Stress modulates intestinal secretory immunoglobulin A

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INTRODUCTION

Stress is a response of the central nervous system (CNS) to environmental stimuli perceived as a threat to homeostasis. The stress response triggers the generation of neurotransmitters and hormones from the hypothalamus-pituitary-adrenal axis, sympathetic axis and brain-gut axis, and in this way modulates the intestinal immune system. The effects of psychological stress on intestinal immunity have been investigated mostly with the restraint/immobilization rodent model, resulting in an up or down modulation of SIgA levels depending on the intensity and time of exposure to stress. SIgA is a protein complex formed by dimeric (dIgA) or polymeric IgA (pIgA) and the secretory component (SC), a peptide derived from the polymeric immunoglobulin receptor (pIgR). The latter receptor is a transmembrane protein expressed on the basolateral side of gut epithelial cells, where it uptakes dIgA or pIgA released by plasma cells in the lamina propria. As a result, the IgA-pIgR complex is formed and transported by vesicles to the apical side of epithelial cells. pIgR is then cleaved to release SIgA into the luminal secretions of gut. Down modulation of SIgA associated with stress can have negative repercussions on intestinal function and integrity. This can take the form of increased adhesion of pathogenic agents to the intestinal epithelium and/or an altered balance of inflammation leading to greater intestinal permeability. Most studies on the molecular and biochemical mechanisms involved in the stress response have focused on systemic immunity. The present review analyzes the impact of stress (mostly by restraint/immobilization, but also with mention of other models) on the generation of SIgA, pIgR and other humoral and cellular components involved in the intestinal immune response. Insights into these mechanisms could lead to better therapies for protecting against pathogenic agents and avoiding epithelial tissue damage by modulating intestinal inflammation.

Keywords: SIgA, pIgR, intestinal mucosa, restraint-stress, glucocorticoids, brain-gut axis
THE NERVOUS SYSTEM AND THE INTESTINAL IMMUNE RESPONSE

The mutual influence of the nervous system and the intestinal immune response has been widely studied using experimental models of stress. ILS and microbiota from the gut can modulate the nervous system. On the other hand, the nervous system can modulate intestinal immunity by several pathways (de Jonge, 2013). Regulation of the BGA is accomplished by the integration of four control levels. Control level one is accomplished by the ENS endowed with local innervations that functionally are independent of the extrinsic nervous connections. Level two entails the prevertebral sympathetic ganglia where peripheral reflex pathways are influenced by preganglionic sympathetic fibers from the spinal cord. Levels three and four are within the CNS. In the level three sympathetic and parasympathetic fibers outflow to the gut is determined in part by reflex with sensory fibers that travel with autonomic nerves. The level four includes higher nerve centers that supply descending signals that are integrated with incoming sensory signals at the level three (Figure 2).

At the intestinal level the bilateral communication between the nervous system and intestinal immune response occurs through sympathetic innervations, which influence (i) the differential distribution of immunocytes in different regions of the small intestine (Ke et al., 2011), (ii) the migration of lymphocytes towards Peyers’s patches and mesenteric lymph node cells (Peyers’ patches; Sigk, secretory IgA; TCR, T cell receptor; TFF, tumor necrosis factor; CB1R ko, cannabinoid 1 receptor knock out; fMLP, formyl-methionyl-leucyl-phenylalanine; ETEC, enterotoxigenic E. coli; T cells in MLN; T cells in PP; in vivo, indicated by an asterisk; n/a, not available).

Figure 1 shows the distribution of immunocytes in different regions of the small intestine (Ke et al., 2011), (ii) the migration of lymphocytes towards Peyers’s patches and mesenteric lymph node cells (Peyers’ patches; Sigk, secretory IgA; TCR, T cell receptor; TFF, tumor necrosis factor; CB1R ko, cannabinoid 1 receptor knock out; fMLP, formyl-methionyl-leucyl-phenylalanine; ETEC, enterotoxigenic E. coli; T cells in MLN; T cells in PP; in vivo, indicated by an asterisk; n/a, not available).

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From an immunological point of view, intestinal SIgA is produced by a multistage process modulated by ILs. This process involves gut nerve fibers modulates the secretion of intestinal IgA and the expression of pIgR (Cox et al., 2007). Additionally, gut nerve fibers release the vasoactive intestinal peptide, neuropeptide Y (Mongardi Fan-taguzzi et al., 2009) and somatostatin (Schmidt et al., 1999), which are then released into the blood. Glucocorticoids and catecholamines influence the production of interleukins, which are involved in the viability and proliferation of immunocompetent gut cells via receptors.

THE GENERATION OF INTESTINAL IgA

From an immunological point of view, intestinal SIgA is produced by a multistage process modulated by ILs. This process involves the activation and class switch recombination of IgM+ B cells, the latter of which are committed to IgA synthesis either by a T-cell dependent or T-cell independent pathway (Cerutti, 2008).

The T-dependent pathway is induced in follicular areas of Peyer’s patches after the interaction between the APCs and helper Th2 lymphocytes (Figure 3). On their surface, APCs (like dendritic cells) express the CD40 antigen and a peptide-derived antigen associated with the major histocompatibility class II molecule (MHC-II). The CD40 antigen interacts with CD40L on Th2 cells, and the peptide-MHC-II complex with the Th2 cell receptor (TCR). In either case, immunological synapses lead to the release of the transforming growth factor (TGF)-β1 by Th2 cells, which is an essential step for the activation and class switch recombination of IgM+ B cells to IgA+ B lymphocytes. Other Th2-derived ILs, including IL-4, -5, -6, and -10, promote the proliferation of IgA+ B cells and their differentiation into IgA secreting plasma cells. In the presence of retinoic acid, IgA+ B cells express gut-homing receptors, such as α4β7 integrin, CCR9 and CCR10, and cause these cells to migrate from Peyer’s patches to the MLN via the circulation offferent lymphatic vessels. From the MLN these cells go to the thoracic duct, enter the bloodstream, and finally home to the lamina propria, the effector site of the gut immune system.

Epithelial cells that line the lamina propria express mucosal adhesion molecules, cell adhesion molecule 1 (MadCAM1) and the chemokines CCL25 and CCL28, which are the ligands for α4β7 integrin, CCR9 and CCR10, respectively, on B cells. In the lamina propria IgA+ B cells mature to plasma cells capable of releasing dimeric or polymers of IgA joined to t-chain (Brandtzæg, 2009, Figure 3).

The T-independent pathway for the production of intestinal IgA occurs in extra-follicular structures, including isolated lymphoid follicles and lamina propria. The class-switch recombination of IgM+ B cells to IgA+ B lymphocytes takes place through two pathways, and both involve a T-independent antigen. IgM+ B lymphocytes express B cell receptors (BCRs) and Toll-like receptors (TLRs). Polysaccharides interact with BCRs and bacterial lipopolysaccharide (LPS) and/or nuclear acids with TLRs (Cerutti, 2008). In the lamina propria IgA+ B cells further differentiate into IgA+ plasma cells.

THE TRANSPORT OF INTESTINAL IgA

The expression of plgR is necessary for the transport (transcytosis) of dIgA or plgA across the epithelial layer. plgR is a 120 kDa transmembrane protein consisting of five extracellular Ig domains, a transmembrane region and a cytoplasmic domain. The amino (NH2) terminal of this protein chain is oriented to the extracellular space, while the carboxyl (COOH) terminal has an intracellular orientation and contains signals for intracellular sorting and endocytosis (Asano and Komiyama, 2011; Johansen and Karetz, 2011). Other Th2-derived ILs, including IL-4,-5,-6, and -10, promote the proliferation of immunocompetent gut cells via receptors.

The expression of plgR can be constitutive or regulated at a transcriptional level by IL-4 and pro-inflammatory cytokines, the latter including tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ) (Johansen and Karetz, 2011). IgA transcytosis begins when plgR uptakes dIgA or plgA released in the lamina propria by plasma cells (Cerutti, 2008). The dIgA-plgR or plgA-plgR complex is transported by vesicles across the epithelial cell, and upon reaching the apical side plgR is cleaved to render SC bound to dIgA/plgA. The resulting SIgA is released into the intestinal lumen (Asano and Komiyama, 2011). The cleavage of plgR to yield SC occurs at the linker that connects domain 5 to the transmembrane region (Figure 4).
Campos-Rodríguez et al. Effects of stress on intestinal IgA

FIGURE 2 | Stress also triggers the activation of the enteric nervous system, including afferent and efferent intrinsic intestinal nerves (afferent nerves send signals from periphery to the brain; efferent nerves from the brain to the periphery) and extrinsic innervations, whether sympathetic (splanchnic) or parasympathetic (Vagus nerve).

The enteric nervous system is connected to the CNS via sympathetic and parasympathetic pathways, forming the brain-gut axis (BGA). Four levels for the control of BGA are shown (Wood et al., 1999). The stress response of the BGA influences the generation of dIgA and/or the pIgR mediated transepithelial transport. NTs, neurotransmitters; NPs, neuropeptides; GCs, glucocorticoids.

Biochemically and morphologically, transepithelial transport involves: (i) the endocytosis of dIgA from clathrin coated pits and its delivery to basolateral endosomes, (ii) microtubule dependent translocation to apical recycling endosomes, and (iii) delivery of the plasma membrane to apical endosomes (Johansen and Kaetzel, 2011).

THE ROLE OF SIgA AND pIgR

Both SIgA and pIgR have an essential role in immune exclusion, which protects against infections caused by enteropathogens. This role has been explored in the murine model of Salmonella typhimurium infection (Michetti et al., 1992; Drago-Serrano et al., 2010).

SIgA helps to limit the adhesion of luminal antigens to the epithelium. These antigens, if not excluded in gut secretions, are able to elicit the release of cell derived inflammatory cytokines, which can enhance permeability and disrupt the functional integrity of the gut. As a result of increased gut permeability, penetration of luminal antigens into the systemic compartment may cause a strong and even life-threatening systemic inflammatory response (Brandtzaeg, 2009; Corthésy, 2007).

pIgA and the different forms of IgA also have an anti-inflammatory role. For instance, pIgA and dIgA protect host tissue by neutralizing pro-inflammatory antigens inside and below the epithelium.
ostasis and lead to intestinal inflammation (Suzuki et al., 2004; modulated, an alteration in one may affect intestinal homeostasis by main-
testinal microflora, contribute to gut homeostasis by main-
(Corthésy, 2007). Furthermore, SIgA and pIgR, along with the
on cells by binding with receptors specific for the Fc
unable to elicit the production of pro-inflammatory cytokines
factors involved in the intestinal immune response via
neuroendocrine pathways. In the restraint procedure, a rodent is
placed (without forced squeezing) inside a cylindrical plastic tube. This
represents mainly psychological stress, as the perception of
confinement mimics a collapsed tunnel for these burrow-dwelling
animals (Dhabhar and Voswanathan, 2003). Another restraint pro-
cedure, known as immobilization, involves adhering outstretched
rodent limbs on a board with tape. Compared to restraint in a
plastic tube, this model has elicited a much more robust stress
response through the generation of neuroendocrine mediators
(e.g., glucocorticoids and catecholamines; Glavin et al., 1994).

The restraint stress model has provided evidence of intricate
neurological pathways underlying the regulation of SlgA. Such
pathways involve neurotransmitters and endocrine hormones
released from the blood flow or produced locally (e.g., glucocor-
ticoids released by intestinal epithelial cells), and their interaction
with the receptors of target cells (Cima et al., 2004).

It is now known that modulation of SIgA production is influ-
enced by the duration (acute or chronic) and intensity of stress.
Generally at a systemic level, acute stress (represented by a single
session lasting a few minutes to a few hours) tends to upregulate
the number of immune cells. Contrarily, the multiple sessions over
a period of several days, weeks or months that represent chronic
stress (Dhabhar, 2009) tend to downregulate the systemic immune
response. Experimental assays with skin delay type hypersensitiv-
ity response in rats corroborate this same general pattern of acute
and chronic stress (Dhabhar and McIwen, 1997).

Intensity of stress is another factor that can influence the
course of its result on the immune response. It is measured by the increase in
levels of adrenal hormones, neurotransmitters and physiologi-
cal parameters (e.g., heart rate and blood pressure), as well as
the period of time that these changes persist (during and after
the stress-inducing event; Dhabhar, 2009). This assay on mice
have shown that (i) the acute stress response elicited by intense
running promtures the accumulation of T lymphocytes in Peyer’s
patches via adrenergic mechanisms, evidenced by the fact that this
exercise-dependent increase was blocked by α-(phentolamine) or
β- (nadolol, adrenoceptor antagonists (Krüger et al., 2008), and
(ii) repeated sessions of chronic restraint stress have a negative
influence on intestinal levels of SlgA, which may be due to the
capability of corticosteroids to decrease the transeptosis of SlgA via
plgR (Jarillo-Luna et al., 2007). Another study on mice reported
that corticosteroids decrease SlgA levels in mucosal secretions and
increase such levels in serum. This effect is due in part to the
greater production in serum of SC, which is derived from hepatic
plgR. The binding of SC to plgR retards the clearance of the latter
from the blood by the liver (Wira et al., 1990).

In addition to reducing intestinal SlgA levels, repeated stress
has a negative influence on the number of lymphoid cells in
Peyer’s patches and the intestinal intraepithelial compartment.
These suppressive effects of restraint stress were mimicked by
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**THE RESTRAINT MODEL AND THE INFLUENCE OF STRESS IN
THE INTESTINE**

Assays based on the restraint model have provided important
insights into the influence of stress on the humoral and cellular
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In the gut lamina propria, IgA+ B cells further differentiate into IgA+ plasma cells that secrete dIgA or pIgA antibodies joined by the J chain. dIgA or pIgA are captured by the polymeric immunoglobulin receptor (pIgR), a transmembrane receptor with five extracellular domains and an intracellular tail expressed at the basolateral side of the enterocytes. The dIgA:pIgR complex is internalized and transported by transcytosis to the apical side, and the extracellular portion of pIgR with five domains is proteolytically cleaved from the transmembrane region. The former is then released to the gut lumen as secretory component (SC) bound to dIgA to yield secretory IgA (SIgA). SIgA and SC secreted into the mucus layer prevent the direct adhesion to the epithelium of pathogenic agents, which are eventually cleared from the lumen. Apart from enterocytes, other cell components of the gut epithelium include enterochromaffin cells with granules of neurotransmitters, Paneth cells with granules containing defensins and lysozyme, and goblet cells with mucin granules and IEL.

Other experimental stress protocols have been reported to have a negative influence on the gut immune response (Table 1). The stress produced in rats by exposure to heat negatively affected some intestinal parameters, including the levels of CD3+ and CD4+ T lymphocytes, the expression of TLR-2 and TLR-4, as well as the transcriptional mRNA expression of IFN-γ and IL-2, -4, and -10 (Liu et al., 2012). Assays on rats with an electric shock protocol showed that stress suppressed the production of IFN-γ through T cells with TCRαβ in the intraepithelial compartment, while at the same time elevating the level of endogenous glucocorticoids (Zhang et al., 2005). Studies on rodents under psychological stress have also reported a decrease in levels of intestinal SIgA, caused by: (i) an expectation of electric foot shock (Yamamoto et al., 2009), (ii) a continuous back and forth transference from housing cages to metabolic cages (Eriksson et al., 2004), and (iii) immobilization, in some cases combined with exposure to loud noise (Ponferrada et al., 2007; Caso et al., 2009; Zoppi et al., 2012).

**CELL MIGRATION**

The aforementioned stress-related changes in the levels of IgA, IgA secreting cells and IgA producing ILs may be related to cell migration pathways—the sympathetic autonomic nervous system and the HPA axis (Jarillo-Luna et al., 2007, 2008; Martínez-Carrillo et al., 2011). In another study, the endogenous production of glucocorticoids, triggered by a continuous 12-h period of restraint stress, decreased the number of T and B cells in Peyer’s patches, which is in line with a reduction in the levels of intestinal SIgA and lymphocytes (Sudo et al., 2001).
Table 2 | Mechanisms of immune modulation by stress.

| Effect | Mechanism | Reference |
|--------|-----------|-----------|
| ↓ SIgA levels by acute immobilization stress | ↓ SIgA attenuated by peroxisome proliferator-activated receptor-γ (PPAR-γ) activation | Ponferrada et al. (2007) |
| ↓ SIgA levels by immobilization and acoustic stress | ↓ SIgA attenuated by cannabinoid 1 receptor (CB1R) activation | Zoppi et al. (2012) |
| ↑ activation/migration of T cells induced by restraint stress | ↑ Activation of adhesion molecules (CD11a and CD11b) on T cells | |
| ↑ number of lymphocytes in spleen by restraint stress | ↑ Apoptosis through p53 and PI3K/NF-κB pathways | Zhang et al. (2008a) |
| ↑ number of T lymphocytes in Peyer’s patches by exercise stress | ↑ Fas/Fas, apoptosis pathway | Krüger et al. (2009) |
| ↑ number of lymphocytes in spleen by chronic restraint stress | ↑ p53-mediated apoptosis, dependent on endogenous opioids and independent of glucocorticoids from activation of HPA axis | Wang et al. (2002) |
| ↑ number of splenocytes by chronic restraint stress | ↑ CD69 (FcRγI)-mediated apoptosis, dependent on endogenous opioids but independent of the activation of HPA axis | Yin et al. (2000) |
| ↑ Immunesuppression by chronic restraint stress | ↑ Apoptosis via TLR4/PI3K signaling | Zhang et al. (2008b) |
| ↑ Immunesuppression by restraint stress | ↑ MHC-II expression in peritoneal macrophages along with corticosterone levels | Zwilling et al. (1995) |
| ↑ Immunesuppression by restraint stress | ↑ MHC-II expression influenced by corticosterone and some hormones not associated with the activation of HPA axis | Zwilling et al. (1993) |
| ↑ T cell proliferation or apoptosis by restraint stress | ↑ Activation of GADD45β and p53 genes, responsible for apoptosis and proliferation, respectively | Flint et al. (2005) |
| ↑ SIgA levels and ETEC proliferation following stress by weaning and short-term exposure to cold | ↑ Catecholamines enable iron acquisition that promotes bacterial proliferation | Jones et al. (2001), Lyte et al. (2011) |

**Migration, a phenomenon that has been studied mostly in the systemic response (Bauer et al., 2001).** Acute restraint stress decreases the number of peripheral helper T lymphocytes, upregulates the expression of adhesion molecules (CD11a and CD11b) on T cells, and increases the levels of circulating NK cells and glucocorticoids. These changes were not found in mice previously exposed to chronic intermittent restraint stress, suggesting an adaptation response to prolonged stress.

One presumable mechanism entails greater restraint-induced levels of glucocorticoids and/or catecholamines, which influence lymphocyte trafficking through the expression of adhesion molecules on endothelial cells (Dietrich, 2004; Krüger and Mooren, 2007; Krüger et al., 2008). This effect was found in mice under stress caused by exercise (Krüger et al., 2008). It seems that stress hormones influence lymphocyte migration and function through specific alterations in the actin cytoskeleton, an effect also found in mice under restraint stress (Flint et al., 2011).

**CELL VIABILITY AND T CELL ACTIVATION**

Another downmodulatory mechanism related to restraint stress is a decrease in cell viability and/or T cell activation. For instance, at a systemic level the restraint stress protocol elicits a reduction in splenic lymphocytes by apoptosis through the activation of p53 and PI3K/NF-κB pathways (Zhang et al., 2008a). p53 is a pro-apoptotic factor which upregulates the expression of Fas. Phosphoinositide 3 kinases (PI3K) are signal transduction enzymes involved in regulating cell proliferation, and the nuclear factor κB (NFκB) modulates the expression of genes involved in the innate and adaptive immune responses, as well as in cell survival and death (Zhang et al., 2008a).

At the intestinal level, the decreased number of viable lymphocytes in Peyer’s patches induced by restraint stress may also lead to apoptosis (Nudo et al., 2001), which seems to be dependent on the Fas/Fas ligand activation signal, as evidenced by T cells in Peyer’s patches of mice under stress by intense exercise (Krüger et al., 2009). One report suggested that glucocorticoids are the main apoptotic inducers involved in the decreased number of intestinal intraepithelial lymphocytes (Brunner et al., 2001), which is in agreement with other studies. The molecular mechanisms of glucocorticoid-induced apoptosis are highly dependent on the binding of this ligand with its receptor (Schmidt et al., 2004), which is a cytosolic ligand-dependent transcription factor. After
binding to the ligand, the glucocorticoid receptor dissociates from
the protein complex, dimerizes and translocates into the nucleus,
where it then binds to regulate the transcription of apoptotic genes
(Schumich et al., 2004).

Another presumable mechanism of lymphocyte apoptosis
induced by restraint stress relies on signals triggered by the
interaction of endogenous opioids with μ-opioid (Wang et al.,
2002) and CD95 receptors (Yin et al., 2000). Cell death caused
by the binding of endogenous opioids with CD95 (also known
as Fas or apot) or μ-opioid seems to be independent of the
HPA axis (Yin et al., 2000). The binding of CD95 with specific
agonists induces the activation of a cascade of caspases, and ulti-
mately nucleases, that results in apoptotic cell death (Yin et al.,
2000). Endogenous opioid peptides (endorphins, enkephalins
and endomorphins) play a critical modulatory role in emo-
tional stress-induced changes in the immune system (Bodnar,
2012).

An additional mechanism by which restraint stress downmod-
ulates lymphocytes is through the activation of TLR-4, which in
turn inhibits the activation of the FSK (Zhang et al., 2000b).
While inhibition of the FSK signaling pathway induces lympho-
cyte apoptosis (Yin et al., 2006), its activation inhibits the same
(Wu et al., 2000). TLR-4 can also mediate signaling that leads to
cell death through the interaction of the death domain of myeloid
differentiation factor 88 (MyD88) with the Fas associated death
domain (FADD; Haase et al., 2003).

THE INHIBITION OF MHC-II

Expression of the MHC-II glycoprotein by APC is essential for
the initiation of the immune response by CD4+ T cells (Blum et al.,
2013). A stress-induced decrease in MHC-II expression is car-
rried out by elevated levels of corticosterone (Zwilling et al., 1998)
and other hormones not associated with the HPA axis (Zwilling
et al., 1993). It seems that a higher level of corticosterone trig-
gered by restraint stress diminishes the number of IFN-γ receptors
on macrophages. Since the binding of IFN-γ to its receptor trig-
gers the signaling necessary for MHC-II expression (Zwilling et al.,
1993), a reduction in the expression of this receptor decreases the
expression of MHC-II.

ENDOGENOUS RECEPTORS CAN ATTENUATE THE STRESS-INDUCED
DOWN REGULATION OF SIgA

Assays conducted on mice under a protocol of immobilization,
in some cases with exposure to loud noise, evidenced that the
immunosuppressive influence of stress on SIgA can be attenuated
by the activation of the cannabinoid 1 receptor (CB1R; Zogbi et al.,
2012) and the peroxisome proliferator-activated receptor (PPAR)-
y (Pamphlett et al., 2007). Both the CB1R (Hill and McEwen,
2010) and PPAR-y nuclear receptors (Dubusquoy et al., 2006) have
an essential role in the modulation of colon inflammation by stress.
Cannabinoid 1 receptor is one of the most prominent recep-
tors for cannabinoids distributed in the CNS and peripherally
in immune cells. It is a G-protein coupled receptor whose
endogenous ligands are arachidonate derived lipophilic molecules,
N-arachidonylthanolamine anandamide and 2-arachidonoyl-
glycerol, which affect emotional behavior (Hill and McEwen,
2010).

Peroxisome proliferator-activated receptor-γ is a nuclear recep-
tor expressed in the colon that forms a heterodimer with the
retinoic X receptor (RXR). It is activated by natural endogenous
ligands, polyunsaturated fatty acids (PUFAs) and eicosanoids,
allowing for its heterodimerization with RXR and its binding
to the nuclear peroxisome proliferator response element (PPRE).
PPAR-γ and RXR play a central role in the regulation of inflam-
matory signaling pathways by acting on kinases and transcription
factors, such as NFκB, and by inhibiting mucosal production of
inflammatory cytokines (Dubusquoy et al., 2006). When PPAR-γ
expression in intestinal epithelial cells is induced by LPS-activated
TLR-4, it leads to the regulation of NFκB and MAPK pathways
and modulation of the inflammatory response. Up regulation of
TLR-4 expression together with impaired expression of PPAR-γ
in epithelial cells may lead to superficial colonic inflammation in
patients with ulcerative colitis.

THE UPMODULATORY EFFECTS OF STRESS

Although stress has been regarded as immunosuppressive, it
can enhance the levels of IgA (Yamamoto et al., 2009) and
CD4+/CD8+ T lymphocytes in the MLN of rats under stress by
electric foot shock or exposure to heat (Li et al., 2012). The capac-
ity of restraint stress to activate the gene expression of purine rich
element binding protein A (purA) has been reported to be responsi-
bly for priming T cells to undergo proliferation (Finst et al.,
2005). Thus, the upmodulatory effects of restraint stress hormones on
SIgA levels and on mRNA expression of pIgR should not be sur-
prising (Reyna-Garfias et al., 2010). Indeed, at the molecular level
it has been reported that glucocorticoids upmodulate the tran-
scriptional mRNA expression of pIgR via a glucocorticoid DNA
response element located in the 5'upstream region of the pIgR
gene in rat duodenum (Li et al., 1999).

Experimental studies have evidenced that stress can trigger SIgA
secretion in response to an enhanced bacterial proliferation, as
reported in feces from piglets infected with ETEC under protocols
involving weaning and short-term exposure to cold (Jones et al.,
2001). In this case, the presumable influence of stress in promoting
bacterial proliferation may be related to catecholamines, which can
make iron available to bacteria by removing it from host proteins
like transferrin and lactoferrin (Lyte et al., 2011).

Although the context of the development of the immune response
in the intestine and systemic compartments is different, the
modulatory influence of the stress response may share some
mechanisms in both cases.

CONCLUSION AND PERSPECTIVES

Gut homestasis results from neuroimmune modulation by anti-
and pro-inflammatory ILs, neurotransmitters and endocrine
hormones, all of which influence the generation of intestinal
SIgA. This immunoglobulin in turn affects intestinal inflamma-
tion and permeability, which are essential factors in the functional
integrity of the gut under stress conditions. Experimental stud-
ies with the restraint/immobilization rodent model have resulted
in an up or down modulation of SIgA levels depending on
the intensity and time of exposure to stress. In the case of
down regulation, there is an increased susceptibility to infec-
tion and intestinal inflammation. Pharmacological modulation
of the cannabinoid system and the PPAR-γ may be therapeutically useful for intestinal dysfunctions resulting from a stress-induced decrease in IgA levels. Future studies should explore the adaptation of experimental models for the evaluation of therapeutic and preventive strategies to control intestinal inflammation and/or infection in patients with high vulnerability to stress.

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