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Glimpses of the mechanisms of hypertension

The steep gradient in the concentration of sodium ions across the membrane of living cells is maintained by a cation dependent ATPase which has been described as a cochemiporter. The enzyme is embedded in the cell membrane, splits ATP, and transports three sodium ions from the interior in exchange for two potassium ions. It contributes to the resting membrane potential, and the resulting ion gradients are a source of energy driving other cation transport mechanisms. At least three of these transporters are relevant in hypertension: bidirectional Na^+/K^+ cotransport, a process inhibited by loop diuretics; Na^+/Ca^{++} countertransport, in which intracellular sodium is exchanged for calcium; and Na^+/Li^+ countertransport.

Many of these transporters have been implicated in the pathogenesis of essential hypertension, but establishing which (if any) of the abnormalities is a primary fault and identifying the mechanism linking this fault to increased vascular resistance has been difficult. Arterioles are small, inaccessible, and difficult to study. Most investigators have therefore turned their attention to erythrocytes, leucocytes, and the larger muscular arteries of animals with experimental hypertension.

The activity of the sodium pump, as measured by fluxes of radioisotopes, is often altered in arterial muscle from rats with experimental hypertension,[1] but the direction of change varies. In arterial muscle from the spontaneously hypertensive rat the pump activity is increased.[1,2] This increase may result from enhanced passive permeability of the cell membrane to Na^+,[1,3] which may be a consequence of increased sympathetic nerve input.[4,5] The activity of the pump is probably also increased in erythrocytes from patients with essential hypertension (both in vitro[6-10] and in vivo[11]) and with pregnancy induced hypertension,[12] although not everybody agrees.[13,14] A recent analysis of pooled data from 20 papers found a small but significant increase in erythrocyte sodium content,[15] but one study that ensured rapid and efficient separation of the cells from the plasma found the opposite.[16]

The rate of sodium efflux from leucocytes is higher than from erythrocytes, but the rate constant for ouabain sensitive sodium efflux is reduced despite an increase in intracellular Na^+ concentration.[17,18] Whether this reduction is genetic is not clear,[18-21] perhaps because of the difficulty in assessing the genetic element in family studies of this sort.[22] Resistance vessels have a faster rate of sodium efflux than leucocytes, but the ouabain sensitive sodium efflux rate constants in the two tissues are correlated.[23]

Although it is over 30 years since Tobian first described an increase in the sodium content of renal arteries from subjects with hypertension,[24] we are still uncertain about Na^+ concentration in smooth muscle cells.[25] The relation between Na^+ concentration in arterial muscle and hypertension may not be constant.[1] Nuclear magnetic resonance may help monitor the intracellular concentration of Na^+,[26] but more data are needed.

The rate of sodium efflux is critically dependent on the intracellular concentration of Na^+ but is also affected by the extracellular concentration of K^+. Why does the sodium pump in leucocytes not respond to the increased concentrations of internal Na^+? Much research has centred on the hypothesis that there is a circulating pump inhibitor in essential hypertension, produced in response to subtle expansion of extracellular fluid volume.[27] Although there is evidence for the existence of such an inhibitor in man,[20-30] and in animals with volume dependent hypertension,[31] it seems to affect leucocytes and not erythrocytes.[28] In contrast, cardiac glycosides inhibit the pump on both of these blood cells. The structure of the inhibitor(s) is unknown, and the atriopeptins with their natriuretic and vasorelaxant effects do not inhibit pump activity.[32] Some membrane phospholipids also affect the activity of the enzyme,[33,34] which is central to the hypothesis that membrane structure is abnormal in hypertension.[35]

But could an increase in intracellular Na^+ concentration increase peripheral vascular resistance? Attention has been focused on the Na^+/Ca^{++} exchange mechanism, which is certainly present in cardiac muscle[36,37] but not perhaps in vascular muscle.[38] Giving cardiac glycosides acutely causes vasoconstriction,[39,40] but less is known about the effects of chronic treatment.[41] In any case, the change of intracellular Na^+ concentration resulting from pump inhibition may not be sufficient to cause calcium mediated vasoconstriction.[41,42]

Since Garay and Meyer first reported abnormal outward cotransport of Na^+ in erythrocytes in hypertension,[43] this carrier mechanism has been investigated exhaustively. Also known as a symport, it probably maintains cell volume when intracellular Na^+ concentration is increased.[44] Most recent evidence suggests that cotransport is normal or increased in erythrocytes in essential hypertension[10,14,15,35]; differences of technique may account for some of the discrepancies.[10,35] Bianchi has suggested that the genetically determined increase in Na^+/K^+ cotransport in erythrocytes of the Milan strain of hypertensive rat is responsible for the increased

proximal tubular reabsorption of sodium which is thought to cause the hypertension.[45]

Canessa and her colleagues first reported increased maximal rates of Na^+/Li^+ countertransport in erythrocytes from some patients with essential hypertension.[46] This has been confirmed, although abnormalities are hardly evident in hypertensive women[47] and blacks,[48] and body weight seems to have an effect in its own right.[49,50] Lithium is not a natural substrate of the exchanger, which may function normally in a Na^+/Na^+ or Na^+/H^+ mode. The Na^+/H^+ antiport is well characterised: it is inhibited by amiloride, helps regulate intracellular pH, and promotes cell growth.[51-53] If Na^+/Li^+ exchange in erythrocytes is equivalent to Na^+/H^+ exchange, which is uncertain,[54,55] then increased Na^+/H^+ exchange might be linked to the pathogenesis of hypertension in two ways: overactivity of the exchanger in the proximal renal tubule might cause sodium retention[53,56]; or overactivity in the erythrocyte might be a manifestation of increased growth factor activity causing hyperplasia or hypertrophy of vascular smooth muscle and hence increased vascular resistance.[57]

Studying sodium transport across the cell membrane has given at best tantalising glimpses of the mechanisms in hypertension. We need to know more about these transporters in the myocytes of resistance vessels and more about their relation to transporters in blood cells.

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1 Friedman SM. Cellular ionic perturbations in hypertension. *Journal of Hypertension* 1983;1: 109-14.
2 Jones AW. Altered ion transport in vascular smooth muscle from spontaneously hypertensive rats. *Circ Res* 1973;33:563-71.
3 Jones AW. Ionic dysfunction and hypertension. *Advances in Microcirculation* 1982;11:134-59.
4 Hermsmeyer K. Altered arterial muscle ion transport mechanism in the spontaneously hypertensive rat. *J Cardiovasc Pharmacol* 1984;6:510-5.
5 Stekiel WJ, Contney SJ, Lombard JH. Small vessel membrane potential, sympathetic input, and electrogenic pump rate in SHR. *Am J Physiol* 1986;250:C547-56.
6 Garay R, Dagher G, Pernollet M-G, Devynck M-A, Meyer P. Inherited defect in a Na^+, K^+ cotransport system in erythrocytes from essential hypertensive patients. *Nature* 1980;284:281-3.
7 Postnov YV, Orlov SN, Shevchenko A, Adler AM. Altered sodium permeability, calcium binding and Na-K-ATPase activity in the red blood cell membrane of essential hypertension. *Pflügers Archiv* 1977;371:263-9.
8 Woods KL, Beevers DG, West M. Familial abnormality of erythrocyte cation transport in essential hypertension. *Br Med J* 1981;282:1186-8.
9 Wambach G, Helber A, Bonner G, Hummerich W, Konrads A, Kaufman W. Sodium-potassium-dependent-ATPase activity in erythrocyte ghosts of patients with primary and secondary hypertension. *Clin Sci* 1980;59(suppl):183-5.
10 Bin Talib HK, Chipperfield AR, Semple PF. Potassium influx into erythrocytes in essential hypertension. *Journal of Hypertension* 1984;2:405-9.
11 Boon NA, Aronson JK, Hallis KF, Grahame-Smith DG. Cation transport abnormalities in vivo in untreated essential hypertension. *Clin Sci* 1986;70:611-6.
12 Weissberg PL, Weaver J, Woods KL, West MJ, Beevers DG. Pregnancy induced hypertension: evidence for increased cell membrane permeability to sodium. *Br Med J* 1983;287:709-11.
13 Walter V, Distler A. Abnormal sodium efflux in erythrocytes of patients with essential hypertension. *Hypertension* 1982;4:205-10.
14 Parker JC, Berkowitz LR. Physiologically instructive genetic variants involving the human red cell membrane. *Physiol Rev* 1983;63:261-313.
15 Hilton PJ. Cellular sodium transport in essential hypertension. *N Engl J Med* 1986;314:222-9.
16 Simon G, Conklin DJ. In vivo erythrocyte sodium concentrations in human hypertension is reduced not increased. *Journal of Hypertension* 1986;4:71-5.
17 Edmondson RPS, Thomas RD, Hilton PJ, Patrick J, Jones NF. Abnormal leucocyte composition and sodium transport in essential hypertension. *Lancet* 1975;i:1003-5.
18 Ambrosioni E, Costa FV, Montebugnoli L, Tartagni F, Magnani B. Increased intralymphocytic sodium content in essential hypertension: an index of impaired Na^+ cellular metabolism. *Clin Sci* 1981;61:181-6.
19 Heagerty AM, Milner M, Bing RF, Thurston H, Swales JD. Leucocyte membrane sodium transport in normotensive populations: dissociation of abnormalities of sodium efflux from raised blood pressure. *Lancet* 1982;ii:894-6.
20 Gray HH, Johnson VE, Poston L, Hilton PJ. Sodium transport by leucocytes and erythrocytes in hypertensive patients and their normotensive relatives. *Journal of Hypertension* 1984;2:467-9.
21 Chien Y, Zhao G. Abnormal leucocyte sodium transport in Chinese patients with essential hypertension and their normotensive offsprings. *Clin Exp Hypertens [A]* 1984;6:2279-96.
22 Watt G. Design and interpretation of studies comparing individuals with and without a family history of high blood pressure. *Journal of Hypertension* 1986;4:1-7.
23 Aalkjaer C, Heagerty AM, Parrin SD, Bell PRF, Bing RF, Swales JD. Cell membrane sodium transport—a correlation between human resistance vessels and leucocytes. *Lancet* 1986;i: 649-51.
24 Tobian L, Binton JT. Tissue cations and water in arterial hypertension. *Circulation* 1952;5:754-8.
25 Aalkjaer C, Kjeldsen K, Norgaard A, Clausen T, Mulvany MJ. Oubain binding and Na^+ content in resistance vessels and skeletal muscles of spontaneously hypertensive rats and K^+ depleted rats. *Hypertension* 1985;7:277-86.
26 Pike MM, Fussel ET, Smith TW, Springer CS. High resolution ^{23}Na-NMR studies of human erythrocytes: use of aqueous shift reagents. *Am J Physiol* 1984;246:C528-36.
27 de Wardener HE, MacGregor GA. Dahl's hypothesis that a saluretic substance may be responsible for a sustained rise in arterial pressure: its possible role in essential hypertension. *Kidney Int* 1980;18:1-9.
28 Poston L, Sewell RB, Wilkinson SP, *et al*. Evidence for a circulating sodium transport inhibitor in essential hypertension. *Br Med J* 1981;282:847-9.
29 Hamlyn JM, Ringel R, Schaeffer J, *et al*. A circulating inhibitor of ($Na^+ + K^+$) ATPase associated with essential hypertension. *Nature* 1982;300:650-2.
30 Gray HM, Hilton PJ, Richardson PJ. Effect of serum from patients with essential hypertension on sodium transport in normal leucocytes. *Clin Sci* 1986;70:583-6.
31 Haddy FJ. Abnormalities of membrane transport in hypertension. *Hypertension* 1983;5(suppl V):66-72.
32 Sagnella GA, Nolan DA, Shore AC, MacGregor GA. Effects of synthetic atrial natriuretic peptides on sodium-potassium transport in human erythrocytes. *Clin Sci* 1985;69:223-6.
33 Niggli V, Adurgah ES, Penniston JT, Carafoli E. Purified ($Ca^{2+} + Mg^{2++}$) ATPase of the erythrocyte membrane. Reconstitution and effects of calmodulin and phospholipids. *J Biol Chem* 1981;256:395-401.
34 Simmons DA, Kern EFO, Winegrad AI, Martin DB. Basal phosphatidylinositol turnover controls aortic Na^+/K^+ ATP-ase activity. *J Clin Invest* 1986;77:503-13.
35 Swales JD. Abnormal ion transport by cell membranes in hypertension. In: de John W, ed. *Handbook of hypertension*. Vol 1. Amsterdam: Elsevier, 1983:239-66.
36 Reuter H, Seitz N. The dependence of calcium efflux from cardiac muscle on temperature and external ion composition. *J Physiol (Lond)* 1968;195:451-70.
37 Kimura J, Noma A, Irisawah H. Na-Ca exchange current in mammalian heart cells. *Nature* 1985;319:596-7.
38 Brading AF, Lategan TW. Na-Ca exchange in vascular smooth muscle. *Journal of Hypertension* 1985;3:109-16.
39 Mulvany MJ, Nilsson H, Flatman JA, Korsgaard N. Potentiating and depressing effects of ouabain and potassium free solutions on rat mesenteric resistance vessels. *Circ Res* 1982;51: 514-24.
40 Robinson BF, Phillips RJW, Wilson PN, Chiodini PL. Effects of local infusion of ouabain on human forearm vascular resistance and on response to potassium, verapamil and sodium nitroprusside. *Journal of Hypertension* 1983;1:165-9.
41 Mulvany MJ. Changes in sodium pump activity and vascular contraction. *Journal of Hypertension* 1985;3:429-36.
42 Hermsmeyer K, Hanler D. Membrane ATPase mechanism of K^+-return relaxation in arterial muscles of stroke-prone SHR and WKY. *Am J Physiol* 1986;250:C557-62.
43 Garray RP, Meyer P. A new test showing abnormal net Na^+ and K^+ fluxes in the erythrocytes of essential hypertensive patients. *Lancet* 1979;i:349-53.
44 Duhm J, Gobel BO. Role of the furosemide-sensitive Na^+/K^+ transport system in determining the steady state Na^+ and K^+ content and volume of human erythrocytes in vitro and in vivo. *J Membr Biol* 1984;77:243-54.
45 Bianchi G, Ferrari P, Barber BR. The Milan hypertensive strain. In: Robertson JIS, Birkenhager W, eds. *Handbook of hypertension*. Amsterdam: Elsevier, 1984:328-49.
46 Canessa M, Adragna N, Solomon HS, Connolly TM, Tosteson DC. Increased sodium-lithium countertransport in red cells of patients with essential hypertension. *N Engl J Med* 1980;302:772-6.
47 Ibsen KK, Jensen HA, Wieth JO, Funder J. Essential hypertension: sodium-lithium countertransport in erythrocytes from patients and from children having one hypertensive parent. *Hypertension* 1982;4:703-9.
48 Canessa M, Spalvins A, Adragna N, Falkner B. Red cell sodium countertransport and cotransport in normotensive and hypertensive blacks. *Hypertension* 1984;6:344-51.
49 Cooper R, Trevison M, Ostrow D, Simpos C, Stamler J. Blood pressure and sodium lithium countertransport: finding in population-based surveys. *Journal of Hypertension* 1984;2:467-70.
50 Hunt SC, Williams RR, Smith JB, Ash KO. Associations of three erythrocyte cation transport systems with plasma lipids in Utah subjects. *Hypertension* 1986;8:30-6.
51 Moolenaar WH, Tsien RY, ven der Saag PT, de Leat SW. Na^+/H^+ exchange and cytoplasmic pH in the action of growth factors in human fibroblasts. *Nature* 1985;304:645-8.
52 L'Allemain G, Franchi A, Cragoe E, Jr. Blockade of the Na^+ antiport abolishes growth factor-induced DNA synthesis in fibroblasts. Structure-activity relationships in the amiloride series. *J Biol Chem* 1984;259:4313-9.
53 Mahnensmith RL, Aronson PS. The plasma membrane sodium-hydrogen exchanger and its role in physiological and pathophysiological processes. *Circ Res* 1985;56:773-88.
54 Escobales N, Canessa M. Amiloride-sensitive Na^+ transport in human red cells: evidence for a Na/H exchange system. *J Membr Biol* 1986;90:21-8.
55 Jennings ML, Adams-Lackay M, Cook KW. Absence of significant sodium-hydrogen exchange by rabbit erythrocyte sodium lithium countertransporter. *Am J Physiol* 1985;249:C63-8.
56 Weder AB. Red cell lithium-sodium countertransport and renal lithium clearance in hypertension. *N Engl J Med* 1986;314:198-201.
57 Lever AF. Slow pressor mechanisms in hypertension: a role for hypertrophy of resistance vessels. *Journal of Hypertension* (in press).

Pacemaker syndrome

Permanent cardiac pacing is the treatment for symptomatic bradycardia due to ventricular conduction defects, sinoatrial disease, and the carotid sinus syndrome. About 114 new pacemakers for every million people are implanted each year in Britain, and the rate is increasing. A stable rate of 300-400 per million may be reached nationally over the next five years and has already been approached by a few British centres and reached in several European countries.[1] It is increasingly important, therefore, that doctors appreciate that apparently satisfactory function of an implanted ventricular pacemaker may be associated with a whole range of cardiac symptoms,