Sodium-Lithium Countertransport Activity Is Linked to Chromosome 5 in Baboons

To the Editor:

We read with interest the elegant work of Kammerer et al on sodium-lithium countertransport (SLC) activity in baboons. Their findings were particularly interesting because they apply the exciting field of genetic characterization to that of SLC research some 20 years after a genetic linkage between SLC expression and hypertension was first proposed. SLC has since been shown to be highly heritable, but the genetic contribution has been difficult to isolate and identify despite work in special populations such as large family groups and identical twins.

However, it was unfortunate that the authors chose to shackle a 20-year-old method to their cutting-edge genetic technology. In doing little more than measuring lithium efflux from red cells, the method used by Kammerer et al makes little or no concession to advances in SLC methodology made over the past 2 decades. In 1980, Rutherford et al described how hypertension may be related to a specific characteristic of the countertransporter, namely a measure of its affinity for sodium. This was achieved by undertaking a kinetic characterization of the transporter. Since its first clinical application, kinetic characterization has revealed a great deal about the behavior of the countertransporter in health and disease. Of particular interest with respect to the present work is the possibility that affinity of the transporter for its substrate may be genetically determined, whereas its maximal rate of turnover may be dictated by it lipid environment, itself under genetic and environmental control.

Kammerer et al appear to have discovered at least 1 genetic loci determining the expression of SLC. If they had performed kinetic analysis, they may have been able to provide data to confirm or reject the proposal for specific influences on different kinetic aspects of the countertransporter. Applied in their animal model, this finding would have been of particular value as one assumes that the baboon population was generally homogenous in its nature, with individual animals sharing a relatively similar environment, thus reducing potentially confounding environmental influences.

One issue that did not receive comment was the conformity between SLC in humans and that in baboons: do baboons show the same degree of inter-individual variation seen in humans? SLC has been claimed to have been measured in several different species. However, the lithium or sodium efflux profiles used to identify the transporter in these species have often shown markedly different characteristics from those seen in humans. Values for SLC in the baboons described here were certainly similar to those reported in humans. The question arises as to whether or not the countertransporter in baboons is under the same influences and controls as that in humans. Certainly, the authors report a quiet significant relationship between expression of SLC activity and age, a relationship that is not repeated in humans.

In conclusion, we cannot fault the reasoning of Kammerer et al and agree wholeheartedly with their assessment that the link between hypertension and elevated SLC activity reflect an aspect of the membrane that may cause or be caused by disease. We can only feel, however, that by applying redundant methodology to characterize the countertransporter a unique opportunity to provide new insights has been missed.


Response

We agree completely with Drs Hardman and Noble’s comment that genetic analysis of kinetic characteristics of sodium-lithium countertransport (SLC) activity, especially the maximal rate of turnover (V_max) and the affinity constant for sodium, should be more informative than the simple, but very robust, measurement of SLC activity used in our linkage study. However, the SLC activity data in baboons were obtained between hypertension and elevated SLC activity reflect an aspect of the membrane that may cause or be caused by disease. We can only feel, however, that by applying redundant methodology to characterize the countertransporter a unique opportunity to provide new insights has been missed.
Finally, we do not believe that our evidence for a quantitative trait locus (QTL) affecting SLC activity in baboons represents a missed opportunity to gain new insights. In contrast, we believe that detection of a QTL in baboons, in combination with knowledge about kinetic characteristics of the countertransporter obtained from numerous studies in humans, provides us with a unique opportunity to identify and characterize candidate genes for SLC activity. Specifically, information regarding characteristics of the countertransporter will greatly facilitate our search for candidate genes among the hundreds of genes located within the region of linkage. To date, no known genes related to hypertension or SLC activity have been mapped to this region of baboon chromosome 5 (which is homologous to human chromosome 4). If the QTL is encoded by a known gene with a product that has been physiologically and/or kinetically characterized, these data will direct our functional studies for determining mechanisms of SLC phenotypic variation encoded by genetic variation. If the QTL is encoded by a novel gene, existing functional data will help prioritize candidate genes for further study. The identification, and subsequent molecular and physiological characterization, of a gene that affects SLC could provide insights into susceptibility to hypertension.
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Hypertension. 2001;38:e35-e36

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