Pathophysiology of stress-induced visceral hypersensitivity
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Chapter 1

Introduction
Figure 1. Schematic representation of the working hypothesis addressed in the different chapters (CH) of this thesis. Stress is a major trigger for visceral hypersensitivity because it leads to central and peripheral release of corticotrophin releasing hormone (CRH). Peripheral CRH induces the release of mast cell mediators like histamine, that modulate (e.g. via the histamine 1 receptor (H1R) afferent expressed transient receptor ion channel 1 (TRPV1). Next to TRPV1 mediated afferent activation, mast cell mediators induce gut barrier dysfunction. The subsequent influx of antigens may explain prolonged post-stress mast cell dependent visceral hypersensitivity. Finally, we hypothesize that susceptibility to stress induced visceral hypersensitivity can be transferred across generations via so called ‘soft inheritance’.
INTRODUCTION

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder. It affects 10 to 20% of the general population in Western countries and involves chronic abdominal pain or discomfort and alterations in bowel movements in the absence of an organic explanation.\(^1\) Next to restrictions in daily life it also leads to high medical costs. Despite the prevalence and socioeconomic impact of IBS the pipeline for novel drugs is limited. One of the main reasons for this lack of therapeutic possibilities is the poor understanding of mechanisms relevant to this disorder. Nevertheless, enhanced sensitivity to colon or recto-sigmoid distension can be diagnosed in an approximate 30%-60% of patients. This so called visceral hypersensitivity is considered a pathophysiological mechanism that may explain abdominal pain complaints. In patients stress is a known trigger for visceral hypersensitivity\(^2,3\) and indications are that mast cells may be involved in the occurrence of the post-stress phenotype.\(^4,5\) However, the exact mechanisms are still poorly understood. Therefore, the aim of the work described in this thesis was to obtain a better understanding of the stress related pathophysiology of visceral hypersensitivity. Investigations were carried out in the rat model of maternal separation. Early life stressors are known to contribute to IBS in adults\(^6,7\) and maternal separation in rats is often used to mimic such predisposing factor.\(^8\) In maternal separated rats, the adverse early life experience pre-disposes for complaints like visceral hypersensitivity and barrier dysfunction in adult animals. In contrast to others who reported differences in baseline responsiveness to distension between nonhandled and maternally-separated rats,\(^9,10\) previously separated Long Evans rats need an acute stress at adult age to bring out the hypersensitive phenotype.\(^11\) Since this feature mimics observations in IBS patients we used Long Evans rats true out our investigations. The possible role of mast cells, their mediators and triggers for their activation are an important focus of this thesis (figure 1).

Because others already indicated that mast cells may be involved in post stress visceral hypersensitivity, we first set out to confirm these observations in our animal model. These experiments are described in chapter 2. Next to pre-stress administration of the mast cell stabilizer doxantrazole we investigated the role of nerve growth factor (NGF) by administering anti-NGF antibodies. NGF was evaluated because, in addition to histamine, it is one of the mast cell mediators known to modulate transient receptor ion channel 1 (TRPV1).\(^12\) This non-selective ligand-gated cation channel is essential for selective modalities of pain sensation.\(^13\) Investigations by Akbar et al. showed that TRPV1 expression was up regulated in recto-sigmoid biopsies of IBS patients and that increased expression correlated with the
degree of abdominal pain. Therefore, we also used two different TRPV1 antagonists to evaluate the functional role of TRPV1 in post stress visceral hypersensitivity. In addition, we compared TRPV1 expression levels in DRG neurons of nonhandled and maternal separated rats.

We next focused on the possible role of corticotrophin releasing hormone (CRH). Others already indicated that central expression of this stress hormone is highly relevant in the occurrence of post-stress IBS like features in animal models. Later it was shown that stress-induced colonic mast cell degranulation depends on peripheral CRH. Despite these evidences, two large clinical trials with CRH-receptor antagonists failed. In chapter 3 we attempted to clarify these contrasting findings. In relation with this, most investigations concerning a role for peripheral CRH only evaluated pre-stress administration of CRH-receptor antagonists. Clearly such results elucidate the role of CRH in an acute stress setting but extrapolating these data to post stress time points may not be appropriate; continued post-stress mast cell activation may depend on factors other than CRH. Here, we first evaluated whether there is such a thing as prolonged post-stress mast cell dependent visceral hypersensitivity in maternally separated rats. Subsequently, we used the CRH-receptor antagonist α-helical CRF (9-41) to compare the possible role of CRH in pre- and post-stress intervention protocols.

In a clinical trial with the supposed mast cell stabilizer ketotifen this compound decreased visceral hypersensitivity and improved intestinal symptoms in IBS patients. However, when pre- and post-therapy rectal biopsies were compared for release of histamine and tryptase, results showed no signs of ketotifen induced mast cell stabilization. Since ketotifen is also a histamine-1-receptor (H1R) antagonist, these data suggested that the observed therapeutic effect depended on the blocking of this receptor. This may open up new possibilities for therapy because a long list of H1R antagonists is available for use in the treatment of allergic rhinitis and urticaria. Importantly, in contrast to ketotifen, these second generation H1-antihistamines do not cross the blood-brain barrier; they are safe, effective and well tolerated. Therefore, in chapter 4, we tested 2 of these peripherally restricted H1R-antagonists (ebastine and fexofenadine) for their capacity to reverse post-stress visceral hypersensitivity.

IBS clusters in families, therefore an important line of international research is directed towards the identification of relevant genetic factors. Although twin-studies confirmed that there is a genetic component in IBS, they also indicated that environmental factors have equal or perhaps even greater influence. Similar conclusions can be drawn from studies showing an increased frequency of IBS in first degree relatives of IBS patients genetic and intra-familial environmental factors may both play a role in the observed familial aggregation. Thus, IBS transfer across generations may largely depend on environmental factors. This is, however, difficult to establish in the human setting. Therefore, in chapter 5, we used our animal model to investigate whether susceptibility to stress

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induced visceral hypersensitivity in maternal separated Long Evans rats can be transferred across generations without further separation protocols and, if so, whether this depends on maternal care. Finally, the possible role of mast cells in the post stress phenotype of these second generation animals was investigated by the use of the mast cell stabilizer doxantrazole.
REFERENCE LIST


