

Salt May Spur Multiple Sclerosis, Autoimmune Disease

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Salt may be a missing link that might explain what's triggering the recent marked increase in the incidence of multiple sclerosis (MS) and other autoimmune diseases, new research suggests.

As the numbers of new MS cases have risen steadily over the past half century, the diet in western developed countries has included ever-increasing amounts of salt. Although no study has found a direct link between high salt intake and increased incidence of MS, an [earlier study](#) by researchers at the University of Erlangen-Nuremberg suggested that excessive salt uptake can affect immune system activity.

Now, 3 new studies published online March 6 in *Nature* provide more evidence of a causative role for salt in MS.

"It's another reason to encourage patients to follow a healthy lifestyle, including a diet that's low in salt," said Bruce Bebo Jr, PhD, associate vice president of discovery research at the National Multiple Sclerosis Society, New York. "From a practical point of view, it's more evidence that there may be additional benefits to reducing salt in the diet."

He stressed, however, that the research is preliminary and "by no means proof" that salt is involved in MS. Numerous other environmental and genetic factors probably play a role, he said.

More Severe MS

The [first study](#), led by Markus Kleinewietfeld, PhD, Departments of Neurology and Immunology, Yale School of Medicine, New Haven, Connecticut, showed that higher than physiologic levels of salt (NaCl) in vivo markedly boosted the induction of interleukin (IL)-17-producing CD4 helper T (T_H17) cells that have been associated with autoimmune disease.

They also showed that adding salt to the diet of mice induced T_H17 lymphocyte cells and that mice fed with a high-salt diet developed a more severe form of an animal model of MS called experimental autoimmune encephalomyelitis (EAE). The pathogenic immune system responses induced by salt were regulated by genes already implicated in autoimmune diseases, the research showed.

"Thus, increased dietary salt intake might represent an environmental risk factor for the development of autoimmune diseases through the induction of pathogenic T_H17 cells," Dr. Kleinewietfeld and colleagues conclude.

"Based on these results, there is potential for dietary salt to influence the incidence or even the severity of MS, although that's highly speculative at this point," said Dr. Bebo.

Role of SGK1

A [second study](#), led by Chuan Wu, PhD, Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, sheds light on the role of serum glucocorticoid kinase 1 (SGK1) in causing salt to trigger autoimmunity.

The authors showed that a modest increase in salt concentration induced SGK1 and promoted expression of IL-23, which stabilizes and reinforced T_H17. Blocking SGK1 prevented the salt-induced increase in T_H17 activity. In mice engineered to be deficient in SGK1, the incidence and severity of EAE were reduced.

"These data demonstrate that SGK1 has a critical role in the induction of pathogenic T_H17 cells and provide a molecular insight into a mechanism by which an environmental factor such as a high salt diet triggers T_H17 development and promotes tissue inflammation," Dr. Wu and colleagues conclude.

"This unbiased investigation of T_H17 signaling pathways revealed that SGK1 was an important node for regulating the pathogenicity of these T_H17 cells," said Dr. Bebo. "This is the same salt-sensitive protein kinase found by the Yale group in their study. This certainly strengthens the argument that SGK and other signaling molecules in this pathway are important to T_H17 cell function."

As an intracellular signaling molecule, SGK1 has been previously shown to mediate the response of other cells, such as renal epithelial cells to salt, but was not previously known to have any involvement in regulation of lymphocyte function, said Dr. Bebo.

Members of this signaling pathway, he added, could be future targets of drug discovery efforts if they can be shown to regulate T_H17 function.

Regulatory Factors

The [third study](#), by a team of researchers headed by Nir Yosef, PhD, Broad Institute of the Massachusetts Institute of Technology and Harvard, Cambridge, Massachusetts, looked at factors that govern responses of the T_H17 immune cells.

"Our study identifies and validates 39 regulatory factors, embeds them within a comprehensive temporal network and reveals its organizational principles; it also highlights novel drug targets for controlling T_H17 cell differentiation," Dr. Yosef and colleagues write.

"This third study revealed a number of previously unknown players in the regulation of T_H17 cells," commented Dr. Bebo. "It remains to be investigated, but it would be interesting to develop agents that could interfere with the development of these cells that are thought to be involved in the pathogenesis of MS and other autoimmune diseases."

The research was a team effort partly funded by the National MS Society Collaborative Research Center and the National Institutes of Health (NIH).

"Salt in the Wound"

In an [accompanying editorial](#), John J. O'Shea, from the Intramural Research Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, Maryland, and Russell G. Jones, from the Rosalind and Morris Goodman Cancer Research Centre, Department of Physiology, McGill University, Montreal, Quebec, Canada, point out that dietary salt is 1 of many factors that influence helper T cells; "cytokines, the microbiota, diet, metabolism and other diverse environmental factors are all important too."

The "bottom line," they say, "is that these kinases and transcription factors represent key nodes for many receptors and signaling pathways that integrate a vast array of stimuli.

"So, although these are exciting and provocative data, it is clearly premature — as also pointed out by both sets of authors — to state that dietary salt influences autoimmune disease in humans and that this is mediated by T-cell-induced production of IL-17," they write.

"However, the work should spur investigation of tangible links between diet and autoimmune disease in people. In doing so, it will be essential to conduct formal, controlled clinical trials. Fortunately, the risks of limiting dietary salt intake are not great, so it is likely that several such trials will be starting soon."

A good next step would be to query a number of public health databases, such as the Nurses' Health Study, to determine whether there is a correlation between high-salt diets and the incidence and/or severity of MS in the population, said Dr. Bebo.

There may also be an opportunity for performing prospective studies on the effect of dietary salt in people who already have MS. The research suggests not only that dietary salt might be a risk factor for MS but also that manipulating dietary salt could regulate the severity of disease, said Dr. Bebo.

"There is evidence suggesting that increased severity of MS is accompanied by increasing activity of T_H17 cells. The research suggests that lowering dietary salt might lower T_H17 function, which in turn might reduce the severity of MS."

Timothy Coetzee, PhD, chief research officer at the National MS Society, agrees that more research needs to be done to confirm a role for salt in triggering MS or to determine whether reducing salt can inhibit MS immune attacks.

"This research sheds new light on factors that may be leading to the increase of MS, and points to potential solutions," he said in a press release. "More research is needed in the emerging area of how diet may influence MS."

The authors have disclosed no relevant financial relationships.

Nature. Published online March 6, 2013. [Kleinewietfeld Abstract](#) [Wu Abstract](#) [Yosef Abstract](#) [Editorial](#)