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Renal Denervation

findings, determine long-term effects, and clarify the
and relatively preserved renal function has a dramatic
cost-benefit analysis, but this analysis could potential-
events, and quality of life?

In summary, the preliminary data suggest that re-
continuation of this experimental approach.

The idea is that body fluids inside and outside the
cells readily equilibrate, resulting in constant
electrolyte concentrations in extra- and intracel-
lular fluids. This concept of constancy of inter-
nal environment composition is perhaps one of the
hallmarks of medical physiology established by
Claude Bernard in the 19th century (1). So-
dium homeostasis seems to perfectly fit into this
model. Sodium is the major cation in the extracel-
lular fluid compartment where it acts to hold wa-
ter, thereby determining the extracellular volume.
Elaborated from this model, three major assump-
tions dominate our clinical and physiological ap-
proach towards sodium balance. First, sodium homeostasis is primarily restricted to the
extracellular space. Second, any extracellular sodium accumulation or loss will inevitably lead to com-
mensurate changes in extracellular fluid content (equilibrium theory). Third, to ensure constancy
of extracellular volume, our body's sodium con-
tent is to be maintained within very narrow lim-
its. Dietary sodium will be completely excreted
when the extracellular volume is normal (steady
state theory).

Our thinking on sodium balance is largely
based on textbook teachings (2); “If dietary in-
take is abruptly increased from a low-sodium diet,
only about one-half is excreted on the first day.
This state of affairs elevates the plasma osmol-
lity, stimulating both thirst and secretion of anti-
diuretic hormone. The increments in water intake
and renal water reabsorption produce water reten-
tion, resulting in increases in effective circulating
volume and weight. After 3-4 days, a new steady
state is achieved in which renal sodium excre-
tion matches intake. The same sequence occurs
in reverse if sodium intake is reduced.” This ex-
periment, which was first described by the 19th
century physiologist Carl Ludwig, places renal
sodium handling into the very center of sodium
homeostasis (3). Today's molecular exploration of
mechanisms of sodium excretion and reabsorption
by renal glomerular or tubular systems in response
to abrupt changes in salt intake is the most logical
continuation of this experimental approach.

However, recent evidence from experiments in
humans and in animals suggests that there are lim-
itations with this well-established concept. Our
research on salt and water balance has tradition-
ally relied on the study of renal short-term adjust-
ment in response to dietary extremes. The reverse
experiment during a simulated long-term space
flight to Mars, namely study of renal excretion of
sodium in response to long-term constant salt
intake, showed astounding results. We found
that humans rhythmically retain and excrete
sodium in their urine over weeks and months,
resulting in significant accumulation and re-
lease of body sodium—without the expected
changes in body weight. This finding was
highly anomalous, because it neither support-
ed the model that dietary salt is excreted by the
kidneys within 24 hours (steady-state theory),
nor that sodium accumulation invariably leads to
fluid retention (equilibrium theory). Sodium had
been stored in tissues. Additional animal experi-
ments have revealed that sodium can be stored in
muscle and in the skin. While the mechanisms of
sodium storage in muscle have not yet been ad-
dressed, skin sodium storage to our surprise leads
to osmotic stress, which triggers an even more sur-
prising regulatory response by immune cells. Ap-
parently, macrophages act as onsite controllers of
interstitial sodium and blood pressure homeosta-
sis. The cells sense sites of sodium storage in the
skin and most presumably modulate electrolyte
and fluid transport by cutaneous lymph capillar-
ies, thereby enhancing removal of interstitial sodi-
um- and chloride-rich fluid from the skin tissue.
Failure of this physiological extrarenal regulatory
homeostatic immune cell response leads to local
electrolyte accumulation in the skin and salt-sen-
sitive hypertension. Investigation of tissue sodium
content has shown that this storage phenomenon
is not an animal-research curiosity, but also exists
in humans. Visualization of reservoir sodium by
31Na magnetic resonance imaging technology re-
vealed sodium storage in human muscle and skin,
which increases with age, is more pronounced in
men than in women and is directly associated with
blood pressure levels.

Emerging basic research questions are how so-
dium storage is organized at the cellular level, and
whether the immune/lymph system forms a ho-
meostatic regulatory network for tissue electrolyte
balance. Clinicians may ask whether humans with
increased sodium storage are at risk for develop-
ing cardiovascular disease, and whether tissue so-
dium content can be modified by lifestyle changes
or medical treatment. The concept of extrarenal
regulation of sodium homeostasis provides new
avenues for the preclinical and clinical research
community.

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By Jens Titze

New Concepts of Sodium Homeostasis

Body sodium content is most intimately
coupled with extracellular water content.

Hypertension: The Good, the Bad, and the Unknown

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