



**Report from IFFGD Research Award Winner:**

## **Functional Gastrointestinal Disorders: New Insights in Enteric Regulation**

By: Martin Storr, M.D., Ph.D., Division of Gastroenterology, University of Calgary, Alberta, Canada

*Martin Storr, M.D., Ph.D. is the recipient of the 2009 IFFGD Research Award for Junior Investigator, Basic Science. Dr. Storr started his research in 1991 as a graduate student and received his M.D. in 1996 at the Technical University of Munich, Germany, where he continued as a clinical fellow with translational work in the field of neurogastroenterology. He received the prestigious Werner Creutzfeld Award of the German Society of Gastrointestinal Diseases, which allowed him to do a sabbatical at the University of Calgary, Canada, where he was appointed Associate Professor in 2007. Dr. Storr's research interests include understanding the regulatory role of the endocannabinoid and the endopioid systems in gastrointestinal function and the potential use as future therapeutics in functional gastrointestinal disorders.*

### **What are functional gastrointestinal diseases?**

Functional gastrointestinal disorders (FGD) are a broad spectrum of different disorders that are grouped together. They are associated with numerous symptoms like nausea, vomiting, bloating, difficulties swallowing, abdominal discomfort and pain, as well as altered bowel habits, just to name some of the possible symptoms. The intensity of these can range from minor occasional symptoms to frequent or daily debilitating symptoms that impair normal daytime activities and the ability to work. To date for most of the functional gastrointestinal disorders no cause is known and thus the ability to diagnose them correctly is sometimes challenging. Since the exact mechanisms underlying some of these disorders, such as functional dyspepsia or irritable bowel syndrome, are unknown many of these disorders are presently diagnosed by criteria that identify constellations of symptoms (the Rome III criteria). Prior to being diagnosed based on symptom criteria only, patients may have to undergo numerous tests and laboratory checks to identify possible functional gastrointestinal disorders or structural diseases where the cause or a functional alteration is already identified.

### **What causes functional gastrointestinal disorders?**

The abnormal function (pathophysiology) of the different functional gastrointestinal disorders is complex. Irritable bowel syndrome (IBS) is one of the most recognized out of this group. The current understanding of the pathophysiology of irritable bowel syndrome, as for many other functional gastrointestinal disorders, incorporates biological and psychosocial factors as playing a crucial role in the onset and propagation of symptoms, and this is known as the biopsychosocial model.

Various additional abnormalities have been reported in different groups of patients with functional gastrointestinal disorders and these include increased gut sensitivity (visceral hypersensitivity), altered gut motility, disturbances of central processing of visceral sensory information, and other disturbances of brain-gut interactions. Furthermore, autonomic, hormonal, psychological, environmental, and genetic factors may contribute to functional gastrointestinal disorders and for some of these the evidence is very strong. On the other hand, it is unlikely that a single factor will explain the pathophysiology in all patients with functional gastrointestinal disorders. Moreover pathophysiology of these functional gastrointestinal disorders is presently viewed as a complex interaction of a variable number of these factors for any given patient.

My present research focuses on how gastrointestinal motility and gastrointestinal defense mechanisms are regulated and how this knowledge might be translated into future drug treatment. Hereby I have one focus on the so called endocannabinoid system, a physiological system that seems to be crucially involved in the regulation of gastrointestinal motility and inflammation and where I try to identify how this nature-derived system could be targeted to being useful for future human use.

## **What is the endocannabinoid system?**

Endocannabinoids are physiological substances that act on cannabinoid receptors and thereby alter motility, sensation, painful sensation (nociception), inflammation, and secretion in the gastrointestinal tract. There are specific enzymes that produce endocannabinoids when needed and there are defined targets, mainly specific receptors for these endocannabinoids. These receptors are named cannabinoid-1 and cannabinoid-2 receptor. Functional studies suggest that additional, presently not identified, cannabinoid receptors must exist and there are at least 5 known structures that may be candidates for being the unidentified cannabinoid receptor.

Termination of the action of endocannabinoids occurs by specific cellular uptake from the space between cells followed by intracellular breakdown involving specific enzymes. Three of these have been clearly identified for the breakdown of the different endocannabinoids. Most of the presently known components of the endocannabinoid system, the receptors, and the degradation pathways are present in the gastrointestinal tract.

## **How can this endocannabinoid system be useful in functional gastrointestinal disorders?**

The endocannabinoid system is crucially involved in the regulation of numerous gastrointestinal functions including gastrointestinal motility, sensation, secretion, inflammation, and defense under both normal and abnormal conditions. Though we presently do not know all the details about this involvement of the endocannabinoid system and on the exact mechanisms that control the correct functioning of the endocannabinoid system, we do know that we can specifically target the endocannabinoid system with drugs and thereby alter bowel function. It is now the mission of researchers worldwide to identify where this knowledge may be useful for human use.

Gastrointestinal motility, for example, can be altered when the endocannabinoid system is targeted. Drugs that increase the activity of the endocannabinoid system, like receptor agonists or degradation blockers, slow down gastrointestinal motility and may be useful in disorders where increased motility is a problem as in diarrhea or gastric dumping. On the other hand drugs that reduce the activity of the endocannabinoid system were shown to increase gastrointestinal motility and may be helpful when slowed gastrointestinal transit, as in gastroparesis or constipation, needs to be treated. Furthermore we were the first to identify

that activation of the endocannabinoid system at a receptor level or a sub-cellular level can protect gastrointestinal tissue against intestinal inflammation when an inflammatory insult occurs. This knowledge may be translated into future treatments where gastrointestinal inflammation is involved.

## **When can these treatments be applied to patients?**

There are still a number of limitations that need to be addressed. Presently the knowledge on the endocannabinoid system is limited to animals and needs to be fully translated into humans. This has to be performed step by step and when this is completed, the most promising patient population needs to be identified for first clinical trials.

In addition, drug treatments that were suggested from animal research are limited by side effects that would presently not allow human use. Thus, basic research has to provide mechanisms by which these side effects can be limited or avoided. We presently aim to identify cannabinoid-like drugs that specifically target the gastrointestinal tract and have reduced or no effects in other tissues. Drugs which have only limited activities in the brain, the region where most of the side effects occur, are especially promising candidates for future human use. Another approach that we test is to more specifically target the cannabinoid-2 receptor, since activation of this receptor type is accompanied by fewer side effects compared to activation of the cannabinoid-1 receptor.

## **Conclusion**

There is still more research needed until drugs targeting the endocannabinoid system may be available for the treatment of functional gastrointestinal disorders. The presently available information looks very promising and allows exciting insights in the understanding of gastrointestinal physiology and pathophysiology.

---

Opinions expressed are an author's own and not necessarily those of the International Foundation for Functional Gastrointestinal Disorders (IFFGD). IFFGD does not guarantee or endorse any product in this publication nor any claim made by an author and disclaims all liability relating thereto.

This article is in no way intended to replace the knowledge or diagnosis of your doctor. We advise seeing a physician whenever a health problem arises requiring an expert's care.

IFFGD is a nonprofit education and research organization. Our mission is to inform, assist, and support people affected by gastrointestinal disorders. For more information, or permission to reprint this article, write to IFFGD, 700 W. Virginia St., #201, Milwaukee, WI 53204. Call toll-free (in the U.S.) 888-964-2001 or 414-964-1799. Visit our websites at: [www.iffgd.org](http://www.iffgd.org) or [www.aboutgimotility.org](http://www.aboutgimotility.org).