HYPOTHESIS

Ion transport in hypertension: are changes in the cell membrane responsible?

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Summary

Disturbances in several, distinct cell membrane ion transport processes have been demonstrated in essential hypertension but their variable relationship to blood pressure in different populations has made it difficult to achieve a unifying hypothesis. We suggest that altered composition of the lipid fraction of the cell membrane is the common underlying factor. This would produce many of the reported perturbations of cell membrane properties and function, not all of which relate directly to the development of hypertension, but which act as markers for the underlying abnormality. However, functions such as phosphoinositol turnover, calcium binding and Ca\(^{2+}\), Mg\(^{2+}\)-ATPase dependent calcium efflux, which are influenced by the lipid composition of the membrane, provide a possible link between the membrane disturbance, intracellular calcium, vascular smooth muscle contraction and blood pressure. Alteration in the lipid content of the cell membrane not only provides an explanation for the variability in the ion transport abnormalities between populations but perhaps also for some of the variability in blood pressure within a single population. It also provides a potential means of influencing blood pressure by dietary intervention.

Introduction

High blood pressure can be regarded as a manifestation of the biological variability of a characteristic that in most populations shows a continuous, unimodal distribution, but which assumes unique importance because of its association with cardiovascular morbidity [1]. Perhaps it is not unexpected that for a multifactorial condition such as essential hypertension no single underlying mechanism to explain the blood pressure rise has been identified. Nevertheless elucidation of the physiological and biochemical mechanisms that underly this variability in blood pressure may lead to a greater understanding of blood pressure control and to the development of new ways of lowering blood pressure.

The first step is to identify abnormalities that are associated with high blood pressure. The increasing number of reports of alterations in cellular cation transport in blood cells in hypertension [2-5] suggests such changes may reflect an aspect of cell membrane function that influences blood pressure by involvement of tissues directly concerned with blood pressure control. The fact that multiple, distinct transport systems appear to be altered makes interpretation difficult. In addition, the relationship between such alterations and blood pressure seems to vary in different populations.

The central question is whether a unifying hypothesis can be put forward to account for these disparate findings and, if so, can this explain the development of hypertension?

Membrane sodium/potassium transport

Increased erythrocyte sodium content in essential hypertension has been reported by the majority of workers although by no means all [2-5], and a similar change has been demonstrated in the leucocyte [6, 7]. This would imply a disturbance in the relationship between sodium influx, sodium pump activity and intracellular sodium. Many groups have observed enhanced sodium and potassium influx in erythrocytes from hypertensive patients, using a variety of methods [2, 3, 5, 8-12]. In some cases, a rise in cell sodium with a fall or no change in the rate constant for sodium efflux suggests the sodium pump is not responding adequately. This has been most consistently observed in the leucocyte [2, 3, 5, 6, 13, 14].
There is other evidence that the disturbances of blood cell ion transport are multiple and only loosely associated with hypertension. Thus, sodium–potassium co-transport first reported to be reduced has in other studies been normal or increased [2, 3, 5, 15-17]. Also sodium–lithium counter-transport has been reported to be raised in the majority although not all of populations studied [2, 3, 5, 17-21]. This measurement is thought to reflect predominantly sodium–sodium exchange; however, its true physiological role is unknown. These discrepancies probably partly reflect differences in methodology but perhaps more importantly differences in the composition of the populations studied [2, 3, 5, 17-21]. Another significant point is that abnormalities in for instance sodium–sodium counter-transport are unlikely to produce a net change in intracellular sodium [24, 25]. It is therefore difficult to see their relevance to blood pressure elevation through a sodium dependent mechanism, although they may reflect a more generalized membrane defect [3, 26].

Explanatory hypothesis

The direct link. Blaustein [27] proposed that accumulation of intracellular sodium in vascular smooth muscle inhibited a postulated sodium–calcium exchange mechanism, resulting in a rise in free intracellular calcium and vascular contractility. Other groups have suggested that intracellular sodium is raised as a consequence of inhibition of the sodium pump by a circulating factor produced in response to an inherited defect in renal sodium excretion [28, 29]. These explanations have not been generally accepted for the following reasons. 

(a) Doubts about the existence of significant sodium–calcium exchange in vascular smooth muscle [30]. (b) Failure to isolate or characterize a specific sodium transport inhibitor from plasma and thus to differentiate it from other factors in plasma, such as noradrenaline, that can influence sodium transport [31] and are altered in hypertension [32]. (c) Difficulty in demonstrating inhibition of the sodium pump as a consistent result of chronic sodium loading [12, 33, 34]. (d) The presence of abnormalities in sodium transport pathways other than the sodium pump, referred to above, and the inability to demonstrate raised intracellular sodium as the final common pathway with these abnormalities.

The lipid hypothesis. An alternative explanation attributes disturbances of ion transport to an intrinsic abnormality in the physicochemical structure of the cell membrane associated with essential hypertension [13, 26]. Since the cation transport systems that are altered in hypertensive populations are, as far as is known, independent of each other and of cell membrane permeability [35], it is necessary to postulate either multiple abnormalities or a global disturbance which influences several pathways. This suggests that the phospholipid bilayer may be implicated since the transport systems are located in that structure. The proportion of different lipids in the cell membrane is known to influence both the physical properties and active processes of the membrane and disturbances in several of these functions have been reported in essential hypertension. Thus an alteration in cell membrane lipids in this condition could explain disturbances in ion transport and in other membrane functions which independently increase vascular smooth muscle activity.

Evidence for the lipid hypothesis

The lipid hypothesis yields a series of testable predictions: (1) Alterations in membrane lipids in vivo should influence cation transport. (2) Changes in cell membrane lipids should be demonstratable in those tissues from hypertensive subjects where cation transport is altered. (3) It should be possible to define a physiological process which links plasma membrane disturbance to elevated blood pressure. (4) Therapeutic interventions which modify plasma
membrane lipids should influence blood pressure as well as ion transport in vivo.

Effect of alterations in membrane lipids

The composition of the lipid bilayer is not fixed and changes in its chemical and physical structure readily occur, for instance when catecholamines bind to adrenoceptors in a target tissue [36]. Similarly, alterations in the proportion of unsaturated to saturated fatty acids in the acyl sidechains of membrane phospholipids have been shown to influence membrane fluidity, transport of ions and Na⁺,K⁺-ATPase activity [37-39]. Ouabain resistant ion fluxes can also be modified by changes in the physicochemical properties of the erythrocyte membrane both in vivo and in vitro [38, 40-42]. Thus, increasing membrane linoleic acid by dietary intervention produces an increase in erythrocyte ouabain resistant fluxes in normal individuals [43]. Also a relationship between plasma lipids, in particular high density lipoproteins, and sodium–lithium exchange has been reported in normotensive and hypertensive individuals [44, 45]. Another approach is to induce a change in the micellar structure of the erythrocyte membrane by altering its electrostatic charge. This can be achieved by substituting the permanent anion nitrate for chloride in the suspension medium [46]. When this is done permeability is increased together with intracellular sodium and absolute sodium efflux rate, although the sodium efflux rate constant for active sodium pumping (i.e. the component of the sodium pump to respond to increased sodium) is decreased [47]. This constellation of changes resembles that described by some groups in essential hypertension [2-5].

Membrane lipids in hypertension

As in the case of ion transport the erythrocyte has been most frequently studied because of its accessibility. Decreased erythrocyte membrane fluidity, which reflects membrane lipid composition, has been reported in essential hypertension [48] and in the spontaneously hypertensive rat [49]. A cell membrane lipid disturbance has been associated directly with altered ion transport in a study by Levy et al. [18]. When the ambient temperature is reduced, cell membrane lipids undergo a change in physical state. At this temperature (the phase transition temperature) lipid dependent membrane functions show an abrupt change. The phase transition temperature for erythrocyte sodium–lithium counter-transport is significantly altered in hypertensive patients and their relatives. There is also some direct evidence of alteration in membrane lipids in essential hypertension: sialic acid content has been reported to be increased [50] and the content of the polyunsaturated fatty acid, linoleic acid, decreased [51]. In addition the linoleic acid content of adipose tissue and platelets has been shown to be negatively correlated with blood pressure [52, 53].

Plasma membrane and hypertension

Haemodynamically most forms of hypertension are characterized by raised peripheral resistance. An essential participant in the control of vascular smooth muscle contraction, and thereby vascular tone, is the intracellular calcium ion concentration [54]. Those abnormalities that could influence intracellular ionized calcium may therefore be of particular relevance to the development of hypertension. This could be altered secondarily as a result of membrane depolarization caused by increased permeability [55]. Alternatively, calcium handling could be influenced directly [56]. Three membrane functions of relevance to calcium handling are altered in essential hypertension: phosphoinositol turnover, calcium binding and Ca²⁺,Mg²⁺-ATPase dependent calcium efflux [37, 57-59]. Hydrolysis of membrane lipid phosphoinositol produces inositol triphosphate. This system has recently been recognized to be important as a second messenger in the release of intracellular calcium stores [60]. Erythrocyte phosphoinositol turnover is abnormal in essential hypertension [61]. Phospholipids may also contribute to the decreased calcium binding to the inner surface of the cell membrane found in hypertension [48, 62], which is also influenced by membrane lipid composition [63]. Ca²⁺,Mg²⁺-ATPase dependent calcium efflux has been shown to be reduced in erythrocytes in hypertension, particularly in the presence of calmodulin [64]. The activity of this enzyme and its responsiveness to calmodulin can be modified by the type of phospholipid in the adjacent bilayer [59].

The measurement of intracellular calcium has until recently been difficult in human cells. Two reports of elevated levels have been made: using ion selective electrodes to measure calcium activity in disrupted erythrocytes [65] and using the fluorescent indicator Quin-2 to measure ionized calcium in intact platelets [66]. In the latter study intracellular ionized calcium was positively correlated with blood pressure. However, studies using human leucocytes have failed to confirm these findings [67, 68], and the role of abnormalities in calcium handling in essential hypertension will have to await studies of human vascular smooth muscle. Nevertheless there is evidence that changes in blood cells do reflect similar alterations in more relevant tissues. Thus, analogous abnormalities of sodium
influx, sodium efflux, phosphoinositol turnover and calcium handling in vascular smooth muscle and other tissues have been reported in the spontaneously hypertensive rat [3, 4, 26, 56, 60, 62, 69, 70]. This supports the view that these membrane defects are widespread and that circulating blood cells may be analogous to vascular smooth muscle.

Therapeutic intervention

Although some aspects of cell membrane composition may be inherited and therefore account for the differences in blood pressure between individuals and for the altered cellular responses to factors such as circulating hormones and stress, they are amenable to modification by environmental factors such as diet. Whilst study of dietary influences on blood pressure has been focused upon electrolyte intake, it is possible that dietary lipids may account for the lower blood pressures repeatedly reported in vegetarians [71]. Increasing polyunsaturated fat intake, or the ratio of unsaturated to saturated fat, has produced a fall in blood pressure in several studies in man [72-75] and in the rat [76, 77]. The relevant dietary change has not been adequately defined. In one study when dietary unsaturated to saturated fat ratio was altered without an overall change in fat intake no blood pressure fall was observed [78]. On the other hand, in a recent double-blind trial linoleic acid supplementation produced a significant fall in systolic blood pressure and an increase in leucocyte ouabain sensitive sodium efflux in normal man [43]. Moreover, exercise induced changes in plasma lipids have been associated with changes in sodium–lithium exchange [44]. The possible manipulation of cell membrane composition by dietary intervention is an attractive one which deserves further study.

To test this hypothesis two major criteria need to be met. Firstly the demonstration that changes in leucocyte and erythrocyte cation transport and/or plasma membrane composition reflect a global change in all cells but in particular the vascular smooth muscle cell. In man data on this are poor but a relationship between ouabain sensitive sodium efflux in leucocytes and mesenteric resistance vessels has recently been reported [79]. Secondly that induced changes in the cell membrane physical properties or lipid composition are associated with changes in blood pressure and membrane cation transport, that reflect the differences described between hypertensive and normotensive subjects. Also the relationship between the distribution of blood pressure and the distribution of cell membrane properties such as fluidity or lipid composition in a single population will show how much of the variability in blood pressure can be attributed to changes in the cell membrane.

Conclusions

Changes in cell membrane lipid composition provide an explanation not only for the multiple disturbances of monovalent cation fluxes in essential hypertension, but also for alterations in vascular smooth muscle contractility through changes in intracellular ionized calcium and partial depolarization of the cell. Because of the number of permutations of lipid content possible, this explanation would account for the variability in the associations reported between blood pressure and ion transport abnormalities in different populations, which has been a feature of the extensive and conflicting studies in this field. Further, it is possible to account for changes in ion fluxes (such as sodium–sodium counter-transport) which would not be expected to change intracellular composition. Such abnormalities can be considered as loosely associated markers for the underlying cell membrane defect. Differences in cell membrane lipids may be inherited but could also be the result of environmental factors such as diet and stress. Further elucidation of the role of cell membrane composition in the control of intracellular mechanisms may not only explain some of the puzzling changes reported in hypertension but also provide a rational basis for public health measures to lower blood pressure.

References


