Charles University

Faculty of Science

Study programme: Molekulární biologie a biochemie organismů

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The Effect of Stress on the Pathology of Idiopathic Inflammatory Bowel Disease

Vliv stresu v patologii idiopatického střevního zánětu

Bachelor´s thesis

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Prague, 2024

Prehlásenie

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K úprave textu po jazykovej stránke bola použitá aplikácia „Grammarly“ využívajúca umelú inteligenciu.

V Prahe, 26.04.2024

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Podpis

Acknowledgment

Firstly I would like to express my sincere gratitude to my supervisor, Mgr. Martin Vodička Ph.D., without whom this thesis would not have been completed. I am grateful for his countless valuable advice, kind words, time, and patience.

I also want to thank my parents, grandparents, partner, and friends for their endless support and encouragement that got me through my studies.

Abstract

Inflammatory bowel disease (IBD), consisting of Crohn's Disease and ulcerative colitis are chronic diseases of the gastrointestinal tract. The incidence of IBD is rapidly rising, most notably in recently industrialized countries. One of the factors contributing to the pathophysiology of these diseases, although often overlooked, is psychological stress. Stress can induce relapses and it can exacerbate IBD through multiple mechanisms affecting the nervous, endocrine, and immune systems. This then results in low-grade inflammation, impaired intestinal epithelial barrier function, and dysbiosis. From the immunological perspective, stress causes mast cell degranulation and shifts in macrophage and T cell differentiation. Both animal models and humans with IBD have significantly altered microbial profiles in their gut, which can be further worsened after undergoing stress.

Knowing that brain-gut interactions are bidirectional, IBD is often comorbid with neuropsychiatric disorders, most commonly with depression and anxiety. This phenomenon was observed not only in cohort studies but also in murine models, where colitis is often associated with depressive-like behavior. While the exact mechanism causing the development of these comorbidities is unknown, multiple factors are speculated to play an important role, such as an impaired epithelial barrier function. Inflammatory mediators can cross the gut barrier, enter the blood circulation, and cause neuroinflammation in the brain. Another factor is dysbiosis, a characteristic of IBD. An altered microbial profile can affect the function of the serotonergic system also known to be associated with depression and anxiety. The understanding of this topic might provide new therapeutic applications. The use of antidepressants can have a positive impact on IBD course and the use of synbiotics can positively influence IBD-associated neuropsychiatric comorbidities. Therefore antidepressants and synbiotics can be a good addition to conventional treatment.

Keywords: inflammatory bowel disease, hypothalamic-pituitary-adrenal axis, stress, brain-gut axis, microbiota, depression, anxiety

Abstrakt

Idiopatické črevné zápalové ochorenia (IBD), zahŕňajúce Crohnovu chorobu a ulceróznu kolitídu, sú chronické ochorenia gastrointestinálneho traktu. Incidencia týchto ochorení rapídne stúpa, hlavne v nedávno industrializovaných krajinách. Jedným z často prehliadaných faktorov prispievajúcich k patofyziológii týchto ochorení je psychologický stres. Stres môže vyvolať relaps a zhoršiť priebeh IBD cez niekoľko mechanizmov, ktoré ovplyvňujú funkciu nervového, endokrinného a imunitného systému. Následne to môže spôsobiť zápal, zhoršenú funkciu črevnej epitelovej bariéry a dysbiózu. Z imunologického hľadiska spôsoubuje stres degranuláciu žírnych buniek, a zmeny v diferenciácii makrofágov a T buniek. Zvieracie modely, ale aj ľudia s IBD majú výrazne pozmenené zloženie mikroorganizmov v čreve, čo môže byť ďalej zhoršené po vystavení stresu.

Vediac, že interakcie medzi mozgom a črevom sú obojsmerné, IBD je často spojené s neuropsychiatrickými ochoreniami, najčastejšie s depresiou a úzkosťou. Tento jav bol pozorovaný nielen v populačných štúdiách, ale aj v myších modeloch, kde zvieratá trpiace kolitídou prejavovali správanie podobné depresii. Kým presný mechanizmus spôsobujúci vývoj týchto komorbidít nie je známy, viacero faktorov pravdepodobne zohráva významnú rolu v ich vývoji, ako napríklad zhoršená funkcia črevného epitelu. Zápalové mediátory môžu preniknúť cez črevnú bariéru do krvného obehu a spôsobiť zápal v mozgu prechodom cez hemato-encefalickú bariéru. Ďalším faktorom je dysbióza, charakteristická pre IBD. Pozmenený mikrobiálny profil môže ovplyvniť funkciu serotonínergného systému, ktorý je taktiež spojený s depresiou a úzkosťou. Pochopenie tejto témy môže priniesť nové terapeutické možnosti. Užívanie antidepresív môže mať pozitívny vplyv na priebeh IBD a užívanie synbiotík zas môže zlepšiť prejavy neuropsychiatrických ochorení spojených s IBD. Antidepresíva a synbiotiká by teda mohli byť vhodným doplnkom ku konvenčnej terapii.

Kľúčové slová: idiopatické črevné zápalové ochorenie, hypotalamo-hypofyzárny systém, stres, os mozog-črevo, mikrobiota, depresia, úzkosť

List of Abbreviations

5-HT 5-hydroxytryptamine

ACE adverse childhood experience

ACTH adrenocorticotropic hormone

ANS autonomic nervous system

APC antigen-presenting cell

AVP arginine vasopressin

BBB blood-brain barrier

BDNF brain-derived neurotrophic factor

BDPP bioactive dietary polyphenol preparation

cAMP cyclic adenosine-monophosphate

CD Crohn's disease

CNS central nervous system

CRH corticotropin-releasing hormone

CRHR1 corticotropin-releasing hormone receptor 1

CRHR2 corticotropin-releasing hormone receptor 2

CRS chronic-restraint stress

CUMS chronic unpredictable mild stress

DCs dendritic cells

DNBS dinitrobenzene sulfonic acid

DSS dextran sulfate sodium

EBA endothelial barrier antigen

ECCs enterochromaffin cells

ED emergency department

ELS early life stress

ENS enteric nervous system

GAS general adaptation syndrome

GC glucocorticoid

GF germ-free

GI gastrointestinal

GR glucocorticoid receptor

GRO-α growth-regulated protein-alpha

HPA hypothalamic-pituitary-adrenal

HRP horseradish peroxidase

IBD inflammatory bowel disease

IBS irritable bowel syndrome

IFN-γ interferon-gamma

IL interleukin

iNOS inducible nitric oxide synthase

Isc baseline short-circuit current

LMR lactulose mannitol ratio

MAOIs monoamine oxidase inhibitors

MC2R melanocortin 2 receptor

ME median eminence

MLN mesenteric lymph node

MPO myeloperoxidase

MR mineralocorticoid receptor

mRNA messenger ribonucleic acid

MSEW maternal separation with early weaning

NF-κB nuclear factor kappa B

NK natural killer

NPY neuropeptide Y

OBx olfactory bulbectomy

OC overcrowding

OF open field

PNMS prenatal maternal stress

POMC pro-opiomelanocortin

PRL prolactin

PRR pattern recognition receptor

PTSD post-traumatic stress disorder

PVN paraventricular nucleus

QOL quality of life

SCFAs short-chain fatty acids

SD social defeat

SDS social defeat stress

SERT serotonin reuptake transporter

SI social interaction

SNRIs serotonin/norepinephrine reuptake inhibitors

SPF specific pathogen-free

SS sham stress

SSRIs selective serotonin reuptake inhibitors

Tc cytotoxic T cell

TCAs tricyclic antidepressants

Th1 T helper 1 lymphocytes

Th17 T helper 17 lymphocytes

Th2 T helper 2 lymphocytes

TNBS trinitrobenzene sulphonic acid

TNF-α tumor necrosis factor-alpha

Treg regulatory T cell

Trp tryptophan

UC Ulcerative Colitis

VN vagal nerve

WAS water-avoidance stress

WBCs white blood cells

Table of Contents

1. Introduction

Inflammatory bowel disease (IBD) is a relapsing-remitting inflammatory disease with an unknown etiology that affects the gastrointestinal tract (GI). It includes Crohn's disease (CD) and ulcerative colitis (UC). UC only affects the mucosa of the colon and rectum, while CD is characterized by a transmural inflammation, that can affect the whole GI tract (Fakhoury et al. 2014).

IBD affects millions of patients worldwide, with a rapidly increasing incidence. These rising trends might be caused by the „westernization" of lifestyles, industrialization, shifts in diet towards higher contents of processed food and less fiber, and increasingly stressful lifestyles (Jairath and Feagan 2020).

Even though stress is critical for organisms to be able to react to potential risks that could threaten their homeostasis, stress, especially chronic stress can have adverse effects on one's health (Selye, 1936). Chronic psychological stress is known to cause low-grade inflammation and is linked to multiple autoimmune diseases (Song et al. 2018; Hänsel et al. 2010). There are multiple ways, through which the effects of stress get translated into gastrointestinal and immune manifestations. One of the most significant pathways is the bidirectional brain-gut axis, which ensures communication between the brain and gut. It utilizes neurological, immune, and endocrine pathways and also involves intestinal microbiota (Bonaz and Bernstein 2013). Stress significantly influences gastrointestinal physiology. It does so by altering the function of the hypothalamic-pituitary-adrenal (HPA) axis, and the autonomic nervous system. It can also alter immune homeostasis, disrupt the intestinal barrier, and cause shifts in microbial composition. All of these factors contribute to the exacerbation of IBD symptoms (Yaribeygi et al. 2017).

While suffering from IBD itself is already a significant mental burden, the factors mentioned above further contribute to the development of neuropsychiatric disorders. Depression and anxiety are very often comorbid with IBD, however, the exact underlying mechanisms are often unclear (Mikocka-Walus, Knowles, et al. 2016). For example, the inflammatory mediators produced in the gut might enter the brain and cause neuroinflammation. The serotonergic pathway, which is largely affected by the already altered microbiota, also plays a significant role. These, and several other possible mechanisms require further research to be fully understood (Craig et al. 2022; Sochal et al. 2023).

Psychological and psychiatric treatment might benefit the disease course and lower the probability of relapses (Mikocka-Walus, Knowles, et al. 2016). Therefore stress, as an environmental etiological factor, should not be overlooked.

1.1 Aims

IBD is an inflammatory disease of the gastrointestinal tract with a multifactorial etiology. One of the leading factors in IBD pathology is believed to be an aberrant immune response against commensal microbiota. Other factors might be either genetic or environmental. Stress belongs to the environmental factors that can impact a person's overall health (Bernstein et al. 2010). My aim in this thesis is to shed light on the complexity of the ways through which stress affects IBD. Many studies and reviews exist on this topic, however, they often fail to provide a full image that connects the intestinal epithelium, microbiota, and the nervous, endocrine, and immune systems. I also investigate the comorbidities between IBD and psychiatric disorders, mostly depression, and anxiety, as IBD patients are more likely to suffer from them (Byrne et al., 2017). I also want to investigate how using antidepressants might influence not only the comorbid psychiatric disorders but also the course of IBD.

2. Characterization of Inflammatory Bowel Disease

Inflammatory Bowel Disease encompasses two diseases affecting the gastrointestinal tract – Crohn's Disease and Ulcerative Colitis. CD and UC are chronic relapsing inflammatory diseases with an unknown etiology. Their symptoms include fatigue, fever, abdominal pain, diarrhea, that may contain blood or pus, nausea, vomiting, or weight loss (Cushing and Higgins 2021). These diseases are often accompanied by various extraintestinal symptoms and are frequently comorbid with depression and anxiety (Feuerstein, Moss, and Farraye 2019).

The exact cause behind IBD is unknown, but research suggests that genetic and environmental factors, the intestinal microbiome, and immune responses play a pivotal role in the pathology of IBD. About 6 – 8 million people suffer from IBD worldwide, with a higher incidence in „Western " countries. The numbers are rapidly increasing in newly industrialized countries. This could be due to a diet lacking fiber, and containing processed foods, dairy, and refined sugar. Other factors that can contribute are exposure to antibiotics during childhood, stress, or the use of non-steroidal drugs. Smoking and appendectomy have surprisingly protective effects in UC but are serious risk factors for CD (Zhang 2014; Jairath and Feagan 2020; (Lynch and Hsu 2024)).

While there is no cure for IBD, prolonged stages of remission can be achieved with the right treatment. Even though UC and CD are very similar in many aspects, there are some significant differences between them.

2.1 Ulcerative Colitis

Ulcerative colitis is a chronic relapsing – remmiting disease that, unlike CD, only affects the rectal and colonic mucosa. The inflammation begins at the rectum from where it can spread further

into the colon in a continuous manner. In severe cases, the whole large intestine can be inflamed. Patients usually suffer from various symptoms, such as diarrhea that might contain blood or pus, abdominal pain, rectal bleeding, fatigue, weight loss, urgency to defecate, or fever (Gajendran et al. 2019). Many patients also suffer from extraintestinal manifestations that can affect joints, such as arthritis, ankylosing spondylitis, or sacroiliitis; the skin, like erythema nodosum and pyoderma gangrenosum; or primary sclerosing cholangitis, which affects the liver. They are also at a substantially higher risk of developing colorectal cancer (Feuerstein, Moss, and Farraye 2019).

Ulcerative colitis is a more common form of IBD than CD, however, the proper diagnosis or the right distinction between them can be problematic. The incidence of UC peaks around the second and third decades of life with a second peak around 50 and 80 years of age with no differences between the two sexes (Gajendran et al., 2019). A higher incidence of IBD is observed in Northern Europe and North America, with a greater prevalence in adults. This is probably caused by a Western lifestyle and diet. A higher incidence is present in the Jewish population, especially in the population of Ashkenazi Jews (Roth et al. 1989).

A disrupted epithelial barrier is typical for UC, involving a defective mucin layer and disrupted tight junctions. An imbalanced colonic microflora and an aberrant immune response against it play an important role in IBD pathophysiology. Leukocyte infiltrates are present in the colonic tissue, with a high number of activated dendritic cells (DCs), natural killer (NK) cells, and T helper 2 (Th2) cells, which exert an atypical cytotoxic response (Lynch and Hsu 2024).

UC is usually treated with 5-aminosalicylates, corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine), methotrexate, and biological therapy (anti-TNF, anti-adhesion, anti-IL-12/IL-23p40 therapies, and JAK inhibitors). Surgery is only indicated after the failure of the previous methods, and after the occurrence of the so-called toxic megacolon (Kobayashi et al. 2020).

2.2 Crohn's Disease

Crohn's disease and ulcerative colitis are very similar in many aspects, however, there are some significant differences (Fig.1). CD is characterized by inflammation penetrating the gastrointestinal wall from the mucosa to the serosa. This disease can affect the GI tract from the mouth to the perianal area, although, inflammation is usually found in patchy lesions. Symptoms include abdominal pain, bloating, diarrhea, weight loss, anemia, fever, and in the case of small intestinal inflammation also malabsorption, anorexia, and enterovesical fistulae. In severe cases, perianal abscesses and cutaneous fistulas can occur (Ranasinghe and Hsu 2024).

CD is often associated with extraintestinal manifestations involving the joints, skin, liver, eyes, and lungs. The etiology, epidemiology, and treatment are similar to UC. The incidence of CD is globally

increasing, especially in recently industrialized countries, with high levels of air pollution and in places with a Westernized diet. The drug therapy is the same as for UC, but it appears that aminosalicylates are not proving to be effective (Cushing and Higgins 2021). Unfortunately, most CD patients require at least one surgery during their lifetime, due to the likely occurrence of strictures, fistulas, or perianal lesions (Feuerstein and Cheifetz 2017).

Crohn's disease is mostly a T helper 1 (Th1)-mediated disease accompanied by a defective innate immune response and a disrupted epithelial barrier. Antigen-presenting cells (APC) interact with bacterial antigens, leading to interleukin (IL)-12 overproduction and the initiation of T-cell differentiation. Many other cells are part of the inflammatory process, including Th2 cells, epithelial cells, innate lymphoid cells, macrophages, dendritic cells, and B cells (Diculescu, Manuc, and Manuc 2016).

Suffering from IBD presents a huge physical and emotional burden to the patients. They are at a higher risk of developing depression and anxiety (Byrne et al., 2017). Many studies indicate, that the previously mentioned pathologic manifestations can be enhanced or even directly caused by psychological stress, therefore, it is crucial to highlight the importance of implementing psychologic and psychiatric therapy into the treatment of IBD.

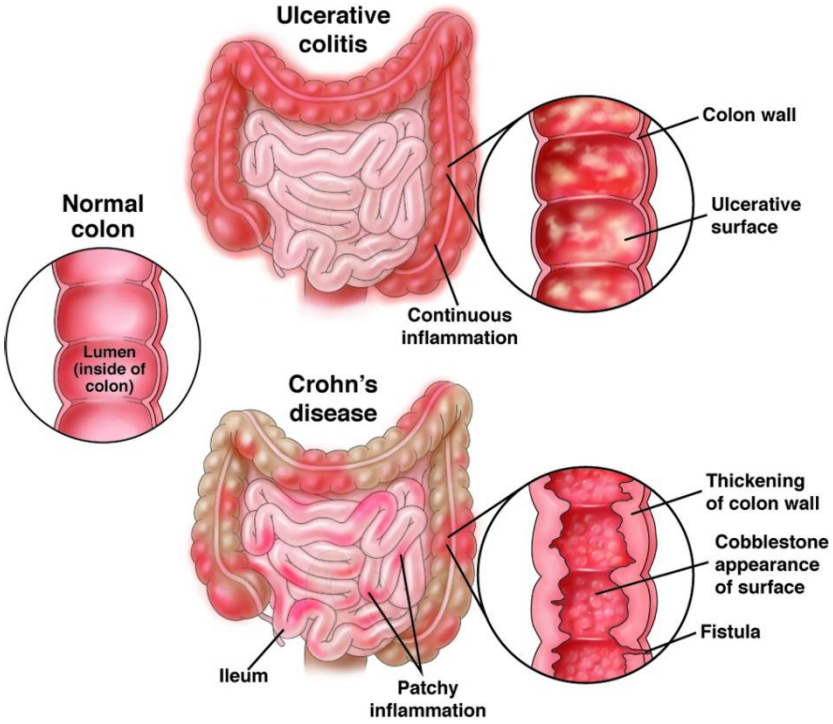

Fig.1 The differences between ulcerative colitis and Crohn's disease. Ulcerative colitis is characterized by a continual inflammation that causes ulcerations of the colonic mucosa. The inflammation in Crohn's disease can affect the whole gastrointestinal tract. It penetrates the intestinal wall and is found in patchy lesions (Stone 2021) .

3. The Hypothalamic-pituitary-adrenal Axis

Humans and animals need to constantly respond to various stressors that might threaten their homeostasis. One of the main pathways responsible for organisms' adaptations to stress is the hypothalamic-pituitary-adrenal (HPA) axis (Sheng et al. 2021). While the stress reaction is physiologic, it has the potential to become pathologic after the body's adaptive capacities are exhausted (Selye, 1936). Chronic stress can result in a chronic activation of the HPA axis, which can negatively affect immune, metabolic, neural, and cardiovascular functions, and can eventually lead to an increased risk of developing various diseases, including IBD (Sheng et al. 2021).

The HPA axis comprises the paraventricular nucleus (PVN) of the hypothalamus, the pituitary gland, and the adrenal gland, and is controlled by a negative feedback loop. Upon activation, the medial parvocellular neurons of the PVN initiate the release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) from the median eminence (ME) (Aguilera and Liu 2012; Vale et al. 1981). CRH and AVP from the ME are transported to the anterior pituitary via the portal bloodstream, where CRH binds to corticotropin-releasing hormone receptor 1 (CRHR1), which is coupled with adenylate cyclase. This results in the production of cyclic adenosine-monophosphate (cAMP) and pro-opiomelanocortin (POMC) from which adrenocorticotropic hormone (ACTH) is formed and released from the pituitary (Chalmers, Lovenberg, and De Souza 1995; Herman et al. 2016).

ACTH is transported to the adrenal glands, where it binds to melanocortin 2 receptors (MC2R) and activates a signaling pathway that results in the production of corticosterone in rodents and cortisol in humans (Gantz and Fong 2003; Payne and Hales 2004).

Glucocorticoids (GC) function as a negative feedback regulator, as they inhibit CRH expression and production in the PVN (Abe and Critchlow 1980; Sapolsky, Romero, and Munck 2000). A decrease in circulating corticosterone due to adrenalectomy increases basal CRH and ACTH levels, suggesting its crucial role as a negative feedback regulator (Dallman et al. 1987; Rabadan-Diehl et al. 1997). Glucocorticoids bind to glucocorticoid receptors (GR) and mineralocorticoid receptors (MR), which have a significant role in the negative feedback loop. Corticosterone binds with a higher affinity to MRs, so they are important when the secretion of GCs is low, whereas GRs bind corticosterone with a lower affinity, therefore they are more crucial, when the concentration of GCs is higher (Reul and Kloet 1985).

Glucocorticoids are released into various tissues, where they mobilize energy stores, such as lipids and proteins, they induce vasoconstriction and suppress reproduction (Papadimitriou and Priftis 2009). However, glucocorticoids can be synthesized *de novo* outside of the adrenal cortex, as well, and they exert their function in an autocrine or paracrine manner. Organs capable of synthesizing GCs include the thymus, skin, brain, and intestines. The skin and intestines represent an important interface

between the outer and inner environment, as they come into contact with the material that has the potential to cause a local stress response, such as inflammation. The thymus, on the other hand, controls T cell selection and maturation. The thymic and intestinal production of GCs has a crucial role in regulating immune homeostasis, and they play a role in the pathology of autoimmune diseases (Talabér, Jondal, and Okret 2013).

4. Stress and Intestinal Barrier Function

Stress is defined as anything that significantly disrupts an individual's homeostasis (Selye, 1936). There are multiple types of stress, physical or psychological, associated with various coping responses. While stress might have a positive impact on an organism, such as maintaining tissue integrity and homeostasis, stress has often adverse effects on multiple systems of the body like the nervous, endocrine, cardiovascular, and gastrointestinal systems (Yaribeygi et al. 2017).

The first author to link stress to physical diseases was Hans Selye in his publication in 1936. Selye described general adaptation syndrome (GAS) as a reaction of organisms to various stressors. GAS has three stages – alarm, resistance, and exhaustion. The stage of alarm is the initial stress response that occurs 6 – 48 hours after exposure to a stressor when the adrenal gland releases cortisol. In this stage, a decrease in the size of the thymus, spleen, lymph nodes and liver can be observed, as well as the formation of acute erosions in the gastrointestinal tract. The stage of resistance begins after 48 hours and is characterized by enlarged adrenals, which regained their lipoid granules. If the treatment with mild stressors continues, animals will build up resistance. However, after prolonged exposure to treatment (1 – 3 months), animals lose their resistance and the phase of exhaustion begins (Selye, 1936).

Since Selye's initial discovery, research in the field of stress progressed significantly, and more and more links correlating stress to various diseases have been described. Stress substantially influences the course and pathology of IBD. It also influences behavioral changes caused by IBD. Its effect is mediated through multiple axes that ensure the communication between the brain and other organ systems. One of the most important is the bidirectional gut-brain axis, which plays a critical role in the stress-related pathophysiology of IBD (Bonaz and Bernstein 2013).

Stress also induces an aberrant function of the HPA axis, resulting in abnormal GC and CRH production. This affects various parts of the body, including the immune or nervous systems. Chronic stress increases the severity of dextran sulfate sodium (DSS)-induced colitis in mice, which is accompanied by impaired corticosterone production. Mice subjected to chronic psychosocial stress by social defeat (SD) and overcrowding (OC) displayed thymic atrophy and adrenal hypertrophy. The light-phase corticosterone-to-adrenal weight ratio was much lower in SD/OC mice. A rise in corticosterone

levels was observed in the dark phase in unstressed mice, but it was significantly less pronounced in stressed subjects. The hypothalamic expression of CRH mRNA and plasma ACTH levels did not differ between the two groups. After receiving DSS treatment, stressed mice had more severe colitis, with more weight loss, stronger signs of histological damage, and a higher expression of pro-inflammatory cytokines. Plasma corticosterone and ACTH concentrations were increased only in chronically stressed mice subjected to DSS treatment. Mice also had an impaired regeneration process and a lower survival rate. The discrepancies in corticosterone production may be due to adrenal glands becoming insensitive and losing their ability to respond to the diurnal rhythm (Reber et al. 2006).

The exact impact of stress on IBD in connection with behavior is highly dependent on the type and duration of the stressor and does not always have to be negative. For example, repeated predictable stress on a model of DSS colitis prevented the behavioral changes in mice. Mice displayed an anxiety-like response in the open field (OF) and social interaction (SI) tests after DSS treatment. This was reversed by repeated water avoidance stress (WAS) exposure. DSS, but not WAS increased plasma neuropeptide Y (NPY) levels, and DSS+WAS significantly increased the levels of plasma corticosterone. The expression of brain-derived neurotrophic factor (BDNF) and NPY was decreased in the hippocampus of DSS-treated, but not WAS-treated mice. On the other hand, WAS caused a decreased CRH mRNA expression. The combination of WAS+DSS enhanced hypothalamic NPY expression, while in the amygdala, WAS significantly reduced the relative NPY mRNA expression. WAS + DSS combined reversed this effect (Hassan et al. 2014).

In another study, WAS also had a slightly anti-inflammatory effect on DSS-induced colitis. This might be due to the anti-inflammatory effects of GCs. Mice displayed altered activity of the HPA axis, with higher corticosterone levels after DSS and/or WAS treatment. The development of colitis had a significant impact on the behavior of mice during WAS, as they displayed a depressive-like phenotype. Increased levels of circulating pro-inflammatory cytokines, IL-6, IL-18, tumor necrosis factor-alpha (TNF-α), and growth-regulated protein-alpha (GRO-α), were found in both DSS-treated groups. The DSS+WAS group had higher IL-17 levels than mice without DSS treatment. Levels of IL-6 in the amygdala, hippocampus, and hypothalamus and the levels of GRO-α in the hippocampus and hypothalamus were elevated as well. After DSS treatment alone, only GRO-α levels were increased in the hypothalamus. An altered expression of CRH and NPY-related genes was observed in distinct cerebral regions. These two peptides have counteracting effects, as CRH induces anxiety and depression-like behavior, and NPY acts in an anxiolytic and anti-depressant manner (Mathé et al. 2007). Colitis enhanced NPY expression in the hypothalamus but decreased it in the amygdala. CRH levels were decreased in the hippocampus and hypothalamus. The effect of WAS was very similar in mice with or without colitis, however, there was a rapid and short-lasting increase of *Crh* mRNA levels in the amygdala and an increase in *Npy* levels in the hypothalamus. Additionally, colitis induced

alterations of *Npy*, *Npy1r*, *Crh*, *Crhr1*, *Bdnf,* and *Nr3c1* gene expression in certain brain regions, which was associated with behavioral changes (Reichmann et al. 2015).

4.1 Corticotropin-releasing Hormone and Gut Health

Corticotropin-releasing hormone is a peptide that mediates behavioral, autonomic, and visceral stress responses (Taché and Million 2015). CRH is comprised of 41 amino acids and acts mostly in the central nervous system (CNS). This peptide is produced by the hypothalamus and it acts on the anterior pituitary gland, where it stimulates the secretion of corticotropin (ACTH) (Vale et al. 1981).

CRH binds to two types of receptors, both 7-transmembrane G-coupled receptors, CRHR1 and CRHR2, with the latter binding CRH with higher affinity (Dautzenberg and Hauger 2002). The CRH1 receptor can be found all over the GI tract of humans, but mostly in the ileum and the rectum. CRH1-positive cells are predominantly located in the lamina propria, but also in the submucosal and myenteric plexus. 79 % CRH1 positive cells of the lamina propria are mostly macrophages, which play an important role in the development of inflammation. Patients with UC have significantly elevated numbers of CRHR1 positive and CRF1/CD163 double-labeled cells independent of their level of inflammation (Yuan et al. 2012).

CRH-mediated epithelial injury in the colon is executed via the CRH1 receptor in a mouse model that underwent neonatal maternal separation. Activation of the CRH1 receptor resulted in a change in mucosal morphology and epithelial permeability. It also triggered a release of proinflammatory cytokines, IL-6, TNF-α, and inducible nitric oxide synthase (iNOS). In contrast, CRH2 receptors mediated the activation of stem cells, proliferation, and their differentiation, as a compensatory mechanism (Li et al. 2017).

CRH is also produced in peripheral tissues, where it influences cardiovascular, immune, and gastrointestinal functions. Peripheral CRH is produced by various cell types of the GI tract (macrophages/ monocytes, lymphocytes, nerves, endothelial cells, enterochromaffin cells, and fibroblasts) and causes changes in gut motility, mucus production, and intestinal permeability (Kalantaridou 2007). Recent studies show, that one of the leading causes of IBD relapse is a change in gut permeability. This disruption of the epithelial barrier allows immunogenic substances in the intestinal lumen to enter the mucosa, causing inflammation. Studies on rodents and humans showed that peripheral antagonism of CRH reduced the detrimental effects of stress on epithelial physiology (Saunders et al. 2002; Vanuytsel et al. 2014).

Wistar Kyoto rats were exposed to cold-restraint stress (physical stress) and water-avoidance stress (psychological stress). Rats treated with cold-restraint stress and WAS both displayed a higher intestinal permeability to ions, macromolecules, and therefore luminal antigens as well. Treatment with a peripheral CRH antagonist prevented these symptoms in rats exposed to either of the stressors. After

peritoneal treatment of control rats and in vitro exposure of colonic tissue to CRH, increased baseline short-circuit current (Isc) and horseradish peroxidase (HRP) flux was observed, but a change in conductance levels was only apparent in peritoneally treated rats. These findings suggest, that peripheral CRH acts locally on the colonic mucosa, where it acts on its receptors. This study has shown, that physical and psychological stress, both affect colonial epithelial barrier function and permeability in a CRH-dependent manner, with slightly stronger responses to physical stressors (Saunders et al. 2002).

4.2 The Impacts of Early Life Stress

Early life stress (ELS) can have immediate, but also long-lasting impacts on an individual's health. Early life stress and adverse childhood experiences are linked to adverse health outcomes and multiple diseases. It is well known, that chronic and early life stress can cause a dysfunctional HPA axis and impaired glucocorticoid synthesis. ELS can also have long-lasting impacts on the regulation of the sympathetic nervous system, and the immune system (Juruena et al. 2021; Atrooz, Liu, and Salim 2019).

In the study of Muir et al, mice that underwent maternal separation with early weaning (MSEW) were monitored to determine, whether ELS impairs corticosterone production and raises the susceptibility to chronic gut inflammation. Results showed that MSEW mice had lower levels of corticosterone in the adolescent period, but also in adulthood, however, there were no significant differences in ACTH levels. In contrast with the expected results, mice undergoing chronic stress did not display increased intestinal permeability. After inducing colitis, intestinal inflammation did not resolve after 20 days and there were sustained elevated levels of TNF-α, suggesting a higher susceptibility to chronic inflammation in contrast to control mice. There was also a tendency towards the emergence of Th1 pro-inflammatory cells, due to delayed differentiation of inhibitory IL-10-producing CD4+ T cells. Similar outcomes were observed after maternal postnatal administration of Dexamethasone (GC analog). TNF-driven inflammation therefore suppresses local colonic GC synthesis and this effect can be further enhanced by prior exposure to ELS (Muir et al. 2023).

There is also a link between adverse childhood experiences (ACE) and autoimmune diseases in humans. People with higher ACE scores had higher chances of getting hospitalized due to autoimmune diseases. Individuals who experienced 2 or more ACEs were at a significantly higher probability of hospitalization, with a 70% increased risk for Th1-type, and an 80% increased risk for Th2-type autoimmune diseases. The likelihood of hospitalization was double with Th2 rheumatic diseases compared to individuals who did not experience any ACE (Dube et al. 2009).

5. The Effect of Stress on Immune Homeostasis

5.1 Mast Cells and Corticotropin-releasing Hormone

Mast cells are part of the innate immune system and they exert versatile functions, from mediating allergic reactions to being the end-effectors of the brain-gut axis. They significantly impact intestinal function via the release of various neurotransmitters and pro-inflammatory cytokines (Farhadi, Fields, Keshavarzian 2007). Mast cells are the key immune mediators of stress response, due to the expression of CRH receptors on their surface (Zhao et al. 2021). In this way, mast cells can react to elevated levels of central and peripheral CRH and can alter intestinal physiology, mostly by increasing permeability. An impaired intestinal barrier can then subsequently exacerbate or induce inflammation (Wallon et al. 2007).

Söderholm et al. conducted experiments on wild-type +/+ control rats and mast cell-deficient Ws/Ws rats, exposing them to water avoidance stress (WAS) or sham stress (SS) for 10 days. Increased ileal and colonic conductance and macromolecular permeability were observed only in +/+ rats submitted to WAS, with signs of epithelial cell damage and bacterial adherence in these individuals. +/+ rats had a thinner appearing mucus layer and a lower number of mucus-containing goblet cells. Following stress exposure, the number of mast cells in the ileal and colonic mucosa doubled with a higher proportion of activated granules than in SS controls. Mild inflammation was observed in these rats, which was associated with a higher number of neutrophils and mononuclear cells in the ileal and colonic lamina propria. Rats had an elevated inflammation score and increased myeloperoxidase (MPO) activity. This indicates a critical role of mast cells in the pathology of IBD. They substantially affect intestinal permeability, by disrupting tight junctions, damaging the intestinal epithelial cells, and thinning the mucus layer. This allows bacteria to adhere and causes an increased uptake of luminal antigens, which can then trigger immune responses (Söderholm et al. 2002). Similar results after CRH administration were observed by Teitelbaum et al. as well (Teitelbaum et al. 2008).

In the porcine ileum, CRH triggers barrier dysfunction and disrupts tight junctions through TNF-α and tryptase released by activated mast cells, with enteric neurons playing a pivotal role. Inhibition of CRH receptors, mast cell stabilization, inhibition of TNF-α, mast cell proteases, and neuronal blockade abrogated CRH-induced alterations in barrier function (Overman, Rivier, and Moeser 2012).

Psychological stress increases intestinal permeability in humans as well. Public speech resulted in elevated cortisol levels in the saliva and an increased lactulose mannitol ratio (LMR) in the urine. Mast cell stabilization before undergoing public speech diminished LMR increase, implicating the critical role of CRH and mast cells in stress-induced gut barrier dysfunction (Vanuytsel et al. 2014).

5.2 Macrophages

Macrophages are cells of the innate immune system that closely communicate with the adaptive system. They ensure homeostasis by cleaning up cellular debris and removing pathogens (Hegarty, Jones, Bain 2023). Macrophages typically exist in 3 states, the unpolarized M0 state, and the polarized M1 and M2 states. M1 macrophages can be induced by Th1 cytokines to produce pro-inflammatory cytokines. On the other hand, M2 cells have a rather anti-inflammatory effect (K. Zhang et al. 2023).

However, in diseases like IBD, macrophage differentiation often shifts towards the pro-inflammatory phenotype, which can be reversed by anti-TNF-α treatment (Vos et al. 2012). This shift can be further enhanced by depression and/or anxiety. UC patients suffering from depression or anxiety had more severe colitis and a lower quality of life. They had elevated numbers of monocytes that were differentiating into pro-inflammatory phenotypes. Monocytes affected the immunological balance of T cells, by inhibiting regulatory T (Treg) cells and promoting the differentiation of Th1 cells. IBD patients with depression and/or anxiety also had higher numbers of macrophages in the mucosa than those without depression/anxiety, and a higher M1 to M2 macrophage ratio. Both monocytes and macrophages displayed impaired phagocytosis (Xin Gao et al. 2023). Very similar results, with increased migration of monocytes to the intestine, were observed in CD patients with depression as well (Tang et al. 2020).

Another mechanism, by which is stress connected to macrophages, is via inducing autophagy (Zhao et al. 2021). Autophagy is an important process that maintains macrophage homeostasis, however, it is also involved in chronic inflammation (Wen et al. 2022). DSS-treated mice were administered CRH to mimic stress, which worsened the severity of colitis and increased intestinal macrophage autophagy activity not only in vivo but in vitro as well. Autophagy blockade by chloroquine reduced the effects of CRH on the severity of DSS-induced colitis (Zhao et al. 2021).

5.3 T cells

T cells are cells of the adaptive immune system. The main types include CD4+ helper T cells, CD8+ cytotoxic T cells (Tc), and CD4+CD25+ regulatory T cells. There are three types of cells in the Th group, Th1 CD4+, Th2 CD4+, and Th17 CD4+ cells (Sauls, McCausland, and Taylor 2024).

T cells are key mediators of mucosal damage in CD and UC. Although patients with inflammatory bowel disease have a normal number of CD4+ and CD8+ cells, they exhibit increased activation levels (Giuffrida and Di Sabatino 2020; Schreiber et al. 1991). A study has shown that stress combined with 2 mg of dinitrobenzene sulfonic acid (DNBS) induced colitis, which was accompanied by higher corticosterone production and MPO activity. Only DNBS failed to induce colitis. However, the full manifestation of this effect was not possible without CD4+ T cells (Qiu et al. 1999). Additionally,

some studies indicate an increased number of anti-inflammatory Tregs in patients with IBD, while others report a diminished count (Veltkamp et al. 2011; Reikvam et al. 2011). Regardless of Treg cell numbers, their Treg populations are often enriched for IL-17^{+} Treg cells (Kryczek et al. 2011).

In a murine model, this enrichment was caused by restraint stress. Although the number of Tregs did not differ between the stressed and non-stressed groups, Tregs of the stressed group displayed a comprised suppressor function. The Treg phenotype of stressed mice was altered, due to their conversion to IL-17+ TNF-α+ Foxp3+ T cells. This conversion was most likely induced by IL-6 and IL-23-producing dendritic cells. The proportion of DCs expressing IL-6 and IL-23 was significantly higher in stressed mice, which was triggered by a stress mediator, prolactin (PRL), through activating nuclear factor kappa B (NF-κB). Treatment of mice with PRL + trinitrobenzene sulfonic acid (TNBS), stress + TNBS, or PRL + DSS induced colitis, while treatment with only PRL, TNBS, stress, or DSS failed to do so. Administration of cabergoline, an inhibitor of prolactin, prevented the induction of colitis (Wei Wu et al. 2014).

The proportion of IL-17-producing cells and Treg cells changed significantly in susceptible mice after being subjected to social defeat stress (SDS). The numbers of IL-17-producing CD8+ and CD4+ cells were elevated and the numbers of Treg cells were decreased, while reduced T cell percentages were apparent in both susceptible and resilient individuals (Ambrée et al. 2019). A higher ratio of Th17 to Treg was observed in patients with depression as well, who also had increased levels of antinuclear antibody and IL-17. These findings suggest that depression might increase individuals‘ tendency towards autoimmunity (Y. Chen et al. 2011). Treatment with synbiotics reversed the alterations in the Th17/Treg ratio and mellowed stress-induced depression- and anxiety-like behavior in mice (Westfall et al. 2021).

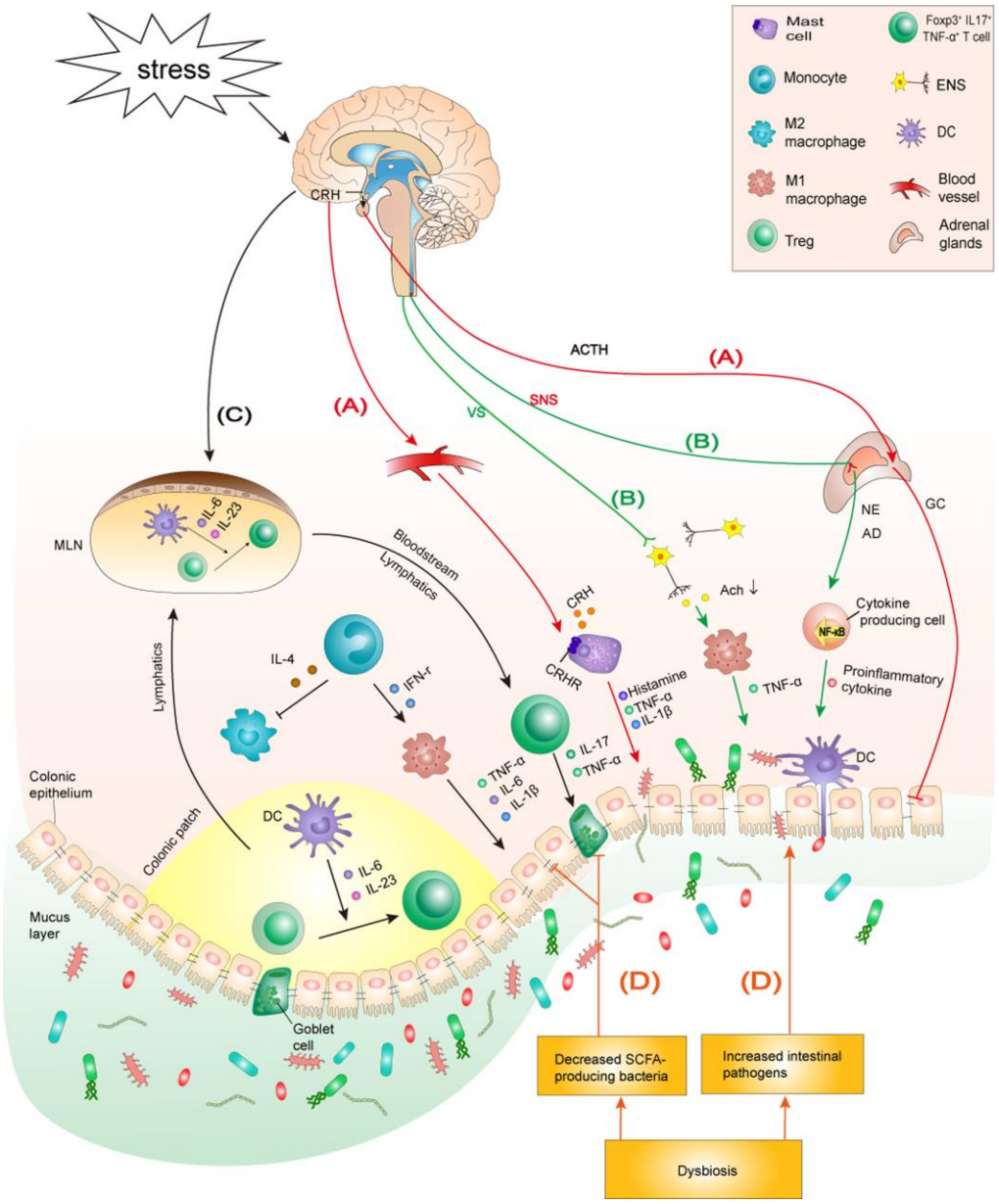

Fig.2 The pleiotropic effects of stress on the intestine. A.) Stress activates the HPA axis, which results in elevated CRH, ACTH, and glucocorticoid production. CRH binds to receptors on the surface of mast cells and induces mast cell degranulation and the release of proinflammatory cytokines. These cytokines act on the intestinal epithelium and cause increased permeability. B.) Stress alters ANS activation, which influences immune cell function and cytokine production. C.) Stress affects dendritic cells to start producing IL-6 and IL-23, impacting the phenotype of Treg cells that differentiate into Foxp3+ IL-17+ TNF-α+ Tregs. Monocytes infiltrate the gut, preferentially differentiating into pro-inflammatory M1, instead of anti-inflammatory M2 macrophages. D.) Dysbiosis in IBD and under stress conditions is characterized by increased levels of potentially pro-inflammatory pathogenic microbes and decreased levels of beneficial SCFA-producing bacteria. Microbiota can translocate through the epithelium into the gut wall, where they can cause inflammation. The altered microbial composition also influences immune function, gut barrier function, and the serotonergic system (Ge et al. 2022).

6. The Microbiota-gut-brain Axis

The human gut is home to approximately 10^{13} microorganisms commonly known as the gut microbiota (Sender, Fuchs, and Milo 2016). The gut microbiota consists of numerous species of bacteria, archaea, and eukarya, which interact with the host organism via various mechanisms and play a critical role in maintaining homeostasis during health and disease (Bäckhed et al. 2005). Microbiota coevolved with their host and they share a mutualistic relationship. For example, microbiota regulates gut integrity, and epithelial physiology (Natividad and Verdu 2013), it consumes, stores, and redistributes energy (Den Besten et al. 2013), protects against pathogens (Bäumler and Sperandio 2016), and plays a role in shaping the host immunity (Gensollen et al. 2016).

Microbiota ferments complex carbohydrates into short-chain fatty acids (SCFAs), most importantly propionate, butyrate, and acetate. SCFAs among many other functions regulate cellular processes in the intestinal epithelium and impact the immune system and inflammatory responses (Corrêa-Oliveira et al. 2016). A disrupted microbial composition is associated with many diseases from gastrointestinal diseases like irritable bowel syndrome (IBS), or IBD to several psychiatric and neurologic disorders like depression, anxiety, Parkinson's disease, or autism spectrum disorders (Martin et al. 2018) (Fig.3).

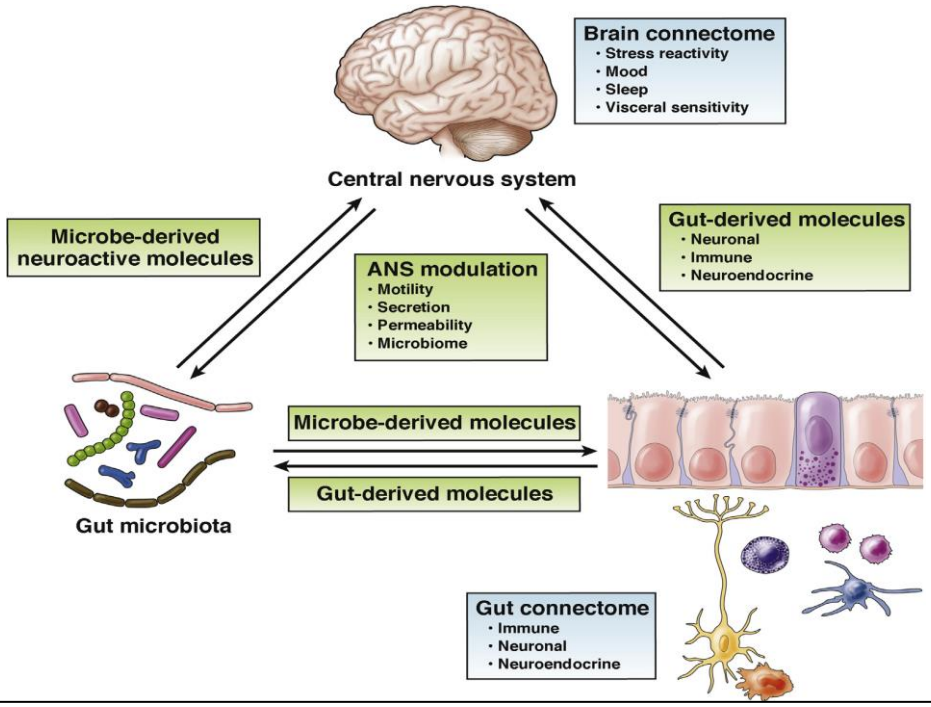

Fig.3 The microbiota-gut-brain axis. The brain, gut, and microbiota communicate via bidirectional pathways. These pathways involve neural immune and neuroendocrine mechanisms that mediate changes in gut motility, permeability and secretion and impact the composition of gut microbiota. These factors can then in turn impact stress reactivity, mood and sleep (Martin et al. 2018).

6.1 Stress-induced Changes in the Composition of Gut Microbiota

Our intestinal microbiota interacts with the HPA axis and plays a crucial role in the development of gastrointestinal and immune systems, ensuring their proper functioning (Sudo et al. 2004; Dimmitt et al. 2010). Therefore, microbial colonization in early life might have long-term impacts on an individual's health and well-being. The consequences of maternal stress persist way until adulthood, where they can not only raise susceptibility to inflammation but can also cause stress dysregulation in offspring and contribute to the development of neuropsychiatric diseases (Schepanski et al. 2018; Wadhwa 2005).

Prenatal maternal stress (PNMS) in mice is believed to impair intestinal development and gut barrier function. Additionally, it causes low-grade inflammation, which is accompanied by dysbiosis. While the relative abundance of bacterial phyla remained unaltered, the differential abundance of bacteria significantly differed between PNMS and control mice. The abundance of pro-inflammatory and potentially pathogenic bacteria, like *Desulfovibrio*, *Streptococcus,* and *Enterococcus,* increased in the PNMS group. The higher abundance of *Desulfovibrio* even persisted until adulthood. On the other hand, the abundance of beneficial bacteria, Bifidobacteriacae, *Blautia,* and *Robinsoniella,* was lower compared to controls. Results after fecal transplantation showed, that the defective barrier function and low-grade inflammation were mostly caused by dysbiosis. After inducing colitis, mice from the PNMS group displayed more severe signs of colitis, which might be associated with a higher abundance of *Desulfovibrio* (Sun et al. 2021).

Early life stress-associated dysbiosis can also be observed in humans. Dutch mothers and their infants were monitored for prenatal maternal stress. Stressed mothers had increased glucocorticoid levels in their saliva and reported higher perceived stress, but these variables seemed to be independent, representing two separate stress mechanisms. However, both variables were associated with changes in the gut microbiota of the infants. Infants in the high cumulative stress group (high perceived stress + high cortisol) had a higher relative abundance of Proteobacteria, while the proportion of Lactic acid bacteria and Actinobacteria decreased. They also tended to display more gastrointestinal and allergic symptoms, however, these findings did not reach statistical significance (Zijlmans et al. 2015). Similar outcomes were observed in the offspring of rhesus monkeys, whose mothers underwent acoustic stress (Bailey et al. 2004).

Not only maternal stress but also chronic stress has adverse effects on one's health. Mice with dextran sulfate sodium-induced colitis were subjected to chronic restraint stress (CRS). This treatment further worsened the symptoms of colitis and aggravated inflammation. Mice had extensive epithelial damage and inflammatory infiltrates were present in the lamina propria. A decreased number of proliferating cells was observed. In the mesenteric lymph nodes (MLN) of the stressed + DSS group, the

numbers of B cells and CD4+ T cells were decreased, and the proportion of CD8+ T cells and NEU cells was increased, highlighting the role of stress in inflammation. The expression of IL-6, but not TNF-α was increased, and the IL-6/STAT3 pathway was activated. Surprisingly, the knockout of IL-6 did not result in the resolution of symptoms. DSS and DSS + CRS mice displayed a distinctive microbial flora. Pro-inflammatory bacteria such as *Helicobacter*, Peptostreptococcaceae, *Streptococcus*, and *Enterococcus faecalis* were more prevalent in the stressed group, but *Rikenella*, *Roseburia*, and Lachnospiraceae levels were lower. When DSS and stress were combined, there was a further significant increase in the levels of *Helicobacter* and *Streptococcus*. After cohousing DSS and DSS+stressed mice, it was apparent, that the stress-related changes were associated with microbiota because the symptoms of DSS-treated mice worsened after cohousing. Antibiotic treatment then prevented these symptoms and stress could no longer sensitize mice to DSS-induced colitis (Xinghua Gao et al. 2018).

6.1.1 Depressive-like Behavior, Depression, and Dysbiosis

The interaction between the brain and the gut microbiota goes both ways. It is often unclear whether dysbiosis is a consequence or a cause of stress and depression. The gut microbiota is known to communicate with the serotonergic system and significantly influences the production and metabolism of 5-HT. Germ-free mice (GF) display lower levels of serum and colon, but not small intestinal serotonin. However, levels can be restored after the postnatal introduction of spore-forming bacteria that promote the production of serotonin, by directly acting on enterochromaffin cells (ECCs) by their metabolites (Yano et al. 2015). The serotonergic pathway is tightly connected to depression and people with depression are known to have altered microbial profiles. The microbiota plays a role in depression by affecting the availability of tryptophan and by influencing the function of the ENS, vagal nerve, and gut-brain axis (Clarke et al. 2013; Irum et al. 2023).

The effects of dysbiosis are not only apparent in humans, but in rodents as well, where it is associated with depressive-like behavior. Mice, that underwent olfactory bulbectomy (OBx) displayed signs of depressive-like behavior accompanied by elevated CRH and serotonin production, and increased colonic motility. However, the expression of pro-inflammatory cytokines remained unchanged. The relative abundance of bacterial phyla significantly differed between mice undergoing OBx or sham operation (Park et al. 2013).

Male mice with DSS-induced colitis were subjected to chronic unpredictable mild stress (CUMS) for 21 days. They displayed signs of depressive-like behavior, with significantly longer immobility times in the forced swim test, while DSS or CUMS alone did not have notable effects. The expression of proinflammatory cytokines, IL-1β and TNF-α, in the hippocampus was mildly increased compared to

the control group, however, the difference did not gain statistical significance. On taxonomic analysis of the gut microbiota, the relative abundance of Bacteroides was higher and the relative abundance of the Lachnospiraceae NK4A136, Lactobacillus spp., Lachnospiraceae A2 spp was lower than in the control group. The development of depressive-like behavior was therefore believed to be due to alterations in microbial composition, that made mice with DSS colitis more susceptible to CUMS (Komoto et al., 2022).

Stress-induced depressive-like symptoms associated with dysbiosis can then aggravate symptoms of colitis in mice after treatment with DSS. The microbial profiles of stressed and nonstressed mice differed significantly. There was also an obvious decrease in *Akkermansia muciniphila* numbers in CRS-treated groups (CRS and CRS+DSS). The same decrease in Akkermansia abundance was observed in UC patients suffering from depression (T. Chen et al. 2021). This bacterium might promote serotonin secretion, suggesting its important role in the pathogenesis of depression (Valles-Colomer et al. 2019). After fecal transplantation from CRS to recipient mice, they started to display depressive-like behavior, which was mitigated by *A. muciniphila* supplementation. Mice with CRS microbiota had more severe colitis, and more damaged gut barrier and mucus layer after DSS dosage than those with conventionally bred microbiota. *Akkermansia* supplementation alleviated the severity of the symptoms and remodeled the gut microbiota. Additionally, it repaired the impaired barrier function and rescued the expression of MUC2 (T. Chen et al. 2021).

Therefore probiotic and synbiotic supplementation might have positive impacts on mood. Anxiety- and depressive-like behavior after CUMS was reversed after the administration of synbiotics, probiotics, or bioactive dietary polyphenol preparation (BDPP). In this study, the concentration of serotonin was reduced in the ileum and prefrontal cortex, but not in plasma. The reason behind this was that tryptophan metabolism was likely directed towards the kyneurine pathway, which is more pronounced during inflammation. Serotonin levels were rescued by synbiotic treatment. However, the effects of synbiotics on kyneurine production, and kyneurine pathway-related gene expression were tissue-specific and had no effect in the prefrontal cortex. Inflammatory mediators were present in the periphery as well as in the brain. The expression of the pro-inflammatory cytokine, IL-1β, was significantly elevated in the serum, prefrontal cortex, hippocampus, cortex and ileum of stressed mice. The levels of IL-6 were increased in the serum, liver, and ileum. While treatment with synbiotics reduced their expression in all of the tissues, probiotic treatment reduced IL-1β levels only in the prefrontal cortex, hippocampus, and cortex and BDPP reduced IL-1β in the prefrontal cortex only. This finding poses an additional treatment option for depression and anxiety, due to the significant effects of microbiota and their metabolites on the inflammatory process and the serotonergic and kyneurine pathways (Westfall et al. 2021).

7. The Link Between Inflammatory Bowel Disease and Psychiatric Disorders

7.1 From Intestinal Inflammation to Neuroinflammation

The brain and the gut communicate via the autonomic nervous system (ANS) and the circumventricular organs. The ANS is comprised of the sympathetic and parasympathetic nervous systems, both of which contain afferent and efferent pathways (Bonaz and Bernstein 2013).

Another part of the ANS, which can function independently of the central nervous system (CNS) and provides innervation to the GI tract, is the enteric nervous system (ENS). It is divided into the submucosal and myenteric plexes. They form a rich neuronal network, where the myenteric plexus innervates the smooth muscles of the GI wall and coordinates motility and secretion, while the submucosal plexus regulates absorption, secretion, and vasodilation. The submucosal plexus might exert immunological functions as well (Fleming et al. 2020). It is well-established that patients with IBD have a structurally and functionally impaired ENS. 75% of CD and 56% of UC patients were found to suffer from myenteric plexitis, however, the significance of this finding is yet unknown (Villanacci et al. 2008).

Many factors contribute to the regulation of intestinal permeability, but the enteric nervous system also plays a key role in this process. The ENS releases neurotransmitters, peptides, and lipids, which regulate epithelial tight junction expression, and mucosal cell regeneration, and help to maintain the integrity of the intestinal barrier. The altered mucus production, tight junction expression, and ENS dysfunction typical for IBD can lead to increased uptake of immunoreactive substances into the lamina propria, where they are recognized by pattern recognition receptors (PRR) on immune cells, which triggers an immune response. It is then followed by the production of various chemokines and proinflammatory cytokines, such as IL-1β, IL-6, TNF-α, or interferon-gamma (IFN-γ) and cytokines involved in the IL-23/Th17 pathway (Craig et al. 2022).

Inflammation leads to endothelial dysfunction, which is typical for IBD patients. Functional and structural changes occur in the vascular endothelium, resulting in elevated leukocyte adhesiveness, leukocyte diapedesis, procoagulant activity, and altered vascular smooth muscle tone (Cibor et al. 2016). Inflammatory mediators then enter the blood circulation, where they can travel to distant regions, such as the brain, where they can cross the blood-brain barrier (BBB) or enter through the leaky regions of the circumventricular organs (Fig.4) (Craig et al. 2022; Banks 2005).

It is suggested, that patients with IBD have a disrupted BBB, as a result of higher circulating levels of cytokines, catecholamines, or the activity of prostaglandins. A rat model with TNBS-induced colitis showed increased permeability of sodium fluorescein and decreased endothelial barrier antigen (EBA) expression in some areas of the brain (Natah et al. 2005). Mice with DSS-induced colitis had

increased levels of proinflammatory cytokines, especially significant levels of IL-1β present in their hippocampus, which was further amplified by microglial activation. Neuroinflammation in the hippocampus then might cause impaired hippocampal neurogenesis, which is associated with neuropsychiatric disorders like depression and anxiety (Casciati et al. 2023). Indeed, mice with induced colitis display depressive-like behavior (Komoto et al. 2022; Takahashi et al. 2023). The role of microglia and the serotonin–kynurenine pathway in behavioral changes is currently also largely discussed, however, the results are often contrasting (Craig et al. 2022).

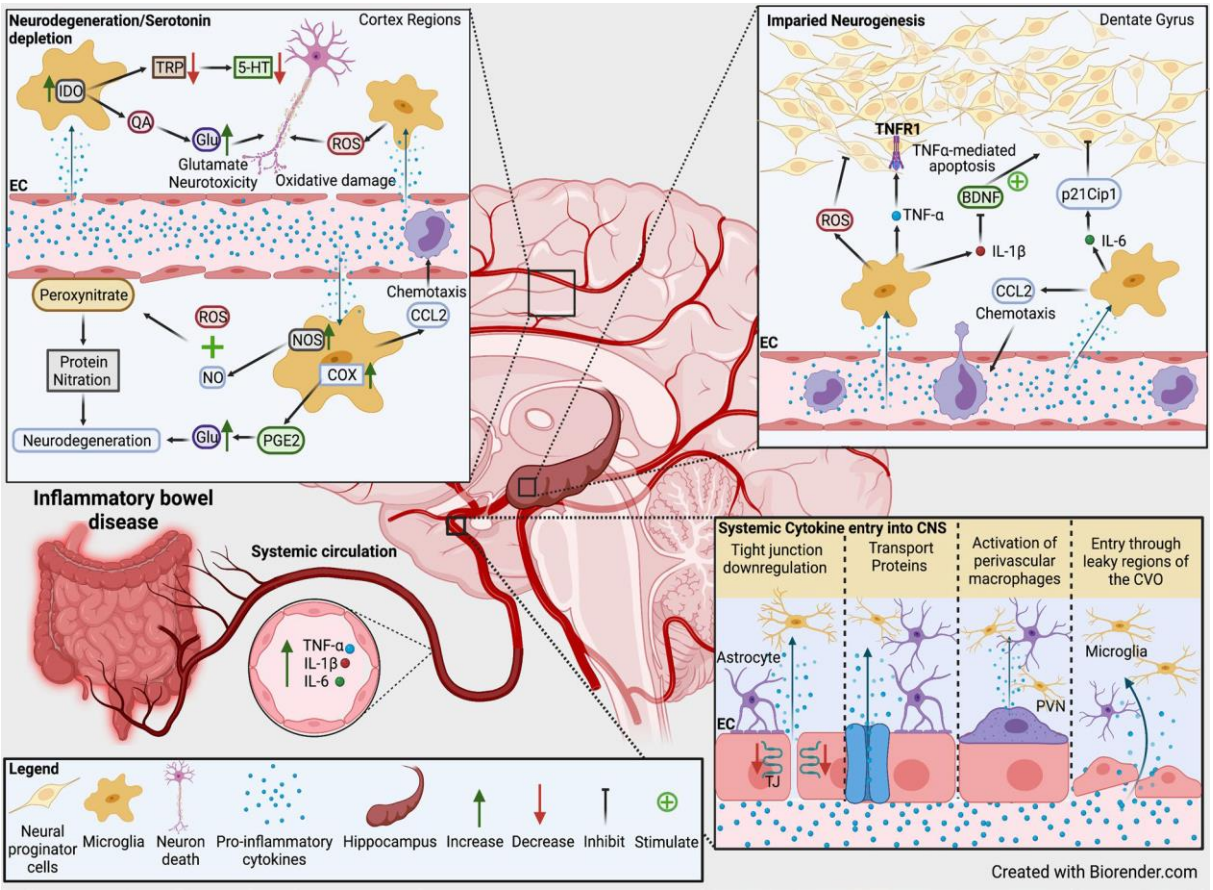

Fig.4 IBD-related neuroinflammation. Inflammatory mediators from the gut enter the blood circulation. After reaching the brain, they can cross the blood-brain-barrier, or enter the brain through the circumventricular organs. The pro-inflammatory cytokines then activate immune cells in the brain and cause inflammation. Neuroinflammation can lead to impaired neurogenesis, neurodegeneriation and serotonin depletion that can trigger the development of depression and anxiety (Craig et al. 2022).

7.2 The Prevalence of Psychiatric Disorders in IBD Patients

Many studies suggest that IBD patients suffer from depression and anxiety at a higher rate than the general population and this connection appears to be bi-directional (Byrne et al. 2017; Gracie et al. 2018). Intestinal inflammation and dysbiosis present in IBD can alter neuronal function in the brain, thus causing behavioral changes. However, anxiety and depression can also worsen the disease course or directly induce IBD relapse through various mechanisms (Craig et al. 2022; Mittermaier et al. 2004).

A longitudinal follow-up study of 405 patients with IBD revealed a clear bidirectional link between the course of IBD and anxiety. Patients with no baseline psychiatric comorbidity, but disease activity, were more likely to develop abnormal anxiety scores over two years. Likewise, patients in remission who had abnormal baseline anxiety scores were more likely to subsequently develop symptoms of IBD, or needed treatment by corticosteroids (Gracie et al. 2018). This phenomenon can also be observed with depression. IBD patients were more susceptible to depression, but depression combined with stress also made people more prone to developing inflammation and IBD. A study showed that people who displayed more depressive symptoms had a more pronounced increase in IL-6 levels after being submitted to stressors than those with fewer symptoms (Fagundes et al. 2013).

Therefore it is often unclear whether neuropsychiatric diseases are a cause or consequence of IBD. While data concerning these comorbidities often differ among studies, the majority of them report a higher prevalence of neuropsychiatric diseases, the rates of which are higher during active disease. It was also observed that CD patients have slightly higher levels of depression and anxiety than those suffering from UC (Mikocka-Walus, Knowles, et al. 2016).

In the study of Byrne et al., information from 327 patients suffering from IBD was assessed. The prevalence of depression was 25.8 %, and the prevalence of anxiety was 21.2 %, with 30.3 % of patients suffering from depression and/or anxiety. Patients with active disease were significantly more likely to suffer from these illnesses. The rate of prevalence did not differ between UC and CD patients (Byrne et al. 2017).

A nationwide study conducted in Korea also reported a higher prevalence. During a mean follow-up of six years, 12.2 % of IBD patients experienced anxiety compared to 8.7 % in controls, and 8.0% experienced depression compared to 4.7 % in controls. In patients with CD, the cumulative incidence of depression 6 years after the diagnosis was 8.0 %. Cumulative incidence of depression in UC was 10.8 %, exhibiting a steep rise, one year after the diagnosis. The cumulative incidences of anxiety were 11.5 % and 16.7 % for CD and UC, respectively (Choi et al. 2019). In comparison, the Manitoba cohort study reported a higher rate of major depression in IBD patients, with more than double the rates compared to controls – 27.2 % vs. 12.3 %. However, the rates of social anxiety disorder were lower – 6 % vs 11 %. Patients with a psychiatric disorder also reported lower quality of life, and

higher perceived stress, were mostly females, and had an earlier onset of IBD symptoms. In most cases, the anxiety or mood disorder predated the diagnosis of IBD by more than 2 years (Walker et al. 2008).

7.3 The Use of Antidepressants and Their Effect on the Course of IBD

There arises a question, considering the undeniable connection between IBD, stress, and neuropsychiatric disorders, whether the use of antidepressants alleviates the detrimental impact of IBD on patients' lives. This topic has been extensively studied, but no universal answer has been found. While antidepressants might be beneficial for IBD patients, due to treating the symptoms of anxiety and depression, they can also have anti-inflammatory effects that are independent of their neuromodulatory properties (Kast 2003; Diamond, Kelly, Connor 2006). This is why the use of antidepressants is often considered as an additional treatment option, however, the outcomes are often debatable.

The most commonly used types of antidepressants include Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs), Atypical Antidepressants, Tricyclic Antidepressants (TCAs), Monoamine Oxidase Inhibitors (MAOIs), and others (Sheffler, Patel, Abdijadid 2024).

The gastrointestinal tract and the gut microbiota are in close connection with the brain in many different ways, one of which is the serotonergic system. It is well known that the GI tract produces 95 % of the body's serotonin (5-hydroxytryptamine), which is mostly released by enterochromaffin cells (Gershon, Ross 1962; Tyce 1990). It is synthesized from tryptophan (Trp) and exerts important functions in the GI tract, such as regulating motility or secretion. Serotonin is reuptaken by the serotonin reuptake transporter (SERT). Only 5 % of the total serotonin is produced in the CNS (Tyce 1990).

The role of the serotonergic system is not only important in the pathology of depression (Pourhamzeh et al. 2022), but is also connected to IBD. UC in humans and TNBS-induced colitis in mice are associated with higher levels of serotonin secretion and SERT expression (Sikander et al. 2015). The levels of 5-HT and SERT protein, but not SERT mRNA were found to be elevated in IBD patients. Anti-TNF-α therapy diminished plasma 5-HT levels, which was accompanied by improved depressive symptoms and better quality of sleep (Sochal et al. 2023).

Due to the facts mentioned above, the use of antidepressants, mainly those affecting the availability of serotonin, is expected to have significant effects on the course of IBD. Patients with depression have a 67 % higher risk of developing Crohn's disease and a 41 % higher risk of developing ulcerative colitis. People from the depression group, who used antidepressants had a lower likelihood of developing these diseases. SSRI and TCA usage appears to have a protective effect against CD. Similarly, treatment with mirtazapine, SNRI, SSRI, serotonin modulators, and TCA was protective

against UC (Frolkis et al. 2019). A nationwide study was conducted in Denmark, where 28 % of the study population reported at least 1 prescription of antidepressants. Antidepressant use, whether mixed-use or monotherapy, was associated with a better disease course, lower relapse rates, and a lower chance of getting hospitalized. The effect was most pronounced in UC and CD patients with no prior antidepressant use. The risk of surgery was lower in UC patients taking antidepressants, however, it was slightly increased in CD patients (Kristensen et al. 2019). However, in another study, the enhanced availability of serotonin, due to SSRI use was expected to be connected to poor clinical outcomes in IBD. The IBD cohort taking antidepressants had a higher likelihood of corticosteroid use, emergency department (ED) visits, and hospitalizations, though they were not more prone to IBD-related complications or surgery. Interestingly, control patients also had a higher likelihood of visiting the ED and being hospitalized (Ba et al. 2024).

In a clinical trial, fluoxetine did not affect the disease activity or mental health of the participants with CD. The proportion of Th Effector Memory cells increased and the proportion of Tc Effector Memory RA cells decreased after 6 months, while there were no differences with placebo. All the other T cell types remained unchanged. The levels of IL-10 were reduced in patients receiving a placebo, while this effect was not observed in patients receiving fluoxetine (Mikocka-Walus, Hughes, et al. 2016). On the other hand, duloxetine did have a significant impact on the decrease in depression and anxiety scores, and improved severity of physical symptoms. Physical, psychological, and social quality of life (QOL) was increased after treatment with duloxetine, unlike after fluoxetine (Daghaghzadeh et al. 2015).

The results on animal models differ from those on humans. Male C57BL/6 mice with DSS-induced colitis were treated with 3 types of SSRI antidepressants – fluoxetine, fluvoxamine, and venlafaxine. All 3 significantly improved the symptoms of colitis, caused the downregulation of pro-inflammatory cytokines TNF-α and IL-1β, and upregulated the expression of tight junction proteins in the intestine, with fluoxetine having the most notable effect. A change in the number of epithelial cells in the fluoxetine-treated group was found, especially in the number of Paneth cells, which produce anti-microbial peptides, that might have a positive anti-inflammatory impact on IBD. There was also an apparent shift from M1 to M2 macrophage differentiation (Teng et al. 2024).

Mice with DSS-induced colitis displayed altered myelination, impaired formation of the nodes of Ranvier in the prefrontal cortex, and a dysfunctional serotonergic system. Treatment with Brexpiprazole, an atypical antidepressant, improved depressive-like behavior in mice by activating the serotonergic system's 5-HT1A receptor-ERK1/2-CREB-BDNF-TrkB signaling pathway and prevented demyelination (Takahashi et al. 2023).

8. Conclusion

The effects of stress on health have been studied for almost a century. Starting from Selye's initial characterization of stress and the general adaptation syndrome, the research in this area has come a long way. However, the effect of stress on IBD has been often overlooked, most likely, because it is a very complex and complicated topic and its full spectrum is just starting to unravel.

We now know that stress has a pleiotropic effect and influences disease course in many ways. It has a negative impact on multiple systems of the organism, including the nervous, endocrine, and immune systems. Unfortunately, only a few studies exist, that would sufficiently connect these phenomena. Stressed individuals have an altered function of the HPA axis which results in disrupted production of CRH and corticosterone, which significantly impacts immune cells and the process of inflammation. Stress is also known to cause shifts in immune homeostasis by influencing mast cells, macrophages, T cells, and other white blood cell subtypes. It also influences microbial composition, as chronically stressed individuals have altered microbial profiles. This further worsens inflammation and the disruption of the intestinal epithelium, leading to an increased uptake of luminal antigens. Inflammation then might lead to endothelial and blood-brain-barrier dysfunction and subsequent neuroinflammation. Inflammation and microbial metabolites also affect the serotonergic and the enteric nervous system. IBD patients are more susceptible to depression and anxiety, however, it is often not clear, whether these psychiatric disorders predate disease onset, or are its consequence. Therefore, it is important to highlight the bi-directionality of brain-gut interactions, as the effects of stress can quickly turn into a vicious cycle. To fully understand the mechanisms by which stress affects IBD, and how IBD in turn affects psychiatric manifestations, a lot of further research has to be done. Unfortunately, the complexity of this topic exceeds the scope of this thesis but poses an interesting possibility for future works.

A proper understanding of this problem might come with new and better treatment options for patients. The use of antidepressants, as well as synbiotics seems to have positive outcomes on disease course, and the associated psychiatric comorbidities. Therefore, it is important for gastroenterologists to be aware of the impact of stress on IBD and to refer susceptible patients to relevant specialists.

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