



# Understanding Pain and Discomfort in Functional GI Disorders

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By: Klaus Bielefeldt, M.D., Ph.D., Director, UPMC Neurogastroenterology and Motility Center, and Associate Professor of Medicine, Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, PA



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Dr. Bielefeldt is the recipient of the **IFFGD 2003 Research Award to Junior Investigator, Basic Science**. He received his MD from Rheinisch-Westfälische Technische Hochschule in Aachen, Germany in 1984 and his PhD from the University of Wisconsin, Madison, Wisconsin in 1992. While in Germany, after serving his residency in internal medicine, he became a clinical research fellow in gastroenterology with a focus on motility disorders of the esophagus and anorectum. He was then invited to spend a year in the U.S.A. as a research associate in the Department of Pharmacology at the University of Wisconsin, Madison. Based on this experience in the laboratory he pursued further training in the Department of Physiology where he studied electrophysiological properties of nerve terminals. He currently practices and teaches at the University of Pittsburgh Medical Center.

Pain, a burning or otherwise uncomfortable sensation in the upper abdomen, nausea, or fullness – all of these are symptoms many patients list when they seek medical advice. While we may think of ulcers, gallstones or perhaps inflammation of the pancreas as the cause, all too often even extensive and sophisticated testing does not show any abnormalities. So, why do all these persons feel pain or any of the other symptoms they complain about? As a scientist, I am trying to find an answer to this important question.

## What Causes Functional Diseases?

Physicians are trained to focus on identifying what we call organic diseases – diseases that are caused by bacteria or other infectious organisms we can isolate, structural changes we can determine with endoscopes or x-rays, inflammation we may see with microscopes, or biochemical abnormalities blood tests may reveal. Whatever does not fall into one of these categories, we tend to label functional. Within the last few decades, we have learned that we need to divide these functional illnesses based on the underlying problem. The normal pattern of contractions may be altered, the balance between secretion and absorption may be offset, or sensory information from the intestine may not be processed properly. My research focuses on the last of the three listed mechanisms: how can nerve function change and lead to an increased sensitivity of inner organs? In the clinic, we call this

*visceral hyperalgesia*, in the laboratory, we prefer the terms *sensitization* or *visceral hypersensitivity*.

## What Causes Visceral Hyperalgesia?

In my clinic, I often meet patients who tell me about a bad "stomach flu" that resolved, but left them with pain or other problems that persisted for months or even years. If we do not find an organic disease, many physicians use the label post-infectious irritable bowel syndrome or post-infectious non-ulcer dyspepsia, depending on the type of symptoms present. In the laboratory, I try to identify whether the initial inflammation changed the function of nerves that send information about the stomach or intestines to the spinal cord and brain. Because these nerves have their processes out in the wall of the gastrointestinal tract, we refer to them as peripheral nerves and call alterations in their function *peripheral sensitization*.

To understand mechanisms that lead to peripheral sensitization, we need to focus on the language of the nervous system: the action potential, an electrical signal, travels along the processes of the nerve cell until it comes to a connection with another nerve cell, called a synapse. At this point, the electrical signal is translated into a chemical message, and the release of signaling molecules (i.e., neurotransmitters). The frequency and pattern of these action potentials, also called spikes, is the code of the nervous system. If a nerve cell can generate in response to a weaker stimulus or produces more of these spikes, it is more excitable.

We study the electrical currents that underlie the generation of action potentials. The main goal of our work is to determine whether injury and inflammation changes these currents, thereby making nerve cells more excitable. And in fact, when we examined nerve cells that send their processes to the stomach, we were able to see many important changes in the electrical properties of nerve cells that were consistent with the development of peripheral sensitization.

Will disease processes stop here? The answer is clearly no. If peripheral nerve cells are sensitized, more information will flow to the spinal cord and brain, structures we collectively refer to as the central nervous system. This ongoing barrage may in turn change the properties of nerve cells in the central nervous system and lead to central sensitization.

## What Causes Peripheral Sensitization?

Considering the potential importance of peripheral sensitization in the development of visceral hyperalgesia, we need to understand more about the signals that trigger changes in nerve function. Staying with the clinical scenario of acute inflammation causing chronic problems, we tried to identify some of the molecules that may affect nerve cells during such acute inflammation. We narrowed in on one potential culprit, *nerve growth factor*. It increased after injury, thus satisfying one important criterion for a possible mediator of peripheral sensitization. When we examined its effect on nerve cells in the test tube, nerve growth factor changed the properties of these cells in ways that reminded us of findings we had originally obtained when we studied nerve cells after stomach injury. Finally, when we blocked the effects of nerve growth factor, we were able to blunt behavioral changes characterizing visceral hypersensitivity.

## What About Patients?

In this short description, I tried to summarize a series of complex experiments we conducted to better understand mechanisms of peripheral sensitization. Can I translate this information into new treatments for patients? At this point, the answer is no. In our experiments, we focused on one of many redundant mechanisms. We also intervened early in a cascade of effects, while our patients typically come at later points in the sequence of events. Moreover, blocking one signaling molecule, such as nerve growth factor, may lead to adverse effects and raise serious questions about the cost-benefit ratio of such treatments. However, we gained insight into important mechanisms that contribute to the development of symptoms. We and many others have to use this information as we try to identify *safe* and *effective* therapies that will come back from the laboratory bench to the bed site.

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### IFFGD

537 Long Point Road, Suite 101  
Mt Pleasant, SC 29464

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