Blood, skin and bone: the complex control of blood pressure

It is well-known that excessive salt intake can be a risk factor for high blood pressure. But how this effect is mediated – and why some people are more susceptible than others – remains up for debate. Collaborators Professor Raymond Harris and Professor Ming-Zhi Zhang, at Vanderbilt University School of Medicine, have uncovered a novel role for immune cells derived from bone marrow in salt-sensitive high blood pressure, hinting at potential new ways to manage and treat the condition.

High blood pressure (hypertension) may affect as many as a quarter of the developed world population, and is a significant risk factor for cardiovascular conditions such as heart attacks and strokes. Although the causes of high blood pressure are many and complex, most cases are at least partially triggered by a high salt diet: high levels of sodium pull water into the bloodstream, increasing the pressure as it passes through the blood vessels. Therefore, the relationship between dietary salt and hypertension is an important public health concern that needs addressing.

A HEALTHY BALANCE

When our bodies function correctly, they can counteract excess salt consumption and maintain ‘homeostasis’ – a constant balance of the chemicals, hormones, and other parameters within the body. A key mediator of salt homeostasis is the cyclooxygenase–prostaglandin pathway, which synthesises hormone-like signalling molecules (prostaglandins) responsible for a range of physiological effects – including inflammation, dilation of blood vessels, and the production of blood-pressure-related hormones.

Inhibition of the cyclooxygenase–prostaglandin pathway has already been linked experimentally to clinically significant salt-sensitive hypertension. Until recently, the action of the cyclooxygenase–prostaglandin pathway in maintaining stable blood pressure was thought to be limited to the kidneys – the organs that, after all, play the major role in our bodies’ salt and water balance. High salt diets were known to increase production of the pathway’s key, rate-limiting enzyme, cyclooxygenase-2 (COX-2) in both kidney tissue and white blood cells circulating in the kidney, resulting in an excretion of excess sodium.

The work of Professor Harris and others, however, is beginning to implicate a range of other tissues in salt homeostasis, including the immune system and even the skin. In particular, Harris and Zhang’s research focuses on the bone marrow, the source of ‘haematopoietic’ cells: stem cells responsible for making all other types of blood cells, including the white blood cells of the immune system.

Previous paradigms about the development of salt-sensitive hypertension are incomplete. The COX-2/mPGES-1/EP4 receptor pathway in macrophages maintains sodium homeostasis by influencing salt excretion in the kidney and extrarenal sodium storage.
pressure through the cyclooxygenase-
prostaglandin pathway. Not only that,
but as Prof Harris points out: “Previous
paradigms about the development of salt-sensitive hypertension are
incomplete.” When the experiment
was reversed, so that mice lacking in
COX-2 throughout their body were
transplanted with normal bone marrow,
their hypertension improved, confirming
the new findings.

Further investigations of the transplanted
mice found changes in the population of
at least two forms of white blood cells,
called macrophages (which usually engulf
invading pathogens and debris) and
T cells (which recognize and attack
pathogens through specific antigens,
contributing to immunity), in their
kidneys and skin. Prof. Harris suggests
that prostaglandins generated from
bone marrow-derived white blood cells
may partner with those from the kidney
to prevent hypertension caused by a
high salt diet.

Very similar results were found
when mice were transplanted with
macrophages lacking a key receptor
further on in the cyclooxygenase-
prostaglandin pathway, EP4, which
mediates prostaglandin signalling,
suggesting that disrupting either
prostaglandin production (by COX-2)
or receptor (by EP4) in these cells
can cause salt-sensitive hypertension.
Overall, the study suggests an
unexpectedly important role for
white blood cells in salt homeostasis,
generated in the bone marrow but
acting at remote sites including the
kidneys and skin. However, according
to Harris and Zhang, the underlying
mechanisms appear to be complex and
multifactorial.

STOP POPPING THE PAINKILLERS
The cyclooxygenase-prostaglandin
pathway has many different roles in
the human body besides salt homeostasis,
for instance mediating inflammation
and pain. Some of the world’s most
popular painkillers – the non-steroidal
anti-inflammatory drugs (NSAIDs),
such as aspirin and ibuprofen – act
by blocking the action of COX-2 to
prevent inflammation triggered by
prostaglandins. Thus, side-effects of
regular NSAID use include both salt-
sensitive hypertension and peripheral
oedema, an associated swelling of the
extremities caused by a build-up of fluid
in the spaces between tissues of the
body. Harris and Zhang’s work shows
that these effects may be more complex
and widespread than previously thought.

Their results so far are tantalising,
suggesting a completely novel route
to hypertension in mammals. In a project
funded by the US National Institutes
of Health, they now propose to further
tax the complex role of the
prostaglandins produced by COX-2
in cells derived in the bone marrow.
They want to find out exactly how
the pathway is triggered into action by the
presence of excess salt, how it relates to
the occurrence of peripheral oedema,
and to quantify the relative roles of
macrophages in the different organs of
the body in managing hypertension.

In light of their findings so far, Harris
and Zhang propose to test whether
hypertension linked specifically to
NSAID use occurs through the inhibition
of the cyclooxygenase-prostaglandin
pathway in bone-marrow derived cells.
They are also considering the possibility
of stabilising the EP4 receptor through
drugs, as a new treatment for salt-
sensitive hypertension. Their results may
ultimately suggest ways to both treat and
prevent this widespread, chronic medical
condition.

Cells produced in the bone marrow
must play a hitherto-overlooked role
in maintaining salt balance and blood pressure

Q&A
How does a high salt diet lead to hypertension?
Although there continues to be
some controversy about the role of
dietary science, most epidemiologic
evidence indicates an association with
hypertension. A significant percentage
of the population is “salt sensitive”,
and increased salt ingestion leads to
either development or exacerbation of
hypertension.

How do the different organs
now known to be involved in salt
homeostasis (for instance, kidneys,
bone marrow and skin) communicate
with one another?
Our understanding of salt homeostasis
is rapidly changing. Although new
studies now clearly show that salt can
accumulate in both skin and muscle,
how these organs communicate with the
kidney, which is ultimately responsible
for salt and water homeostasis, remains
uncertain. However, there is increasing
evidence that increased salt ingestion
activates an inflammatory response in the
affected organs, which may be a major
predisposing factor for development of
salt-sensitive hypertension.

How can you be sure that your results
from mouse studies are applicable to
humans?
Ongoing clinical studies using sodium
MRI clearly show that humans also
accumulate sodium in skin and muscle,
and studies with COX-2 selective
inhibitors have shown a predisposition
for development or exacerbation of
salt-sensitive hypertension.

What do your results mean for the
use of NSAIDs?
It is well known that both non-selective
and COX-2 selective NSAIDs can
predispose to development of salt-
sensitive hypertension. These studies
provide a mechanistic understanding
of underlying mechanisms.

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