IS RED CELL ACETYLCHOLINESTERASE RELATED WITH ARTERIAL HYPERTENSION?

J. MARTINS E SILVA, M. CARLOTA SALDANHA
Institute of Biochemistry. Faculty of Medicine of Lisbon. Lisbon. Portugal

In addition to the suggestive involvement of the noradrenergic system,[1] there is substantial evidence that blood pressure regulation in the man and some other mammals (e.g. cat, dog and rat) is dependent on the cholinergic activity.[2] Many experimental and some clinical studies have demonstrated that the stimulation of the central cholinergic system by direct receptor agonists or acetylcholinesterase (AChE) inhibitors, mediates a rise in arterial pressure (Fig. 1)

According with these findings (still questionable), the activation of the cholinergic system might play a role in the pathogenesis of essential hypertension (EH) as well as in SHR, apparently via increased peripheral sympathetic activity. Meanwhile, other studies have claimed to a suppressed parasympathetic activity in the SHR and humans with essential hypertension.[3, 4]

The AChE activity might be interpreted as an index of the parasympathetic innervation if it were more specific than observed; the AChE activity is identified in regions containing pacemaking and conducting tissues and, also, in red blood cells and other non-neural tissues.[5] Nevertheless, pharmacologic and kinetic studies in all molecular forms of AChE have identified a remarkable similarity in their enzymatic sites. Beyond this, a high level of homology is shown between the AChE from human erythrocytes and neuromuscular junctions.[6]

Although the presence of AChE activity in non-neural regions seems to be a factor hardly involved in the pathogenic mechanisms of hypertension, a very significant elevation in red cell AChE activity has been detected by us in humans with essential hypertension.[7] This observation was not confirmed by others,[8] being the discrepancy with our results attributed to differences in technical methodologies or the patients studied. Recently, we could reaffirm an increase in AChE activity in hemoglobin-free membranes from hypertensive patients without evidence of renal insufficiency.[9]

Acetylcholinesterase from human erythrocytes is a membrane bound enzyme with still obscure function.[10] Among other mechanisms, there is increasing evidence that AChE might be involved in sodium exchanges across the erythrocyte [11] and other cell membranes.[12] However, if the increase on red cell AChE activity is related to the well known altered cation transport in patients with EH [13] is still a matter to further studies.

Furthermore, it might be conjectured that erythrocyte AChE activity is dependent on cell membrane alterations, consequent to the external or internal effect of some released factor, or viewed as reflection of a localized change in lipid-protein interactions in EH.

Acetylcholinesterase is a lipid-glycoprotein complex molecule with an assymetric orientation on the outer surface of the erythrocytes;[14] the allosteric properties of the enzyme depend on the fatty acid composition of the red cell membrane.[15] Any change in the membrane lipid composition,[15, 16] as such as a modification in the transmembrane potencial,[17] might interfere with the hydrophilic environment and the enzymatic activity of acetylcholinesterase. These facts would confirm that red cell AChE sensitivity probes the dynamics of the membrane integrity [18] and its dependence on the membrane fluidity.[15] No data are yet available to steadily confirm or deny these possibilities in what concerns the increased activity of AChE in red cells of EH patients.

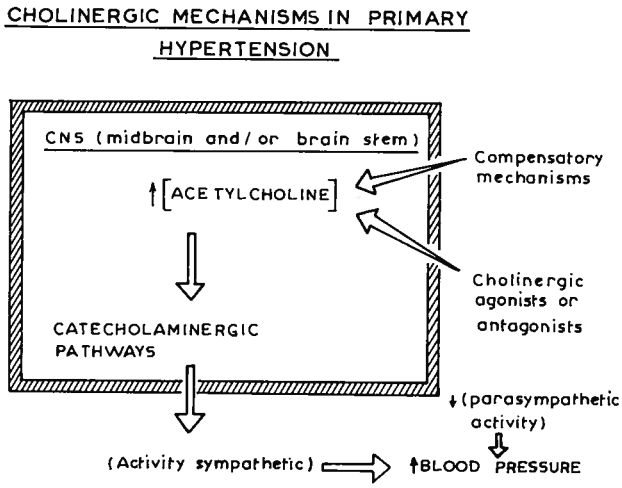

Figure 1: Cholinergic mechanisms in primary hypertension

Received: May 17, 1985

REFERENCES

1. ELGHOZI, J. L.; MIACH, P.; MEYER, Ph.: Hypertension artérielle: rôle du systeme nerveux central. II. Étude expérimentale et clinique. *Nouv. Press. Méd.*, 1978; 4: 743-751.
2. BREZENOFF, H. E.; GIULIANO, R.: Cardiovascular control by cholinergic mechanisms in the central nervous system. *Ann. Rev. Pharmacol toxicol.*, 1982; 22: 341-381.
3. JULIUS, S.; PASMAL, A. V.; LONDON, R.: Role of the parasympathetic inhibition in the hyperkinetic type of borderline hypertension. *Circulation*, 1971; 44: 413-418.
4. FROHLICH, E. D.; PFAFFER, N. A.: Adrenergic mechanisms in human and SHR hypertension. *Clin. Sci. Molec. Med.*, 1975; 48: 225s-238s.
5. KOELLE, G. B.: Cytological distribution and physiological function of cholinesterase. In: GB Koelle (ed), Handbook of Experimental Pharmacology, vol.v15, Springer Verlag, Berlin 1963, pp. 701-740.
6. FAMBROUGH, D. M.; ENGEL, A. G.; ROSENBERRY, T. L.: Acetylcholinesterase of human erythrocytes and neuromuscular junctions; homologies revealed by monoclonal antibodies. *Proc. Natt. Acad. Sci. USA*, 1982; 79: 1078-1082.
7. MARTINS E SILVA, J.; PROENÇA, M. C.; BRAZ NOGUEIRA, J.; GORJÃO-CLARA, J.; NOGUEIRA COSTA, J.; MANSO, C.: Erythrocyte acetylcholinesterase in essential hypertension. *J. Neural Transm.*, 1980; 49: 127-132.
8. WALTER, U.: Studies on erythrocyte acetylcholinesterase in essential hypertension. *Klin. Wochenschr*, 1982; 60: 853-857.
9. PROENÇA, M. C.; BRAZ NOGUEIRA, J.; RIBEIRO, M. H.; NOGUEIRA DA COSTA, J.; MARTINS E SILVA, J.: Acetylcholinesterase and Na^+, K^+ adenosine triphosphate activities on red cell membrane from humans with essential hypertension. Meeting of Portuguese Society of Cardiology, Lisbon, June 1982. *Rev. Port. Cardiol.*, 1982; 1: 188 (abstract).
10. HELLER, M.; HANAHAN, D. J.: Human erythrocyte membrane bound enzyme acetylcholinesterase. *Biochim. Biophys. Acta*, 1972; 255: 251-271.
11. LINDVIG, P. E.; GREIG, M. E.; PETERSON, S. W.: Studies on permeability. V.: The effect of acetylcholine and physiostigmine on the permeability of human erythrocytes to sodium and potassium. *Arch. Biochem. Biophys.*, 1951; 30: 241-250.
12. VAN DER KLOOT, W. G.: Cholinesterase and sodium transport by frog muscle. *Nature*, 1956; 178: 366-367.
13. POSTNOV, Y. V.; ORLOV, S. N.: Cell membrane alteration as a source of primary hypertension. *J. Hyper.*, 1984; 2: 1-6.
14. ROMER LUTHI, C. R.; OTT, P.; BRODBECK, U.: Reconstitution of human erythrocyte membrane acetylcholinesterase in phospholipid vesicules. Analysis of the molecular forms by cross-linking studies. *Biochem. Biophys. Acta*, 1980; 601: 123-133.
15. BLOG, B.; MORERO, K. D.; FARRAS, R. N.; TRUCCO, R. E.: Membrane lipid fatty acids and regulation of membrane bound enzyme. Allosteric behaviour of erythrocyte Mg^{2+}-ATPase, (Na^+, K^+)-ATPase and acetylcholinesterase from rats fed with different fat-supplemented diets. *Biochim. Biophys. Acta*, 1973; 34: 67-79.
16. FRENKEL, E. J.; MOELOFSEN, B.; BRODBECK, U.; VAN DEENEN, L. L. M.; OTT, P.: Lipid-protein interactions in human erythrocyte membrane acetylcholinesterase. Modulation of enzyme activity by lipids. *Europ. J. Biochem.*, 1980; 109: 377-382.
17. LIONE, A.; BAR-YAAKOV, O.: Sensitivity of erythrocyte acetylcholinesterase to inhibition by linolenoyl sorbitol. Dependence on a transmembrane potential. *Biochim. Biophys. Acta*, 1976; 419: 358-364.
18. ALOIN, B.; LIVNE, A.: Acetylcholinesterase as probe for erythrocyte — membrane intactness. *Biochim. Biophys. Acta*, 1974; 339: 359-366.

Address for reprints: J. Martins e Silva
Institute of Biochemistry
Faculty of Medicine of Lisbon
1600 Lisbon. Portugal