Membrane Physiology — Bridging the Gap between Medical Disciplines
Markus Bleich, M.D.

The general separation between medical disciplines has, for decades, been a strange tradition. For example, neurologists and nephrologists have each had their defined patient groups, and many are barely interested, if at all, in the other discipline’s research. Even within a specific field of basic science, such as physiology, neurophysiologists do not necessarily talk with other physiologists. Thus, the blood–brain barrier has been dividing more than two extracellular spaces. A credible exception may be found among clinical disciplines that focus on the patient as a whole, such as pediatrics. Children often present with complex syndromes that may be considered sporadic and without known genetic origins. Not having a specific diagnosis in such situations is frustrating for the patient, the family, and the physician. In addition, medical treatments for such patients are too often based on empirical measures rather than scientific grounds. Interestingly, some of these syndromes have turned out to be the result of single-gene disorders.

In recent years, the diagnosis and treatment of some single-gene disorders have been substantially improved when the findings of basic and clinical research were combined. Major progress in molecular biology, molecular genetics, and cellular physiology has enabled development of both the tools and the mechanistic understanding to facilitate genetic identification of one disease after another, revealing the functional proteins involved in the observed pathophysiology.1

In this issue of the Journal, Bockenhauer and colleagues2 describe the molecular and functional features associated with a rare syndrome consisting of epilepsy, ataxia, sensorineural deafness, and salt-wasting renal tubulopathy and present data showing that the syndrome is due to mutations in a potassium-channel gene, KCNJ10. This syndrome, which they term the EAST syndrome, is accompanied by compensatory disturbances in ion and acid–base balance. The authors used single-nucleotide polymorphisms as genetic markers to map the disease locus in four symptomatic children from a single consanguineous family; sophisticated bioinformatics and data processing in the context of the whole pedigree led to the identification of KCNJ10 as the causal functional link to the syndrome.

The homozygous missense mutations in patients with the EAST syndrome interfere with a very basic physiologic process that occurs in every cell. The activity of the sodium–potassium pump Na+/K+-ATPase generates a concentration gradient for potassium. Normally, the positively charged potassium channels translate the potassium gradient into a negative membrane voltage. This voltage, or the respective potassium current, is then used to drive a variety of cell functions, such as attenuation of neuronal excitation or secondary active electrolyte and substrate transport. Given these functions, it is hardly surprising that any cell or organ system with functionally relevant expression of KCNJ10 and a mutation might contribute to the constellation of symptoms of patients with the EAST syndrome. Such cells include glial cells, intermediate cells of the stria vascularis in the inner ear, and renal epithelial cells in the distal nephron (Fig. 1).

A closer look into the functional organization of renal epithelial transport in the thiazide-sensitive segment of the renal tubule directly reveals that a defect in basolateral potassium conductance (now established as occurring mainly...
through KCNJ10) must influence the transport of sodium and chloride as well as that of calcium and magnesium (Fig. 1). This is the case in the EAST syndrome, in which renal loss of magnesium becomes evident while partial compensation for the loss of sodium chloride occurs at the expense of hypokalemia, metabolic alkalosis, and hypocalciuria. Similarly, inactivating mutations of the sodium-chloride cotransporter in this segment of the kidney tubule lead to hypocalciuria in the Gitelman syndrome.

A mouse model in which Kcnj10 was ablated, or knocked out, had already existed for several years, but the animals died very early in life. The lethal phenotype of these Kcnj10 knockout mice suggested a key role for the potassium channel in embryonic development, but it also made an integrative analysis of channel function almost impossible. Retrospectively, the findings in this model also suggested an important role for this gene in vital functions such as the maintenance of salt and water balance, as also observed, for example, in animal models of other conditions caused by abnormalities in other electrolyte transport channels, such as Bartter's syndrome and pseudohypoaldosteronism. From the perinatal period until weaning, animals (and humans) with such abnormalities are especially sensitive to the loss of salt and water.

In the brain, the KCNJ10 channel is located in astroglia. The central nervous system houses far more glial cells than neurons, and it has become clear that interactions between neurons and glia play an essential role in the proper functioning of the central nervous system. In the brain, KCNJ10 provides what is termed spatial buffering, as both potassium and neurotransmitters must be removed from the small extracellular fluid space
in the brain into the glia, thereby providing a
stable environment for controlled neuronal excit-
ability. If spatial buffering becomes lost, hyper-
excitability and impaired function of neuronal
networks would be expected, as is the case in the
EAST syndrome.

At least two clinically relevant lessons may be
derived from the study by Bockenhauer and col-
leagues. First, connections have yet to be made
between thousands of genes in the human ge-
nome and many physiologic functions and dis-
eases. The present example indicates that the
signs and symptoms of renal tubular defects pro-
vide the opportunity to discover a variety of
potential hereditary disorders involved in the func-
tion and regulation of ion channels, tight-junction
proteins, transporters, and pumps, since clinical
measurements may provide excellent phenotyping.
In addition, the mutation that defines the
EAST syndrome shows that it is clinically reward-
ing to look to the kidney, even if the primary
symptoms of a disease originate in a completely
different organ, such as the brain.

The next step in the study of the EAST syn-
drome may be the exploitation of the new func-
tional understanding of KCNJ10 to optimize cur-
rent treatment strategies or even to develop new
ones, some of which might have relevance beyond
this syndrome. The KCNJ10 gene is important in
epilepsy, ataxia, the inner ear, and renal salt trans-
port. Even the possibility of a link between KCNJ10
and hypertension does not seem implausible.

Many forms of epilepsy cannot be diagnosed
by traditional means, since patients often have
normal electroencephalograms, as seen in patients
with the EAST syndrome. Building informative
animal models with the use of KCNJ10 mutations
might facilitate the development of diagnostic
measures that are more precise and treatments
that are more effective.

With the delineation of the EAST syndrome,
KCNJ10, a gene that has been known for some
time, has been unmasked as a key regulator of
salt transport in the kidney and as an important
player in brain function. The story of this research
demonstrates how conducting a careful clinical
study of patients with a rare disorder may provide
an informative approach to diagnosis and treat-
ment that is of benefit to patients, doctors, and
progress in the medical sciences.2

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From the Physiologisches Institut der Christian-Albrechts-Univer-
sität zu Kiel, Kiel, Germany.

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