, and Esler MD. Losartan increases bradykinsin in hypertensive humans. *Circulation* 2005; 111: 315–320.
20. Duka A, Duka I, Gao G, Gavras I and Gavras H. Role of bradykinin B_1 and B_2 receptors in normal blood pressure regulation. *Am J Physiol* 2006; 291: E268–E274.
21. Pelegrini-da-silva a, Martins AR etal., A new role for the renin-angiotensin system in the rat periaqueductal gray matter: angiotensin receptor-mediated modulation of nociception. *Neuroscience* 2005; 132 (2): 453–463.
22. Yien HW, Chan JY, Tsai HF, Lee TY, Chan SH. Microinjection of renin-angiotensin system peptides in discrete sites within the rat periaqueductal gray matter elicits antinociception. *Brain Res* 2003 May 16; 972(1–2): 207–215.
23. Cohn PF. Silent myocardial ischemia in patients with a defective anginal warning system. *Am J Cardiol* 1980; 45: 697–702.
24. Sheps DS, Mainxer W, Hinderliter AL. Mechanisms in pain perception in patients with silent myocardial ischemia. *Am Heart J* 1990; 11: 983–987.
25. Rohit, Chakradhar Rao US, Gopala Krishna HN. Effects of captopril and losartan on thermal and chemical induced pain in mice. *Indian J Physiol Pharmacol* 2006; 50(2): 169–174.
26. Staibach RA. Deems LM, Timmermans G et al., On the sensitivity of the tourniquet pain test. *Pain* 1977; 3: 105–110.
26. Gohlke P, Pees C, and Urger T. AT_2 receptor stimulation increases aortic cyclic GMP in SHRSP by a kinm-dependent mechanism. *Hypertension* 1998; 31: 349–355.
27. Campbell DJ, Krum H, Esler MD. Losartan increases bradykinsin in hypertensive humans. *Circulation* 2005; 111: 315–320.
28. Duka A, Duka I, Gao G, Gavras I and Gavras H. Role of bradykinin B_1 and B_2 receptors in normal blood pressure regulation. *Am J Physiol* 2006; 291: E268–E274.
29. Pelegrini-da-silva a, Martins AR et al., A new role for the renin-angiotensin system in the rat periaqueductal gray matter: angiotensin receptor-mediated modulation of nociception. *Neuroscience* 2005; 132 (2): 453–463.
30. Yien HW, Chan JY, Tsai HF, Lee TY, Chan SH. Microinjection of renin-angiotensin system peptides in discrete sites within the rat periaqueductal gray matter elicits antinociception. *Brain Res* 2003 May 16; 972(1–2): 207–215.
31. Cohn PF. Silent myocardial ischemia in patients with a defective anginal warning system. *Am J Cardiol* 1980; 45: 697–702.
32. Sheps DS, Mainxer W, Hinderliter AL. Mechanisms in pain perception in patients with silent myocardial ischemia. *Am Heart J* 1990; 11: 983–987.
33. Rohit, Chakradhar Rao US, Gopala Krishna HN. Effects of captopril and losartan on thermal and chemical induced pain in mice. *Indian J Physiol Pharmacol* 2006; 50(2): 169–174.