Mintage Journal of Pharmaceutical & Medical Sciences
REVIEW ARTICLE
ISSN 2320 –3315

REVIEW OF ANTI PARKINSONIAN EFFECTS OF ACE INHIBITORS DEMONSTRATED IN VARIOUS ANIMAL AND CLINICAL STUDIES

FAZEEL ZA *[1], VENKATA RAO Y [2]

[1] Junior resident, Dept. of Pharmacology, Kamineni Institute of Medical Sciences, Narketpally, Nalgonda, AP. 508254 ,[2] Professor and HOD, Dept. of Pharmacology, Kamineni Institute of Medical Sciences, Narketpally, Nalgonda, AP. 508254.Email : fazeel_zubair@yahoo.com

Received -08-05-2013; Reviewed and accepted -12-05-2013

ABSTRACT

Parkinsons' disease is the second most common neurodegenerative disorder of the world characterized by involuntary muscle movements. It occurs due to degeneration of dopaminergic neurons in substantianigra and deficiency of dopamine in neostriatum. Brain Renin angiotensin system has been identified which is distinct but similar to peripheral renin angiotensin system. It comprises of angiotensin I to IV as mediators; pro-renin receptor, AT1 AT2 and AT4 receptors. Angiotensin converting enzyme (ACE) and AT1 receptor have been identified in substantianigra. Increased activity of ACE and their pro-inflammatory role have been demonstrated in animal models of parkinsons' disease. Anti-inflammatory action of certain ACE inhibitors and Angiotensin Receptor Blockers (ARB's) in Parkinson induced neurons have also been demonstrated in animal models. The preceding findings have also been identified in some clinical studies.

Key words: ACE Inhibitors,Anti Parkinsonian effects, Animal Studies,Clinical studies.

INTRODUCTION

Parkinson's disease, also referred to as "Paralysis Agitans" is a neuro-degenerative motor disorder characterized by involuntary movements in skeletal muscles. Parkinsons's disease (PD) is the second most common neurodegenerative disorder affecting 0.3% of world population. [1] Degeneration of dopaminergic neurons in substantianigra and deficiency of dopamine in neostriatum is the pathology seen in PD. Functional balance between dopaminergic and cholinergic neurons is lost in PD as a result of which cholinergic transmission becomes hyperactive leading to involuntary movements in skeletal muscles.

RENIN ANGIOTENSIN SYSTEM IN BRAIN

Renin angiotensin system (RAS) has been identified in brain which is quite distinct yet similar to renin angiotensin system seen peripherally. Angiotensinogen serves as the precursor for angiotensin I. This cleavage of angiotensin is brought about by renin. (pro) renin receptor [(P)RR] has been identified in this brain RAS which binds to renin and pro-renin. Binding of renin and pro-renin to [(P)RR] results in increased formation of angiotensin I. [2] Angiotensin converting enzyme hydrolyzes Angiotensin I to Angiotensin II, which is the major role playing peptide. Angiotensin II is also formed directly from angiotensinogen by cathepsin G, a unique pathway seen only in brain RAS. [3] Aminopeptidases convert Angiotensin II to Angiotensin III which is further converted to Angiotensin IV. It has been debated that Angiotensin IV also has major neurotransmitter role in brain along with Angiotensin II. [4]

Angiotensin II acts mainly on AT1 and AT2 receptor subtypes. [5] AT1 recpetors are present densely in hypothalamus and brainstem while AT2 receptors have been identified in neonate brain. [6] Angiotensin IV acts on AT4 receptor which is an insulin regulated aminopeptodase. (IRAP). [7]

ROLE OF RENIN ANGIOTENSIN SYSTEM IN PARKINSON'S DISEASE

Identification of Angiotensin Converting Enzyme (ACE) and AT1 receptors in substantianigra, caudate nucleus and putamen of human and rat brain suggest central activity of angiotensins modulating dopamine release. Reduction of angiotensin receptors has been associated with degeneration of nigrostriatal dopaminergic neurons in PD. Angiotensin II via AT1 receptors activate NADPH dependent oxidases. The major contributor in pathogenesis of Parkinsons Disease, oxidative stress is induced by Angiotensin II via AT1. Rodriguez-Pallares et al., 2008 demonstrated 6-hydroxydopamine induced dopaminergic cell death, generation of superoxide in neurons and microglia, NADPH oxidase mRNA expression via Angiotensin II in rat mesencephalic cultures. [8] Rey etal., 2007 conducted an in vivo study where 6-hydroxy-dopamine injected intravenously resulted in bilateral reduction in number of dopaminergic neurons and terminals. [9] Angiotensin II injected singly did not induce any significant effect. When Angiotensin II was injected along with 6-hydroxydopamine toxic effect of the latter was enhanced. Grammatopoulous et al., 2007 compared Angiotensin IV with Angiotensin II and found the latter to be moderately effective in Parkinsons Disease models when compared to Angiotensin II. [10] Allen et.al., 1992 measured decreased AT1 receptor binding in substantianigra and striatum in post mortem brains of Parkinsons Disease patients. It has also been shown in various studies that ACE metabolizes bradykinin and modulates inflammation in brain. [11]

AT1 stimulation results in activation of NFK signal transduction pathway leading to synthesis of chemokines, cytokines and adhesion molecules which play important role in inflammatory cell migration into regions of tissue injury. [12]

AT2 receptor is found in several fetal tissues including brain. AT2 receptor expression decreases as the animal matures. AT2 receptor levels in striatum and substantianigra is low in adult mammalian brain. AT2 is involved in cell proliferation, differentiation and tissue regeneration. A study demonstrated that Angiotensin II on AT2 caused differentiation of precursors cells into DA neurons. [13] AT2 has also been demonstrated to inhibit NADPH oxidase activation. Rodriguez-Pallares et.al., 2008 discussed that Angiotensin II treated 6-OHDA lesioned rats increased Dopamine cell death. This could be due to comparatively higher numbers of brain AT1 compared to AT2. [14] The effect of chronic hypoperfusion in rats was studied and it was found that striatal DA levels, number of dopaminergic neurons were reduced. Additionally highest AT1 receptor expression was found in substantianigra and AT2 expression was lower in these chronic hypoperfused models.

ACTION OF ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS IN PARKINSONS DISEASE

In a clinical study done by Lopez-Real et.al., 2005 it was found that ACE inhibitors exerted certain antioxidant properties in several tissues hence it has been argued that ACE inhibitors could suppress oxidative stress, the major role player in

Parkinsons Disease. [15] In the experiment by Rey et.al., 2007 described above, when rats were treated with AT1 antagonist before 6-hydroxydopamine induced oxidative stress and degeneration. [16]

A clinical study revealed that hypertensives also suffering from Parkinsons Disease treated with perindopril showed improved motor responses to DA precursor 3,4-dihydroxy L phenylalanine. [17] This finding was further supported by an experimental study where elevated striatal dopamine levels were seen in perindopril treated mice. [18]

In MPTP treated animal models and 6-OHDA rat models, ACE inhibitors offered protection against dopamine neuron loss. [19] The most likely mechanism explained for this protective action is reduced synthesis of Angiotensin II which acts at AT1 thus suppressing NADPH oxidase complex activation and inhibiting NFK signal transduction. [12] In a chronic hypoperfusion experiment in rats, dopamine neuron loss was prevented by oral candesartan. Candesartan also attenuated AT1 expression in the above experiment. [20]

DISCUSSION AND CONCLUSION

From the above experiments and observations, it is now very clear that the brain renin angiotensin system has important role in parkinsons disease. Angiotensin II and AT1 receptors play key role in pathogenesis of PD. This opens a new field for research in anti-parkinsonian drugs. The current available treatments for Parkinson Disease are largely symptomatic and have no significant disease retarding or reversing or prophylactic properties. ACE Inhibitors and Angiotensin Receptor Blockers have shown their anti-parkinsonian effects in above described experiments. Hence more animal and clinical studies are required for having a disease retarding ACE inhibiting compound for PD which should be cerebroselective affecting only parkinson's pathology and not disturbing the peripheral haemodynamics.

REFERENCES

1. Olanow CW, Schapira AHV. Parkinson's Disease and Related Disorders. In: Longo, Fauci, Kasper, Hauser, Jameson, Loscalzo, editors. Harrison's principles of internal medicine. 18th ed. USA:McGraw Hill;2012.p3317-3333.
2. Shan Z, Cuadra AE, Sumners C, Raizada MK. Characterization of a functional (pro)renin receptor in rat brain neurons. Exp Physiol 2008:93;701–8.
3. Lippoldt A, Paul M, Fuxe K, Ganten D. The brain renin–angiotensin system – molecular mechanisms of cell-to-cell interactions. Clin Exp Hypertension 1995;17: 251–66.
4. Ferrario CM, Barnes KL, Block CH, Brosnihan KB, Diz DI, Khosla MC et al. Pathways of angiotensin formation and function in the brain. Hypertension 1990;15: I13–I19.
5. Alexander SP, Mathie A, Peters JA. Guide to Receptors and Channels, 3rd ed. Br J Pharmacol. 2008; 153 Suppl 2: S1–S209.
6. Reagan LP, Flanagan-Cato LM, Yee DK, Ma LY, Sakai RR, Fluharty SJ. Immunohistochemical mapping of angiotensin type 2(AT2) receptors in rat brain. Brain Res 1994: 662; 45–59.
7. Albiston AL, McDowall SG, Matsacos D, Sim P, Clune E, Mustafa T et al. Evidence that the angiotensin IV (AT4) receptor is the enzyme insulin-regulated aminopeptidase. J BiolChem 2001; 276:48623–6.
8. Rodriguez-Pallares J, Rey P, Parga JA, Munoz A, Guerra MJ, Labandeira-Garcia JL. Brain angiotensin enhances dopaminergic cell death via microglial activation and NADPH-derived ROS. NeurobiolDis 2008;31: 58–73.
9. Rey P, Lopez-Real A, Sanchez-Iglesias S, Munoz A, Soto-Otero R, Labandeira-Garcia JL. Angiotensin type-1-receptor antagonists reduce 6-hydroxydopamine toxicity for dopaminergicneurons. Neurobiol Aging. 2007: 28; 555–567.
10. Grammatopoulos TN, Outeiro TF, Hyman BT, Standaert DG. Angiotensin II protects against alpha-synuclein toxicity and reduces protein aggregation in vitro. BiochemBiophys Res Commun 2007;363:846–51.
11. Allen AM, MacGregor DP, Chai SY, Donnan GA, Kaczmarczyk S, Richardson K. et al. Angiotensin II receptor binding associated with nigrostriatal dopaminergic neurons in human basal ganglia. Annals of neurology 1992; 32 (3): 339-44.
12. Okamura A, Rakugi H, Ohishi M, Yanagitani Y, Takiuchi S, Moriguchi K, et al. Upregulation of renin-angiotensin system during differentiation of monocytes to macrophages. Journal of hypertension 1999; 17(4): 537-45.
13. Rodriguez-Pallares, Quiroz CR, Parga JA, Guerra MJ, Labandeira-Garcia JL. Angiotensin II increases differentiation of dopaminergic neurons from mesencephalic precursors via angiotensin type 2 receptors. European journal of neuroscience 2004; 20(6): 1489-98.
14. Rodriguez-Pallares J, Rey P, Parga JA, Munoz A, Guerra MJ, Labandeira-Garcia JL. Brain angiotensin enhances dopaminergic cell death via microglial activation and NADPH derived ROS. Neurobiology of disease 2008; 31(1): 58-73.
15. Lopez-Real A, Rey P, Soto-Otero R, Mendez-Alvarez E, Labandeira-Garcia JL. Angiotensin-converting enzyme inhibition reduces oxidative stress and protects dopaminergic neurons in a 6-hydroxydopamine rat model of parkinsonism. J Neurosci Res 2005;81:865–73.
16. Rey P, Lopez-Real A, Sanchez-Iglesias S, Munoz A, Soto-Otero R, Labandeira-Garcia JL. Angiotensin type-1-receptor antagonists reduce 6-hydroxydopamine toxicity for dopaminergic neurons. Neurobiol Aging 2007; 28: 555–67.
17. Reardon KA, Mendelsohn FA, Chai SY, Horne MK. The angiotensin converting enzyme (ACE) inhibitor, perindopril, modifiesthe clinical features of Parkinson's disease. Aust N Z J Med. 2000: 30; 48–53.
18. Jenkins TA, Mendelsohn FAO, Chai SY. Angiotensin-converting enzyme modulates dopamine turnover in the striatum. Journal of Neurochemistry 1997; 68(3): 1304–11.
19. Munoz A, Rey P, Guerra MJ, Mendez-Alvarez E, Soto-Otero R, Labandeira-Garcia JL. Reduction of dopaminergic degeneration and oxidative stress by inhibition of angiotensin converting enzyme in a MPTP model of parkinsonism. Neuropharmacology 2006; 51(1); 112–20.
20. Rodriquez-Perez I, Dominquez-Meijide A, Lanciego JL, Guerra MJ, Labandeira-Garcia JL. Dopaminergic degeneration is enhanced by chronic brain hypoperfusion and inhibited by angiotensin receptor blockage. Age (Dordr). Epub 2012 Sep 18.
21. Doris Albrecht. Physiological and pathophysiological functions of different angiotensins in the brain. British Journal of Pharmacology 2010; 159:1392-401.

.