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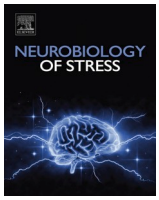

Psychosocial stress-induced intestinal permeability in healthy humans: What is the evidence?

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ABSTRACT

An impaired intestinal barrier function can be detrimental to the host as it may allow the translocation of luminal antigens and toxins into the subepithelial tissue and bloodstream. In turn, this may cause local and systemic immune responses and lead to the development of pathologies. In vitro and animal studies strongly suggest that psychosocial stress is one of the factors that can increase intestinal permeability via mast-cell dependent mechanisms. Remarkably, studies have not been able to yield unequivocal evidence that such relation between stress and intestinal permeability also exists in (healthy) humans. In the current Review, we discuss the mechanisms that are involved in stress-induced intestinal permeability changes and postulate factors that influence these alterations and that may explain the translational difficulties from in vitro and animal to human studies. As human research differs highly from animal research in the extent to which stress can be applied and intestinal permeability can be measured, it remains difficult to draw conclusions about the presence of a relation between stress and intestinal permeability in (healthy) humans. Future studies should bear in mind these difficulties, and more research into *in vivo* methods to assess intestinal permeability are warranted.

1. Introduction

The interplay between the intestinal barrier and central nervous system has received increasing interest in the past decade. The intestinal barrier is the main interface between the external environment and the host, and maintains an equilibrated homeostasis by allowing the passage of selective nutrients such as amino acids, carbohydrates, electrolytes, lipids, and water, while hindering the entrance of toxins and bacteria (Vancamelbeke and Vermeire, 2017). Disruption of the intestinal barrier increases the permeability, which may be detrimental to the host as it may allow the translocation of luminal antigens and toxins through the intestinal wall into the subepithelial tissue and bloodstream. In turn, this translocation may induce both local and systemic immune responses, possibly leading to the development of pathologies. Indeed, increased intestinal permeability has been associated with various autoimmune diseases (e.g., diabetes type 1) (Secondulfo et al., 2004) and gastrointestinal (GI) disorders, such as celiac disease (Heyman et al., 2012), inflammatory bowel disease (IBD) (Hilsden et al., 1996; Söderholm et al., 1999), and irritable bowel syndrome (IBS) (Martínez et al., 2013; Piche et al., 2009; Mujagic et al., 2014).

Psychosocial stress comprises one of the factors that may increase intestinal permeability. The hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) system are the two core endocrine systems that are activated in response to psychosocial stress. Prolonged or exaggerated activation of the HPA axis and SAM system may exert deleterious effects on various physiological systems, including the central nervous system (brain), GI tract (gut) and their interaction (gut-brain axis) (Koolhaas et al., 2011; Leigh et al., 2023). In the present narrative review, we summarize the existing knowledge on the effect of psychosocial stress on intestinal permeability and the putative mechanisms that may be involved therein.

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2. The intestinal barrier

2.1. The intestinal barrier and intestinal permeability

The intestinal barrier and intestinal permeability are terms representing two different functions of the intestinal wall. The intestinal barrier comprises a complex multilayer system that consists of a 'physical' barrier and a 'functional' barrier (Bischoff et al., 2014). The physical barrier comprises cellular and stromal components including the epithelial cell lining as well as the mucus layer which consists of a gel formed by mucosal secretion interactions. The functional barrier, on the other hand, includes digestive secretions, cytokines, and antimicrobial peptides. The interaction between the physical and functional elements maintains a balanced intestinal permeability. The functional status (i.e., a measurable feature) of the intestinal barrier is described by 'intestinal permeability'. Intestinal permeability reflects the transfer of defined molecules across the intestinal wall (Bischoff et al., 2014).

Contents of the intestinal lumen can cross the barrier either via transcellular or paracellular pathways. As shown in Fig. 1., the transcellular route comprises (1) active transport used by selective nutrients such as sugars, amino acids, and vitamins, which require specific transporters and energy, (2) passive diffusion used by small hydrophilic and lipophilic compounds, or (3) endocytosis of larger peptides, proteins, and bacterial components or even whole bacteria (Vanuytsel et al., 2021). More specifically, the uptake of antigens and bacteria occurs in follicle-associated epithelium by macropinocytosis (Keita et al., 2013; Keita et al., 2006). The paracellular route (4) is used for the transport of ions, water, and hydrophilic compounds (up to 10–20 kDa) that cannot cross the intestinal epithelium transcellularly. Tight junctions (TJs) regulate at least two different pathways within the paracellular route: pores permeable to ions and small uncharged molecules, and a pathway permeable to larger molecules irrespective of charge. These pathways are commonly referred to as the pore and leak pathway, respectively. The leak pathway can be activated rapidly by the phosphorylation of the myosin light chain (MLC) by myosin light chain kinase (MLCK), which is followed by contraction of the cytoskeleton and opening of the TJs. On the other hand, the synthesis of new proteins (e.g., claudin-2) to increase pore pathway flux develops more slowly and is longer lasting (Shen et al., 2011).

2.2. Methods to assess intestinal permeability

All methods that measure intestinal permeability have in common that they use defined molecular probes (e.g., electrolytes or sugars of different molecular weight), that can cross the epithelium (Bischoff et al., 2014). The current review will focus solely on methods for *in vivo* measurement of intestinal permeability which all relate to the paracellular pathway. In contrast, *ex vivo* measurements allow evaluation of both transcellular and paracellular permeability (for a detailed review on intestinal permeability measurements see Vanuytsel et al., 2021.

2.2.1. Urinary excretion of orally ingested probes

Methods that measure intestinal permeability *in vivo* rely on the fractional urinary excretion of orally ingested probes. Commonly used probes include sugars, such as lactulose, sucralose, rhamnose, erythritol, and mannitol, as well as polyethylene glycols (PEG) and tracer molecules, such as radiolabeled chromium-ethylenediaminetetraacetic acid (^{51}Cr-EDTA). Ideally, the probes should not cross the epithelium via the

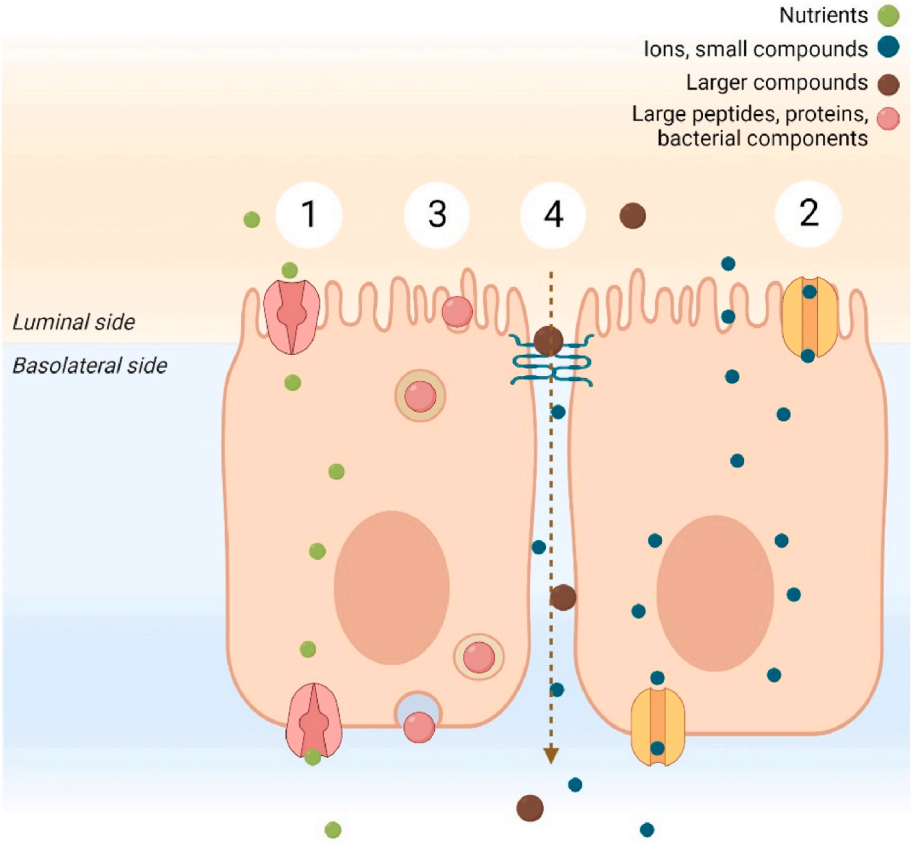

Fig. 1. Intestinal permeability transport routes. 1) The transcellular route for nutrients such as glucose, amino acids, and vitamins using active transport, 2) the transcellular route for small compounds, 3) endocytosis of larger peptides, proteins, and bacterial components (in follicle-associated epithelium by macropinocytosis), and 4) the paracellular route used by larger compounds, ions, and water. Created with Biorender.com. Adapted from Vanuytsel et al., 2021). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

transcellular route, be freely filtered at the glomerulus without reabsorption, and excreted in the urine (Edelblum and Turner, 2015). Moreover, the probes should be selected carefully, as some probes may be metabolized by digestive enzymes or colonic bacteria (Meddings and Gibbons, 1998). Importantly, the urinary recovery of the probes does not only depend on the intestinal permeability but also on motility and renal function. To take interindividual variability in these potential confounding factors into account, the use of two different-sized probes is recommended, assuming that an individual's transit time and kidney function affect both probes similarly (Rao et al., 2011). It is important to note that all probes can easily cross damaged areas of the barrier (i.e., where epithelial cells including their intercellular junctions are destroyed), such as in conditions as intestinal ischemia. Consequently, increases in the absorption of the probes may not necessarily reflect changes in TJ permeability (Edelblum and Turner, 2015).

A combination of different sugars allows to assess regional intestinal permeability. To assess small intestinal permeability, the combination of lactulose and mannitol has been used most frequently. Mannitol is a monosaccharide (molecular diameter: 6.7 Å) that is hypothesized to cross the barrier along the entire crypt-villus axis, where only the flux of small molecules is allowed (pore pathway). In contrast, lactulose, a disaccharide (molecular diameter: 9.5 Å), cannot cross through these small channels but uses larger – immature - ones found in the villus base or at sites of permeability of the leak pathway or epithelial damage (unrestricted pathway) (Odenwald and Turner, 2013; Shen et al., 2011). To avoid interference of mannitol present in the background diet with the interpretation of the test, the use of ^{13}C-labelled mannitol has been proposed (Grover et al., 2016). As lactulose and mannitol are degraded by colonic bacteria (Meddings and Gibbons, 1998), these sugars cannot be used to reliably measure colonic permeability. Instead, probes that are resistant to bacterial degradation should be used, such as sucralose and PEG (Bjarnason et al., 1995; Meddings and Gibbons, 1998). However, as both sucralose and PEG also permeate in the small intestine, data obtained using these probes reflect both small intestinal and colonic permeability (Edelblum and Turner, 2015). There is also a multi-sugar test which combines sucrose, lactulose, sucralose, erythritol, and rhamnose and reflects gastroduodenal (sucrose), small intestinal (lactulose, erythritol) and large intestinal (sucralose, rhamnose) permeability but validation of this approach is missing (van Wijck et al., 2013).

It should be noted that the permeability pathways of many probes are still unclear. Some authors suggested that mannitol also uses the transcellular pathway, although no studies so far support this hypothesis (Bjarnason et al., 1995). The tracer molecule ^{51}Cr-EDTA may be used as an alternative for sugar probes but does not allow to distinguish between small and colonic permeability and does not take variability in transit and renal function into account. Furthermore, the radiation burden (although limited) induced by the isotope ^{51}Cr may preclude its use in large-scale studies (Edelblum and Turner, 2015).

2.2.2. Potential blood biomarkers

Various biomarkers in blood have been proposed as additional strategies for measuring intestinal permeability *in vivo*. For instance, the detection of lipopolysaccharide (LPS) in serum signals translocation of bacteria or the bacterial wall from the gut lumen to the circulation as a consequence of intestinal barrier dysfunction (Bischoff et al., 2014). However, it remains difficult to measure LPS in peripheral blood in humans due to technical limitations of the assay and therefore LPS-binding protein (LBP) or soluble CD14 can be used as a by-proxy readout (Bischoff et al., 2014). Similarly, endotoxin core antibodies (EndoCAb) assays measure the concentration of immunoglobulins (IgG, IgM, and IgA) (Grootjans et al., 2010). Importantly, it should be noted that LBP is an acute-phase protein that can also increase due to processes not related to bacterial translocation, and soluble CD14 is not always correlated with LPS (Nier et al., 2017). Moreover, anti-endotoxin immunoglobulins concentrations vary greatly within individuals (Barclay, 1999) and, similar to LBP and soluble CD14, may reflect acute intestinal damage rather than intestinal permeability.

Plasma concentrations of intestinal fatty-acid binding protein (I-FABP) or TJ molecules have also been proposed as markers of intestinal permeability. I-FABP is a small cytosolic water-soluble protein that transports fatty acids from the apical membrane of the enterocyte to the endoplasmic reticulum where complex lipids are synthesized (Bischoff et al., 2014). Elevated concentrations of I-FABP indicate (predominantly small) intestinal epithelial cell damage rather than increases in intestinal permeability, and have been reported in patients with intestinal ischemia (Relja et al., 2010). It should be noted that since concentrations of LPS and I-FABP only rise when epithelial cells are damaged, these measures are not well suited for measuring intestinal permeability in healthy individuals as these subjects typically do not show intestinal epithelial cell damage or bacterial translocation.

Plasma concentrations of TJ molecules reflect paracellular barrier integrity loss. Several studies have reported higher systemic concentrations of claudins as a marker for impaired intestinal barrier function, for instance in patients with Crohn's disease (Zeissig et al., 2007). Nevertheless, validation of claudins in serum as a marker of intestinal permeability is still lacking (Vanuytsel et al., 2021).

Zonulin, a hypothesized regulator of intestinal barrier function (Fasano, 2012), has been widely used as a biomarker for intestinal permeability. Increased levels of zonulin have been reported in many patients, including IBD, celiac disease, and type 1 diabetes (Fasano, 2020). Unfortunately, the commercially available enzyme-linked immunosorbent assay (ELISA) kit for zonulin quantification lacks specificity (Scheffler et al., 2018; Ajamian et al., 2019). Zonulin is a family of structurally and functionally related proteins, the zonulin family peptides, including prehaptoglobin-2 and properdin, which, however, might not be the main targets of the antibody used in the commercially available ELISA kit (Fasano, 2021). Therefore, the literature on permeability using zonulin assays should be interpreted with caution.

2.2.3. Confocal laser endomicroscopy and mucosal impedance testing

Two upcoming technologies to measure intestinal permeability are confocal laser endomicroscopy (CLE) and mucosal impedance measurements. CLE is an endoscopic-assisted technique that can acquire high magnification and resolution images of the cellular structures of the epithelium in real-time after IV injection of fluorescein. CLE seems to be a promising tool to evaluate intestinal permeability, especially in clinical populations such as in patients with IBD (Chiriac et al., 2023) and IBS (Turcotte et al., 2013). Mucosal impedance measurement is the resistance of an alternating current between two adjacent electrodes on a luminal probe. It can be used to evaluate the integrity of the gastrointestinal mucosal lining, although most studies have focused on the esophagus (Vanuytsel et al., 2021). Unfortunately, both methods are invasive and induce stress to some extent and are therefore less suitable to study the effects of stress on intestinal barrier function.

3. Stress

Stress has been defined as a serious threat to our homeostasis or well-being, either physical (objective) or psychological (subjective), to which the host has to respond with an adaptive response (Selye, 1936; Kagan, 2016). Compared to psychological stress, psychosocial stress includes a social component (e.g., being evaluated by the individual's environment). Any type of stress exposure induces release of mediators including corticotropin-releasing hormone (CRH) and glucocorticoids (e.g., cortisol), which activate their receptors in different bodily regions to ensure a wide range of changes that lead to behavioral, cognitive, and functional changes to serve as a coping response to stress. Exposure to stress is not 'bad' *per se* as it prepares the body to fight-or-flight to ensure its survival. However, when the coping responses are not achieved or when exposure to stress is exaggerated or prolonged, coping behaviors such as anxiety may lead to a decrease in performance and cognition, and consequently limit our adaptation to the stressor. Similarly,

long-term activation of the physiological stress response may exert deleterious effects on various physiological systems, including the central nervous system (brain), GI tract (gut), and their interaction (gut--brain axis) (Dhabhar, 2014).

3.1. The stress systems

Upon the perception of a stressor, two core stress systems are activated, namely the hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal-medullary (SAM) axis (Fig. 2). The rapid fight-or-flight response is initiated within seconds by the stimulation of sympathetic ganglions by the locus coeruleus located in the brainstem. Sympathetic fibers that end in the adrenal medulla stimulate the secretion of adrenaline and, to a lesser extent, noradrenaline. These catecholamines regulate cardiovascular, pulmonary, skeletal muscle, hepatic, and immune systems, and prepare the body for rapid action to ensure its survival. This cascade is referred to as the SAM axis. Simultaneously, a somewhat slower cascade, the HPA axis, starts with the central secretion of CRH and vasopressin from the paraventricular nucleus (PVN) of the hypothalamus. CRH stimulates the secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland into the bloodstream, which in turn leads to the release of glucocorticoids (mainly cortisol in humans and corticosterone in rodents) from the adrenal cortex (Carabotti et al., 2015). The SAM and HPA axis participate in a positive, reverberatory feedback loop, meaning that the activation of one axis stimulates the activation of the other axis (Chrousos and Gold, 1992). Together, these stress systems affect many organs, including the GI tract.

3.2. Methods to assess the stress response

The HPA axis response to stress is commonly measured by detecting concentrations of the major glucocorticoid cortisol (or corticosterone in

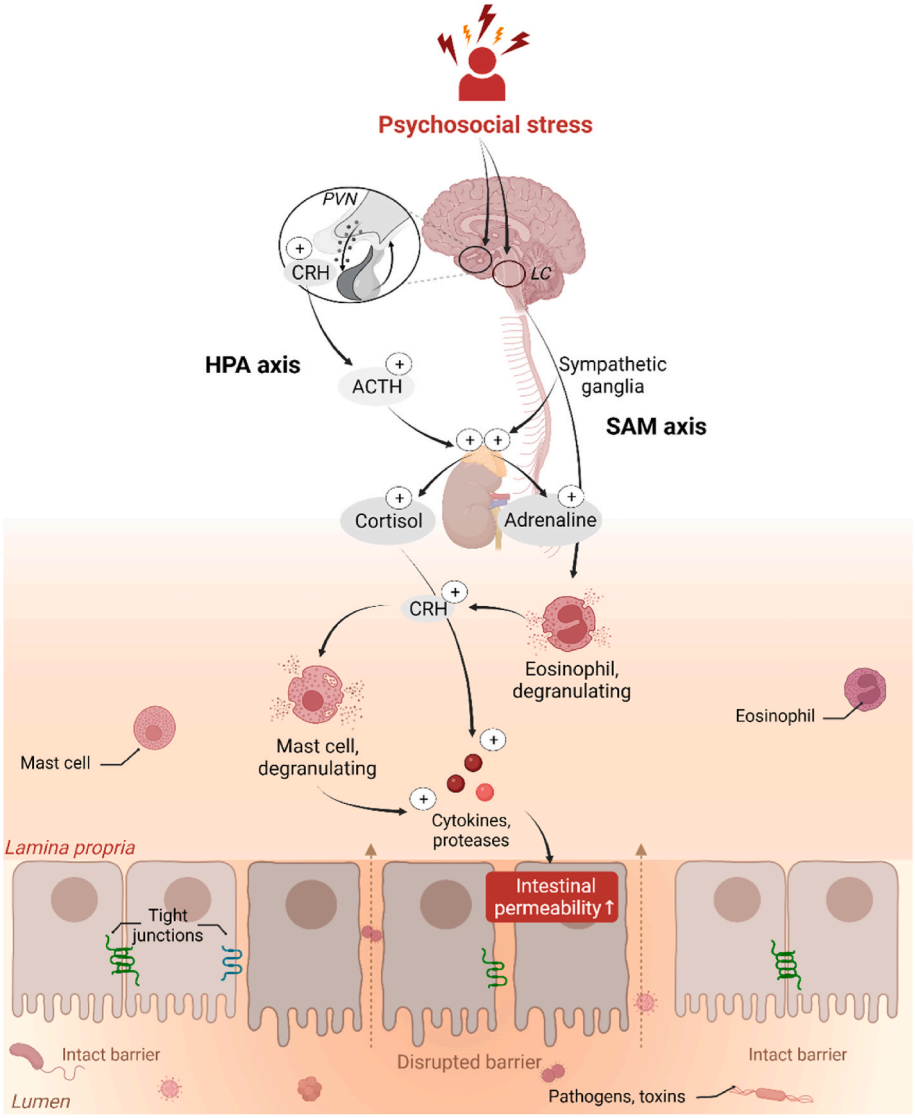

Fig. 2. Psychosocial stress activates the two core stress systems, namely, the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) axis. Activation of the SAM axis starts with neuronal activation in the locus coeruleus (LC), which consequently stimulates sympathetic ganglia to send excitatory signals to sympathetic nerves. This stimulates the adrenal medulla to secrete adrenaline but also stimulates the eosinophils to degranulate. Consequently, eosinophils release corticotrophin releasing hormone (CRH), which stimulates mast cells to degranulate and release inflammatory cytokines that increase intestinal permeability. The HPA axis starts with the central secretion of CRH from the paraventricular nucleus (PVN) of the hypothalamus, which stimulates the secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland. In turn, the adrenal cortex secretes glucocorticoids (e.g., cortisol) which can induce negative effects on the intestinal barrier by stimulating inflammation. Created with Biorender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

rodents). In plasma, cortisol is predominantly bound to corticosteroid-binding globulin (CBG) and, to a lesser extent, to albumin. The biologically active (i.e., free) fraction of cortisol comprises 2–5% of the total cortisol concentration (Turpeinen and Hämäläinen, 2013). Cortisol is commonly measured in saliva (which reflects free cortisol), serum (total and free cortisol), plasma (total and free cortisol), hair (free cortisol), or urine (free cortisol) using immunoassays and chromatographic methods. Salivary cortisol is most used in research as it is quickly, easily, and non-invasively obtained and correlates very well with free serum cortisol concentrations (Vining and McGinley, 1987). Many studies use the measure repetitively to sketch the cortisol response over a short period of time (i.e., for minutes to hours). This makes it an ideal measure for studies that use stress tasks as it can quantify the cortisol response to the stressor. In contrast, if overall cortisol concentrations over a longer period of time (e.g., months) are preferred, hair cortisol may be more suitable. Alternatives for measuring cortisol are, for instance, androgen precursors dehydroepiandrosterone (DHEA) and its metabolite dehydroepiandrosterone-sulphate (DHEA-S). DHEA and DHEA-S responses are positively correlated to that of cortisol and are increased in response to acute stress (Lennartsson et al., 2012).

The SAM axis response to stress can be assessed by measuring physiological parameters such as blood pressure, heart rate or the galvanic skin response, or by measuring biochemical markers such as alpha amylase in saliva or (nor)adrenaline in blood (Weissman and Mendes, 2021; Ali and Nater, 2020). Although both axes are likely involved in stress-induced hyperpermeability, studies investigating the effect of stress on intestinal permeability have primarily focused on measuring the HPA axis.

4. Mechanisms by which stress alters intestinal permeability

4.1. Cortisol

Cortisol is the major glucocorticoid released in response to stress. The release of cortisol in the blood stream facilitates the coordination between the brain and peripheral effectors to regulate GI-functions such as motility, secretion, and immunity.

The involvement of cortisol in stress-induced increases in intestinal permeability became evident from animal studies. Adrenalectomy inhibited the glucocorticoid response to stress and attenuated stress-induced increases in intestinal permeability in male Wistar rats (Meddings and Swain, 2000). In the same study, an identical result was obtained by pharmacologic blockade of glucocorticoid receptors. In contrast, dexamethasone, a synthetic corticosteroid, increased intestinal permeability (Meddings and Swain, 2000). Furthermore, psychological stress induced by water avoidance for 10 consecutive days led to a significant increase in plasma corticosterone and resulted in a decrease of TJ occludin and claudin-1 in male Sprague-Dawley rats. Similar alterations in expression of TJ proteins in Caco-2/BBE cells (clone of Caco-2 cell line) along with increased paracellular permeability could be recapitulated by treatment with cortisol (500 nmol/L) pointing to a causal role for cortisol (Zong et al., 2019). The fact that administration of a glucocorticoid receptor antagonist (mifepristone) for 8 days prevented an increase in intestinal permeability in male C57BL/6J mice caused by psychological stress further corroborates the role of cortisol in stress-induced hyperpermeability (Yoshikawa et al., 2017). Nevertheless, the exact mechanism by which glucocorticoids affect intestinal permeability and the minimal concentrations required remains unclear.

4.2. CRH

CRH is a crucial mediator of the stress response as it integrates physiological responses across different organs systems to react against a stressor. Of relevance here, besides in the brain, CRH receptors 1 (CRH-R1) and 2 (CRH-R2) are also widely expressed throughout the intestinal tract in various cell types (neuronal, endocrine, and immune) of both humans and rodents (Moeser et al., 2007; Larauche et al., 2009a; Porcher and Bonaz, 2005).

Both centrally and peripherally released CRH play an important role in gastrointestinal responses to stress. Centrally released CRH stimulates for instance colonic secreto-motor function and induces visceral hypersensitivity (CRH-R1) but also inhibits gastric motor function (CRH-R2) (for an extensive review see Tache et al., 2017). However, consistent evidence shows that especially peripheral CRH-R1 activation is involved in stress-induced intestinal barrier dysfunction, and is dependent on mast cells.

4.2.1. Peripheral CRH

Preclinical studies have shown that peripheral injections of CRH mimic increased paracellular and transcellular intestinal permeability induced by acute or chronic stress exposure (Keita et al., 2010; Barreau et al., 2007; Santos et al., 1999; Teitelbaum et al., 2008; Larauche, 2012) and that this effect can be blocked by pretreatment with peripheral injections of CRH receptor antagonists (Barreau et al., 2007; Santos et al., 1999; Teitelbaum et al., 2008; Saunders et al., 2002; Larauche et al., 2009b). Also, in humans, intravenous bolus injection of 100 μg CRH increased intestinal permeability, which was reflected by a higher urinary lactulose-to-mannitol (L/M) ratio compared to the control condition (Vanuytsel et al., 2014).

Peripheral CRH can be released by eosinophils (Overman et al., 2012). Eosinophils are immune cells residing in the mucosa and are involved in initiation and propagation of a variety of inflammatory responses (Hogan et al., 2008). The exact mechanism by which stress stimulates eosinophils to degranulate remains unclear. However, one study found that substance P, which is released by nerve endings upon stress (Zheng et al., 2009), and its receptors mediated the effect of stress in the expression of CRH in eosinophils (Zheng et al., 2009). More specifically, substance P seemed to increase the release of CRH via activating neurokinin-2 receptors in jejunal segments of chronically stressed (restraint stress of 1h for 10 consecutive days) mice. The authors concluded that substance P induced CRH release from eosinophils and subsequently activated CRH receptors on mast cells resulting in mast cell degranulation (Zheng et al., 2009). Another study in patients with ulcerative colitis found that cholinergic nerves mediated eosinophil activation resulting in colonic barrier dysfunction (Wallon et al., 2011). More specifically, the study found that eosinophils in human colonic mucosa are a source of CRH and express muscarinic acetylcholine receptors M_2 and M_3. Muscarinic acetylcholine receptors are G-coupled protein receptors and can be activated by ACTH released from preganglionic sympathetic fibers (Brown, 2013). Interestingly, increases in *ex vivo* intestinal permeability were blocked by a muscarinic receptor antagonist, a CRH receptor antagonist, as well as with a mast cell stabilizer (Wallon et al., 2011). These studies suggest that (sympathetic) nerve endings trigger eosinophils to stimulate CRH expression, which consequently activates mast cells and increases intestinal permeability (Fig. 2).

4.2.2. Mast cells as effector cells

Peripheral CRH activates mast cell degranulation via CRH-R1 and CRH-R2, which are located on mucosal mast cells (Cao et al., 2005). Mucosal cells contain large granules that store pro- and anti-inflammatory mediators (Krystel-Whittemore et al., 2016). Intestinal mast cells maintain homeostasis by regulating endothelial functions (e.g. vascular permeability), neurological functions (e.g. neuro-immune interactions), tissue transformation (e.g. wound healing), host defense (e.g. against bacterial and viral infections), as well as epithelial function-(e.g., epithelial permeability) (Bischoff, 2007).

Upon activation, mast cells release biologically active products that may contribute to an impaired epithelial integrity such as proteases, histamine, and cytokines (including IL-1, IL-3, IL-6, IL-18, and tumor necrosis factor [TNF]-α) (Albert-Bayo et al., 2019). Stress-induced mast cell degranulation likely functions as a host defense strategy to reinforce

innate and adaptive immune responses. However, prolonged or exaggerated mast cell activation may induce detrimental effects to the host such as immune dysregulation and tissue damage as well as intestinal barrier dysfunction.

The involvement of mast cells in barrier function was apparent from animal experiments using mast cell stabilizers. Whereas long-term exposure to psychosocial stress induced by 15 days of crowding stress promoted mucosal inflammation and barrier dysfunction in Wistar-Kyoto rats (a stress sensitive strain) (Vicario et al., 2010), stabilizing mast cells with doxantrazole abolished CRH-stimulated increases in intestinal permeability in male Wistar-Kyoto and Wistar rats (Keita et al., 2010; Santos et al., 1999). Similarly, mast cell-deficient Ws/Ws rats were resistant to chronic stress-induced effects on epithelial function, whereas wild-type control rats exhibited increased macromolecular permeability and depletion of mucus (Söderholm et al., 2002). In healthy human subjects, CRH stress-induced hyperpermeability was prevented after oral pre-treatment with the mast cell stabilizer disodium cromoglycate (DSCG) (Vanuytsel et al., 2014). Moreover, intravenous injections of 100 μg CRH prior to biopsy collection increased jejunal water secretion (indicator of absorptive/secretory ability) and luminal albumin (measure for macromolecular permeability) secretion in jejunal biopsies of patients with diarrhea-predominant irritable bowel syndrome (IBS-D) and healthy controls compared to saline placebo injections, with greater effects in the IBS-D group (Guilarte et al., 2020). The same study also found higher tryptase release in the jejunum reflecting mast cell activation, in both groups after CRH injections compared to placebo (Guilarte et al., 2020). Collectively, these results strongly suggest that CRH induces hyperpermeability in a mast-cell dependent fashion.

Ex vivo studies using an Ussing chamber model with a porcine ileum demonstrated that CRH disturbed intestinal epithelial barrier function which involved mast cell dependent TNF-α and protease release and disruption of TJs (Moeser et al., 2007; Keita et al., 2010; Overman et al., 2012; Smith et al., 2010). The exact mechanism by which proteases, histamines, and cytokines affect intestinal permeability is discussed extensively elsewhere (Suzuki, 2013). Briefly, proteases and cytokines have shown to increase intestinal permeability by disrupting the TJ barrier. Cytokines such as TNF-α, IFN-γ, interleukin (IL)-1β, and IL-6 can disrupt TJ protein distribution, for instance, via MLCK-mediated phosphorylation of the MLC (TNF-α) (Ye et al., 2006), downregulation of ZO-1 (TNF-α and IFN-γ) (Wang et al., 2019; Youakim and Ahdieh, 1999) and occludin (TNF-α) (Wang et al., 2019), c-Jun N-terminal kinase (JNK) activation of activator protein (AP)-1 (IL-6) (Al-Sadi et al., 2014), and activating the MEKK-1 gene (IL-1β), which encodes mitogen-activated protein kinase kinas MAPKKK and is involved in cell survival and apoptosis (Al-Sadi et al., 2010; Widmann et al., 1998). The release of tryptase, the most abundant secretory granule-derived serine protease, can affect TJ proteins through the activation of protease-activated receptors (PAR-2) (Compton et al., 2001) which are expressed on both apical and basolateral membranes of intestinal epithelial cells leading to increased intestinal permeability.

5. Acute psychosocial stress induction and intestinal permeability: human evidence

Although mechanistic evidence from in vitro and animal studies convincingly indicates that acute psychosocial stress increases intestinal permeability, evidence from experimental studies in humans is limited and the results are equivocal. From the 4 experimental studies that assessed the effect of an acute psychosocial stressor on intestinal permeability in healthy individuals, 1 study found an effect on colonic paracellular permeability and 1 study found an increase in intestinal permeability after stress induction in a subset of participants (Vanuytsel et al., 2014) (Table 1). It should be noted that there are 3 additional studies that assessed the effect of stress on intestinal permeability. However, as 2 of these studies measured albumin secretion (Alonso et al., 2008, 2012) (which refers to the transport oriented towards the lumen rather than from the lumen) they do not directly reflect changes in intestinal permeability and are therefore not included in the present Review. The other study used zonulin as a measure of intestinal permeability, which due to the ambiguity of the commercially available ELISA kit should be interpreted with caution.

In the following section, we summarize factors that likely influence the effect of psychosocial stress on intestinal permeability and may explain the difficulties to translate results from mice to humans.

Table 1
Human studies assessing the effect of psychosocial stress on intestinal permeability.

Stress		Intestinal permeability		Design	Results	Reference
Test	Measure	Test	Measure for			
Public speech	Salivary cortisol	L/M ratio (2h)	Small intestinal permeability (paracellular)	Within-subjects, $N = 23$ (11 females)	In subjects with cortisol elevation (P > 90*) had increased intestinal permeability ($p = 0.02$)	Vanuytsel et al. (2014)
Skydiving	Salivary cortisol	L/R ratio (5h)	Small intestinal permeability (paracellular)	Within-subjects, $N = 19$ (9 females)	Cortisol levels were significantly elevated after skydiving ($p < 0.0001$). No significant effect on gastroduodenal, small intestinal, or colonic permeability	Rubio et al. (2021)
		S/E ratio (5–24h)	Colonic permeability (paracellular)			
		Sucrose (5h)	Gastroduodenal permeability (paracellular)			
Public speech	Salivary cortisol	L/M ratio (2h)	Small intestinal permeability (paracellular)	RCT, intervention with *L. rhamnosus CNCM* I-3690 vs. placebo, $N = 46$ per group (26 and 28 females, respectively)	No significant increase in L/M ratio in the *L. rhamnosus CNCM* I-3690 group nor in the placebo group. An increase in FEM but not FEL was observed in the placebo group ($p < 0.05$)	Wauters et al. (2022)
Dichotomous listening	Heart rate, blood pressure	^{51}Cr-EDTA	Colon permeability (paracellular)	Within-subjects, N = 16 (10 female). All subjects underwent a stress condition and control condition. Endoscopic biopsies were taken from the rectosigmoid region	Subjective stress, objective stress, as well as ^{51}Cr-EDTA were significantly elevated in the stress condition compared to the control condition ($p < 0.0001$, $p < 0.0001$, and $p < 0.05$, respectively). No effect on TER nor on HRP	Gerdin et al. (2022)
		TER	Colon permeability (paracellular and transcellular)			
		HRP	Colon permeability (transcellular)			

*P > 90 refers to subjects with cortisol levels above the 90th percentile of the control condition during the public speech. Abbreviations: L/M, lactulose/mannitol ratio; L/R, lactulose/rhamnose ratio; S/E, sucralose/erythritol ratio; V-TSST, Virtual-Trier Social Stress Test; FEM, fractional excretion of mannitol; FEL, fractional excretion of lactulose; ^{51}Cr-EDTA, ^{51}Chromium-EDTA; TER, transepithelial electrical resistance; HRP, horseradish peroxidase.

6. Factors that influence stress-induced barrier alterations

6.1. Stress intensity and duration

The discrepancy between the findings of human and animal studies may, at least partly, be explained by a different intensity of stress exposure. Meddings and Swain (2000) found that although the glucocorticoid response to stress was significantly increased after both conditions, only intense stress (forced swimming for 20 min) and not moderate stress (restraint stress for 3h) increased the lactulose-to-mannitol ratio and fractional sucralose excretion in rats (Meddings and Swain, 2000). The fractional excretion of sucrose was increased after both stress conditions, however, after intense stress the increase was more profound.

Similarly in humans, intestinal permeability in healthy subjects was only increased after acute psychosocial stress in subjects with stress-induced cortisol exceeding the P90 percentile (Vanuytsel et al., 2014). Also, Li et al. (2013) only found a significant increase in small intestinal permeability in soldiers who experienced GI symptoms during combat-training (IBS-symptom severity scores [SSS]≥75) (Li et al., 2013). Interestingly, IBS-SSS were significantly correlated with morning serum cortisol concentrations after combat-training. Potentially, changes in intestinal permeability can only be detected when the stress response is sufficiently stimulated.

Also, the duration of stress induction differs between animal and human studies. In animal studies, stress is typically induced for hours to days, with acute stress induction usually lasting for 2h and chronic stress ranging from 7 to 14 days. On the other hand, in human studies acute stress is typically induced for only 10–15 min and chronic stress can, for obvious ethical reasons, only be observed under naturally stressful conditions such as in caregivers of dementia patients or the anticipation of a public defense (Vanuytsel et al., 2014; Gilhooly et al., 2016). It is therefore difficult to compare stress research in animals with that of humans. Possibly, it is more difficult to reach the state of stress-induced hyperpermeability in humans because the stress induction is less intense and shorter than in animals. In addition, it remains possible that the human body is able to adapt and protect against these stress intensities and its negative effects.

6.2. Physical versus psychological stress

Another explanation for the discrepancy between animal and human studies may be that the experimental stress paradigms used in animal studies often involve both physical and psychological components of stress. It has been established that intense physical exercise increases intestinal permeability (Keirns et al., 2020). In animal experiments such as the forced swim test, rodents need to swim without solid support. Besides a psychological stress component (the inability to escape), a physical stress component is present as the rodents exhibit climbing or swimming behavior to cope with the stressor until exertion is reached. Similarly, restraint stress paradigms, in which the animal is fully immobilized and placed in a small Plexiglas cylinder produce inescapable psychological and physical stress to which adaptation is rarely reached (Atrooz et al., 2021).

Some human studies used military combat training to assess the effect of stress on intestinal permeability (Table 2). Military combat training combines both psychological and physical stressors, and these stressors typically induce severe short-term biochemical, physical, and behavioral responses that exceed those measured during skydiving or laboratory-based simulations (Lieberman et al., 2005, 2016). Indeed, high-intensity military combat training (i.e., a combination of severe psychological and physical stress) increased colon intestinal permeability in male soldiers as measured with an increase in sucralose compared to when measured at rest (Li et al., 2013; Phua et al., 2015). In the studies of Phua et al. (2015) and Li et al. (2013), healthy male soldiers underwent an intense combat-training for 6 weeks including physical and mental challenges, which included simulating combat situations and practicing immediate medical evacuations. Some of these exercises required participants to wear heavy chemical warfare protection suits, all while dealing with an average temperature of approximately 30°C and a relative humidity exceeding 80%. Stress and intestinal permeability were assessed in both studies during the 4th week of continuous combat training and 12 days after completion of combat training (rest period). In the study of Li et al. (2013), small intestinal permeability (measured with lactulose-to-mannitol ratio) was also higher in soldiers with GI symptoms (IBS-SSS≥75) during combat training compared to those without (Li et al., 2013). One combat-training study did not find an increase in LPS binding protein (LBP) concentrations after combat training compared to baseline (Varanoske et al., 2022). In this study, healthy male marines were studied during an 18-day Survival, Evasion, Resistance, and Escape (SERE) training, which consisted of classroom training, structured physical, survival, captivity, and evasion training, as well as stressful mock interrogations. The soldiers also had to endure severe dietary restraints (e.g., a severe energy deficit (~-4200 kcal/day) for 5 days and a severely limited for another 2.5 days). Stress and intestinal permeability were measured on day 2 (classroom training), following completion of the field training, and after a 27-day recovery period. Interestingly, no increases in cortisol nor intestinal permeability were found. However, the intestinal permeability results should be interpreted with caution as LBP levels can also change due to processes not related to bacterial translocation. It should be noted that severe physical stress may increase

Table 2
Human studies assessing the effect of combat-training on intestinal permeability.

Stress duration	Study population	Study design	Intestinal permeability test	Intestinal permeability measure	Results	Reference
18 days	71 male U.S. marines	Within-subjects design	LBP	Increased transepithelial uptake of LPS	LBP concentrations decreased from pre to post combat training ($p < 0.001$)	Varanoske et al. (2022)
6 weeks	38 male Asian Medical Response Force soldiers	Within-subjects design	Sucralose (24h)	Total gastrointestinal permeability	Total gastrointestinal permeability was increased in the combat-training group compared to the rest group ($p < 0.001$)	Phua et al. (2015)
6 weeks	39 male Asian Medical Response Force soldiers	Within-subjects design	Sucrose (5h)	Gastroduodenal permeability	Significantly higher in solders during combat-training compared with rest ($p < 0.01$)	Li et al. (2013)
			L/M ratio (5h and 24h)	Small intestinal permeability	Significantly increased in a subgroup of soldiers with IBS-SSS≥75 during combat training compared with soldiers IBS<75 ($p < 0.05$)	
			Sucralose (5h and 24h)	Total gastrointestinal permeability	Significantly higher in soldiers during combat-training compared with rest ($p < 0.01$ and $p < 0.001$, respectively)	

Abbreviations: LBP, lipopolysaccharide binding protein; LPS, lipopolysaccharide; L/M, lactulose/mannitol ratio; IBS-SSS, irritable bowel syndrome symptom severity score; IBS, irritable bowel syndrome.

intestinal permeability not only via CRH-mediated mechanisms, but also, for instance, by inducing hyperthermia (Pires et al., 2017) and hypoxia (Lee et al., 2018) which may collectively result in tissue damage and intestinal barrier dysfunction (Hall et al., 2001).

6.3. Type of stressor

Animal studies apply stress paradigms such as maternal separation, restraint stress, and immobilization (Atrooz et al., 2021). These paradigms involve some sense of defeat, in which the animal struggles over recourses associated with behaviors related to fighting. This often result in wounding, exhaustion, or death (Blanchard et al., 2001). Contrastingly, stressors in human studies involve primarily psychological stress as this is a constant occurrence in the lives of highly social animals. However, psychological stress results in different behavioral and physiological patterns compared to animal stress paradigms. Therefore, stress paradigms in humans represent a different concept of stress than animal stress paradigms.

There are also different types of stressors used within human research investigating stress-induced intestinal permeability (Table 1). Of the human studies, two used a similar naturalistic/academic public speech task (Vanuytsel et al., 2014; Wauters et al., 2022), one dichotomous listening stress, and one study used skydiving (Rubio et al., 2021) to induce acute psychosocial stress. Although skydiving is a validated paradigm to increase the cortisol response to stress, skydiving is generally perceived as enjoyable (Franken et al., 2006), in contrast to aversive psychosocial stressors such as a public speech task or dichotomous listening stress. This is in line with the findings of Rubio et al. (2021), in which cortisol levels were not significantly increased 1h before the skydive (Linninge et al., 2018).

During the dichotomous listening stress test, subjects hear two different narrations through each ear and have to repeat aloud the narration heard through one ear whilst ignoring the other. Every 15 min, the subjects had to change the narration. To induce more stress, the subjects were told that their performance was related to intelligent quotient (IQ) and that they would be evaluated based on their performance (Mcrae et al., 1982). Indeed, subjects had a significant elevation in their stress response to dichotomous listening compared to a control condition in the study of Gerdin et al. (2022). However, as cortisol concentrations were not measured, it remains difficult to compare their stress response with the other studies of Table 1.

Other studies assessing the effect of acute psychosocial stress on LBP and albumin output have used a virtual version of the TSST (V-TSST) (Linninge et al., 2018) and cold pain stress (Alonso et al., 2008, 2012). The V-TSST is similar to the TSST in that subjects had to give a speech and do an arithmetic task in front of a jury but is executed in a virtual reality environment and not in person. Noteworthy, the V-TSST induces cortisol elevations to a lesser extent compared to the TSST executed in person (Helminen et al., 2019). Indeed, in the study of Linninge et al. (2018) cortisol levels were elevated to a lesser extent compared with the experimental studies of Table 1 (Linninge et al., 2018). In the studies of Alonso et al., 2008, 2012, cold pain stress was used as a stressor. Although cold pain stress has been shown to stimulate a cortisol response, there is ample evidence demonstrating that adding a socio-evaluative component leads to an exaggerated cortisol response (Smeets et al., 2012; Schwabe et al., 2008). Nevertheless, cortisol concentrations in the studies of Alonso et al., 2008, 2012 were comparable to the study of Vanuytsel et al. (2014). Unfortunately, as albumin output reflects transport oriented towards the lumen rather than from the lumen it does not reflect intestinal permeability and therefore remains unclear whether intestinal permeability was altered by cold pain stress in the studies of Alonso et al., 2008, 2012.

Particular about the studies of Vanuytsel et al. (2014) and Wauters et al., 2022 is that the public speech task was a naturalistic stress paradigm as opposed to the experimental paradigms used in the other studies. The participants were students that had already scheduled an oral presentation (bachelor or master thesis) in front of an examination jury followed by questions with a total duration between 30 and 45 min. Likely, the students were already stressed long before the actual date of the oral presentation. Indeed, Vanuytsel et al. (2014) reported that subjects had increased cortisol levels already 1h before the oral presentation. These results may suggest that the increases in intestinal permeability require the stress response to be activated for a prolonged period (i.e. not only during the stress task itself). However, it remains unclear why the findings of Vanuytsel et al. (2014) were not replicated in the study of Wauters et al. (2022) even though the same stress test was used. Wauters et al. (2022) note that the higher inter- and intra-individual test variability for the stress response, FEL, and LMR may potentially explain the discrepant results on LMR with the study of Vanuytsel et al. (2014) and suggest that a strong protracted cortisol response may be needed for stress to induce changes in intestinal permeability.

6.4. Methods to measure intestinal permeability

Methods used to measure intestinal permeability are different in animal studies compared to human studies. Animal studies typically use Ussing chambers to assess paracellular and transcellular permeability of different GI segments by assessing the TEER. This technique is considered the gold standard technique for measuring epithelial integrity (Vanuytsel et al., 2021), but is not well-suited to measure stress-induced changes in intestinal permeability in humans because the invasive procedure of taking biopsies induces stress (Tønnesen et al., 1999). In the study of Gerdin et al. (2022), rectosigmoid biopsies of healthy subjects were taken after dichotomous listening stress and after a control condition. Paracellular permeability, which was measured using Ussing chambers, was significantly increased after dichotomous listening stress compared to the control condition. However, it may thus be plausible that the subjects experienced anticipatory stress for the endoscopic biopsies which may have led to an accumulation of the stress response. It remains therefore difficult to attribute the observed effects on intestinal permeability solely to the dichotomous listening stress test.

To circumvent the practical and cost-related issues related to taking biopsies, the majority of human studies evaluate the paracellular route with *in vivo* sugar tests (e.g., lactulose-mannitol tests). In principle, *in vivo* sugar tests can be combined with laboratory stress tests as the sugars can for instance be administered prior to the stress induction and the urine sample collection after. However, these sugar tests take at least 2h whereas most stress tests usually only induce stress for 10–15 min. The stress-induced effects may therefore be too transient to subsequently affect the probe tests. Moreover, other transepithelial transport routes (Fig. 1) may be potentially more relevant for GI disorders (Vanuytsel et al., 2021).

Additionally, multiple factors can affect sugar tests, such as gut motility and transit as these vary substantially between and within individuals (Nandhra et al., 2020). Additionally, stress can also affect gut transit time as peripheral as well as central injections with CRH inhibited small-intestinal transit but stimulated colonic transit and motility through the activation of CRH-1R (Fukudo et al., 1998; Kellow et al., 1992; Williams et al., 1987). Moreover, each sugar test has a pre-defined fixed temporal window (i.e., the time between the sugar administration and urine collection) and varies from 2 to 24h. This is assumed to reflect a specific type of intestinal permeability (i.e. small, colon, or whole intestinal permeability). However, as gut transit and motility vary greatly between individuals and is influenced by multiple factors, the fixed temporal window of sugar tests may be rather arbitrary and, in reality, may not reflect the respective regional permeability very well.

6.5. Prior insult to the intestinal barrier

Other environmental factors such as intestinal infection may

facilitate the negative effects of stress. Several independent animal studies suggest that psychological stress *per se* cannot induce overt GI disorders such as colitis, but that it preconditions the intestinal mucosa by inducing an pro-inflammatory state that augments the consequences of a colitogenic trigger (Schneider et al., 2023; Gué et al., 1997). Indeed, ample evidence shows that psychological stress can trigger a symptomatic as well as inflammatory flare-up in patients with GI disorders, such as IBD or IBS (Hirten et al., 2021; Qin et al., 2014; Labanski et al., 2020). Interestingly, Wouters et al. (2016) found that having anxiety symptoms at the time of an acute infection increased the risk of developing infectious gastroenteritis (IGE), and 20% of these IGE patients later developed post-infectious (PI-) IBS (Wouters et al., 2016). Moreover, in patients with inactive ulcerative colitis acute psychological stress induced systemic and mucosal proinflammatory responses, whereas this was not present in healthy controls (Mawdsley et al., 2006). Unfortunately, intestinal permeability was not measured in these studies. However, many studies have shown that patients with GI disorders, and specifically those with a history of infection, have increased intestinal permeability (Vanuytsel et al., 2021; Hanning et al., 2021). We speculate that psychological stress may induce negative effects on the intestinal barrier specifically in subjects with prior insult to the intestinal barrier (e.g., IBD or IBS patients). However, this hypothesis needs to be confirmed in human studies that assess whether an acute psychological stressor can indeed increase intestinal permeability in patients with a history of GI infection.

7. Conclusion

Both in vitro and animal studies have shown that stress disrupts intestinal barrier integrity. However, experiments in humans yield equivocal results. As animal and human studies vary highly in both stressor type and duration and intestinal permeability measure, the results are difficult to compare. Even though it will remain difficult to achieve an intense stress response similar to in animal studies, future studies should keep in mind that there is a possibility that there is a 'threshold' for the induced stress response required to affect intestinal permeability. Moreover, methods to assess stress-induced changes in intestinal permeability *in vivo* remain limited and researchers should be aware of their limitations. When an *in vivo* sugar test is used, it is recommended to use two sugars as their ratios control for variability in transit and renal function. Moreover, future studies should take into account that interindividual differences in GI motility and transit time may substantially affect the region that is reflected with the *in vivo* intestinal permeability tests.

Author contributions

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Declaration of competing interest

Authors D.L.T., L.V.O., T.V., and K.V. declare none.

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