a step closer to discovering the connection between these conditions. Unfortunately, several methodologic limitations have restricted interpretation of the data from the present study. Gaspardone et al. use the method first proposed by Canessa et al., without making allowances for changes to assay methodology over the past two decades. First, the issue of using magnesium in the sodium-free media has not been addressed. This may have had subtle effects on outcomes of SLC characterization (5,6). Second, Gaspardone et al. fail to recognize the issue of distribution of SLC activity within populations (1). Activity of SLC is not normally distributed and as such should not be reported as a mean value ± SD (4,5). Finally, determining activity as opposed to performing kinetic characterization prevents the work of Gaspardone et al. from being put into context with recent investigations into SLC behavior. Kinetic investigations have confirmed the critical roles of the maximal rate of turnover (Vmax) and external affinity constant (k_m) in the relation between SLC behavior and various disease processes (4,5). These two constants appear to represent two distinct SLC characteristics operating under different influences. In hypertension, k_m is altered—expressed in the form of a lower k_m, possibly reflecting a higher affinity for external sodium that may have a genetic basis (4,5). With regard to the broader issue of vascular disease, there is evidence to suggest low k_m in patients with coronary artery disease (7). In the case of diabetes, reduced k_m occurs when the patient has nephropathy; however, Vmax is also reduced (4,5). In contrast, patients with chronic diabetes with no evidence of renal damage demonstrate elevated Vmax. Furthermore, Vmax is related to fluidity of the erythrocyte membrane (4,5). This suggests that environmental factors such as plasma lipids may be exerting effects on the countertransporter. Changes in SLC behavior associated with diabetes may therefore relate to pathologic changes in lipid metabolism and membrane fluidity.

Gaspardone et al. make two controversial assumptions in their work. First, in claiming to have determined Vmax using the method of Canessa et al., Gaspardone et al. is incorrect (1). The method of Canessa et al. measures a lithium efflux rate under highly specific conditions that are not representative of the biochemical constant Vmax (4,5). Second, in their interpretation of their findings, Gaspardone et al. relate the abnormal SLC activity in their patients with syndrome X to the expression of abnormal behavior in the sodium–hydrogen exchanger (SHE) (1). We recognize that similarities between these membrane transporters support the hypothesis that SHE and SLC represent different functional responses of a single membrane protein. However, it is well accepted that there are several missing links that stand in the way of the confirmation of this otherwise attractive theory, and we caution against too ready acceptance (5,8). Furthermore, the cluster of “dowels” that Gaspardone et al. suggest may be linked by enhanced SHE activity, including coronary prearteriolar dysfunction, hyperinsulinemia and the predominance of sympathetic activity, could equally be explained by defects in the cell membrane itself. The membrane resident receptors, enzymes and transporters that mediate many of these processes are sensitive to the composition of the cell membrane, and major changes in the properties of the membrane can be imposed by minor alterations in lipid composition (9). Such alterations could also explain the abnormal SLC behavior noted in the study of Gaspardone et al. (1). The aforementioned hypothesis does not require a specific error in the coding of a single transporter and relates these observations more to environmental rather than genetic factors.

REFERENCES


REPLY

Considerations by Hardman et al. about the recent identification of a clearcut elevation of the maximal velocity (Vmax) of red blood cell sodium−lithium countertransport (SLC) in patients with cardiac syndrome X (1) are of interest. These authors state that the identification of increased SLC activity in essential hypertension (2) has not been confirmed by some subsequent studies, and they conclude that it is not possible to predict hypertension on the basis of the Vmax of SLC. We fully agree with these conclusions. However, it needs to be clarified that our study was carried out in a very select group of patients with cardiac rather than metabolic syndrome X (3) who are by definition normotensive. Thus, Hardman et al. seem to mistake cardiac for metabolic syndrome X. Consequently, it is difficult for us to comment on the role of a condition (i.e., hypertension) that was absent in our patients and was an exclusion criterion for patient selection.

Timothy C. Hardman, Research Fellow, BSc, PhD
Heart Function Group
Imperial College School of Medicine
Charing Cross Hospital
London
United Kingdom

Ruth H. Clifford, Research Assistant, BSc
Pharmacology Group
King’s College London
London
United Kingdom

Simon W. Dubrey, Senior Registrar, MD
Department of Cardiology
Hillingdon Hospital
Uxbridge, Middlesex
United Kingdom

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956 Letters to the Editor
With regard to essential hypertension, we agree that this is a multifactorial condition. Obviously, all variables, including blood pressure levels itself, cannot show clear cutoff differences between normotensive and hypertensive patients, and there is no possibility of identifying a marker of hypertension in the whole population. As a consequence, neither an elevated $V_{\text{max}}$ of red blood cell SLC nor any other variable can represent a marker of essential hypertension. In contrast, this assumption is not true for the identification of hypertensive patient subsets or hypertension sequelae, which could both be influenced by major genes rather than polygenes. With the use of the method by Canessa et al. (2) with appropriate modifications, Redgrave et al. (4) and our group (5) have clearly demonstrated the elevation of SLC activity in a subset of patients with essential hypertension known as “nonmodulators.” An elevated $V_{\text{max}}$ of red blood cell SLC predicted the blood pressure responses to changes in sodium intake in salt-sensitive but not salt-resistant subsets of patients with essential hypertension (6,7). Nosadini et al. (8) clearly linked SLC hyperactivity to the pressure responses to changes in sodium intake in salt-sensitive but normotensive and hypertensive patients, and there is no possibility of identifying a marker in the whole population.

The aforementioned studies also showed the ability of elevated SLC activity to act as a marker of familial hyperlipidemia or hypertension. Therefore, there is a clear association among an elevated $V_{\text{max}}$ of red blood cell SLC, hypertension subtypes and hypertension sequelae in hypertensive patients and their families. Again, our study did not focus on such associations because hypertensive patients were excluded.

A second observation made by Hardman et al. is related to the well-known bimodal distribution of SLC in hypertensive patients and hypertensive relatives. Again, we had no hypertensive patients and hypertensive relatives among our patients and gender-matched control subjects. Furthermore, in Figure 1 of our study, individual data of SLC appear to be normally distributed.

Hardman et al. raised another interesting point regarding the controversial assumption that SLC is an in vitro expression of the behavior of the sodium–hydrogen exchanger. This subject is still a matter of controversy. However, there has been great interest in the recent report of Koren et al. (10), who observed an increased activity of the sodium–hydrogen exchanger in a group of patients with cardiac syndrome X.

Claudio Ferri, MD
Achille Gaspardone, MD
Divisione di Cardiologia
Università di Roma “Tor Vergata”
European Hospital
Rome, Italy

REFERENCES


Angina Pectoris, Myocardial Infarction and Verapamil

The excellent review of unstable angina (UA) and non–Q-wave myocardial infarction by Zaacks et al. (1) contained a statement that may mislead the reader: “The Multicenter Diltiazem Post Infarct Trial found a significant reduction of adverse cardiac events in patients receiving diltiazem who did not have pulmonary edema on presentation. Similar favorable findings cannot be extrapolated to include other calcium channel blockers such as verapamil . . .”

Zaacks et al. do not include the results from the Danish Verapamil Infarction Trial (DAVIT) II (2) in their review. The DAVIT II, a double-blind, randomized, placebo-controlled postinfarct trial of verapamil (120 mg t.i.d.), which included 1,775 patients, demonstrated a significant reduction in major events (i.e., first reinfarction or death in verapamil-treated [18.0%] compared with placebo-treated patients [21.6%]; hazard ratio [HR] 0.80, 95% confidence interval [CI] 0.64 to 0.99). In an a priori–determined subgroup analysis, in relation to treatment for congestive heart failure (CHF) before randomization, in patients without CHF verapamil significantly prevented death (7.7%) as compared with placebo (11.8%) (HR 0.64, 95% CI 0.44 to 0.94). Also, the reinfarction rate was significantly lower in the verapamil group (9.2% vs. 12.7%) (HR 0.67, 95% CI 0.46 to 0.97). No harm was found in patients with CHF.

In a recent, small, double-blind postinfarct study of patients with CHF being treated with the angiotensin-converting enzyme inhibitor trandolapril, verapamil significantly prevented reinfarction, UA and CHF (3).

A post hoc analysis of DAVIT I demonstrated that verapamil prevented the development of myocardial infarction in patients admitted to the hospital with UA (4). Verapamil also prevented post infarct angina (2,5). In conclusion, the statement of Zaacks et al. should be changed to: “Verapamil also prevented death, reinfarction and angina pectoris in postinfarct patients; the effect is most pronounced in patients without CHF.”

Jørgen Fischer Hansen, MD, PhD
Kresten Mellemgaard, MD, PhD
The DAVIT Study Group
Department of Cardiology
Bispebjerg University Hospital
DK-2400 Copenhagen NV
Denmark

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