

Unraveling the link between leptin, ghrelin and different types of colitis

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Abstract

Leptin and ghrelin are hormones with a tight inverse functional connection. Their inverse association is observed not only in the modulation of metabolism but also in the interaction with the immune system. A large number of studies have been launched regarding their association with various disorders, including different types of colitis. The majority of the available literature, however, focuses on inflammatory bowel disease. The role of leptin and ghrelin appears to be aggravating in most of these studies. Concerning intestinal infections, their levels seem to depend on the presence of certain species of micro-biota. As for models of ischemic and miscellaneous colitis, both hormones seem to act protectively, although evidence deriving from human studies is needed before any safe conclusions can be made. Conclusively, it seems that available data, from *in vitro*, animal and human studies, suggest of a multifarious role for leptin and ghrelin, in the face of different triggers, which in turn cause diverse types of colitis. Bearing this in mind, gaps and loose ends are detected in the associated literature to encourage further research through which the association of leptin and ghrelin with intestinal inflammation could be clarified and expanded so that other types of colitis could also be included.

Keywords adipokines, leptin, ghrelin, colitis, inflammatory bowel disease, infection, ischemia

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Introduction

During the past decade a family of hormones, referred to as adipokines, has drawn the attention of the scientific community, with leptin being in the center of intense scientific research. Another hormone with tight functional connection with adipokines is ghrelin. Leptin and ghrelin participate in a broad spectrum of biological pathways, which in turn modulate metabolism as well as immunity. Due to their multiple roles, they have also been studied with respect to a variety of diseases of the gastrointestinal (GI) tract, including those of inflammatory or malignant nature. In this GI tract-focused repertoire, different types of colitis are also included: infectious, ischemic and drug-induced colitis as well as inflammatory bowel disease (IBD).

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Leptin

Leptin is a member of the type I cytokine superfamily and an adipokine, predominantly produced by adipocytes and to a lesser extent by the placenta, muscles, pituitary gland and gastric epithelium [1]. Leptin is considered a multi-task hormone [2-7] as well as an important regulator of inflammation [8,9] [Table 1]. Besides, in cases of a congenital leptin deficiency, a much higher incidence of infection-related deaths is observed during childhood [10].

Ghrelin

Notwithstanding the fact that the majority of its circulating levels originate from the stomach, ghrelin is also produced in the small and large intestine [11], pituitary gland, hypothalamus, lung, heart, pancreas, kidney, testis [12] and immune system cells [13]. As for its biological tasks, they seem to be antagonistic to that of leptin, even in the regulation of the immune system [Table 2] [9,11-14].

As briefly shown, the contribution of both hormones in the regulation of immunity is multifarious. Due to their functional and anatomical link with inflammation and the GI tract respectively, they have been studied with respect to

Table 1 Biological tasks of leptin

<i>Immunological tasks</i>
↑ synthetic activity and chemotaxis of macrophages
↑ synthetic activity and chemotaxis of monocytes
↑ release of ROS by neutrophils
↑ proliferation, differentiation, activation and cytotoxicity of NK
↑ maturation and ↓ apoptosis of dendritic cells
↑ Th1 response
↑ secretion of IL-1, IL-6 and TNF α by T-cells
<i>Non-immunological tasks</i>
regulation of digestion and food intake
regulation of metabolism
angiogenesis
bone metabolism
regulation of TSH expression
regulation of reproduction

ROS, Reactive Oxygen Species; NK, Natural Killer cells; Th1, T helper 1; IL, Interleukin; TNF α , Tumor Necrosis Factor alpha; TSH, Thyroid-Stimulating Hormone

Table 2 Biological tasks of ghrelin

<i>Immunological tasks</i>
↓ leptin-induced proinflammatory responses in macrophages
↓ leptin-induced proinflammatory responses in T cells
↓ TNF α secretion
↓ IL-1 β secretion
↓ IL-6 secretion
↓ IL-8 secretion
↓ adhesion of PBMC
↑ prostacyclin production by endothelial cells
<i>Non-immunological tasks</i>
stimulation of growth hormone secretion
inhibition of leptin expression in the stomach and gut
stimulation of adipogenesis in WAT
regulation of food intake

WAT, White Adipose Tissue; IL, Interleukin; TNF α , Tumor Necrosis Factor alpha; PBMC, Peripheral Blood Mononuclear Cells

a variety of GI disorders, including those of an inflammatory nature, affecting the colon. In an effort to elucidate the implication of leptin and ghrelin in colitides, the associated literature has been thoroughly reviewed so that eligible studies offering similar results could be selected and classified together so as to allow critical comparison and evidence-based conclusion.

Infectious colitis

Several studies have been performed so far, investigating the role of leptin and ghrelin in infectious colitis which, however, reported conflicting results, varying according to the type of pathogen involved i.e. bacterium, parasite etc.

Bacterial colitis

Leptin-bacterial interactions

Initial reports were suggestive of a protective role against infections of the colon since leptin could induce mucin production through direct stimulation of colonic epithelial cells and activation of leptin's receptors thus, providing a static external barrier against pathogens [15]. Further assessment of leptin in bacterial infections, however, showed that neither bacterial invasion (*Salmonella typhimurium*) [16] nor endotoxin (*Salmonella abortus equi* [17] or *Escherichia coli* [18] (endotoxin) release could influence circulating leptin levels. These data stand in sharp contrast with a study on the infection by *Clostridium difficile*, the main cause of diarrhea after prolonged administration of antibiotics. The injection of its toxin in wild type (WT) mice caused significant elevation in plasma leptin levels and in mucosal expression of its receptor, both suggestive of a direct pro-inflammatory effect of leptin on intestinal epithelial cells. Besides, in animals either genetically lacking leptin (ob/ob) or resistant to leptin's effects (db/db), the response to toxins was substantially reduced, while it was normalized in ob/ob mice but not in db/db mice upon leptin administration. The participation of leptin in the pathophysiology of intestinal secretion and inflammation in response to the enterotoxin was also rendered [19].

Ghrelin-bacterial interactions

It is well-known that the diarrhea induced by bacterial intestinal infection is mediated by the interaction of the human immune system with bacterial lipopolysaccharides, also associated with a disturbance of GI motility. In mice treated with ghrelin, this endotoxemia-induced dysmotility was improved mainly through down-regulation of the nitric oxide (NO) pathway in the GI tract [20], reduced production of the pro-inflammatory cytokines interleukin (IL) -1 β and

tumor necrosis factor alpha (TNF α) as well as augmented release of the anti-inflammatory IL-10 [21].

Parasitic colitis

Two basic animal models have been extensively used in order to “simulate” helminth and nematode infection in humans: *Nippostrongylus brasiliensis* infection in mice and rats, resembling *Ancylostoma duodenale* and *Necator americanus* infection, in humans [22] and *Heligmosomoides bakeri* in mice, simulating human nematode infection.

According to Fox, *Nippostrongylus brasiliensis* can suppress appetite through a leptin-mediated decrease in the production of neuropeptide Y within hypothalamus [23]. Infection of Balb/c mice by another nematode, *Heligmosomoides bakeri*, was found to be less pronounced in mice fed with protein deficient diet compared to those fed with protein sufficient diet. This difference was accompanied by higher levels of leptin in the first group in association with reduced expulsion of the parasite [24]. These two studies are indicative of the crucial role that leptin plays in the parasitic infectious colitis.

Inflammatory Bowel Disease (IBD)

Among the diverse metabolic manifestations of IBD and especially Crohn's disease (CD) are anorexia, malnutrition, altered body composition, and development of mesenteric white adipose tissue (mWAT) hypertrophy. Since all these phenomena are also associated with fluctuations in the production of adipokines and ghrelin [9,25,26], several studies have been performed, *in vitro* and *in vivo*. In those studies carried out in animals, experimental models of CD and ulcerative colitis (UC) have been applied. Human studies, on the other hand, included immunochemical analysis on tissue and blood specimens, from CD as well as UC patients.

The role of leptin in IBD: evidence from experimental studies

Leptin's involvement in the pathogenesis of IBD seems to implicate enterocytes, T-cells and adipocytes. Markedly elevated leptin concentrations, possibly originating from the IBD-inflamed colonic epithelium, interact with leptin's receptor, found in brush border, basolateral membrane and cytoplasm of enterocytes in human, rat, and mouse small intestine [27]. The outcome of this interaction is the activation of nuclear factor kappa B (NF- κ B), the induction of epithelial wall damage, neutrophil infiltration and formation of crypt abscesses, a characteristic histological finding in intestinal inflammation, also accompanied by cellular proliferation, differentiation and apoptosis, through an increase in butyrate transport [1].

Using experimental models of CD-similar colitis in mice -transfer of CD4(+) CD45RB(high) T-cells or administration of 2,4,6-trinitrobenzene sulfonic acid (TNBS)- it has been shown that leptin is capable of modulating immune response and chronic intestinal inflammation, being expressed on T-cells and adipose tissue [28-30]. These results have been replicated in ob/ob mice [31] as well as IBD patients [32]. As far as the potential mechanisms through which leptin exerts its proinflammatory role are concerned, studies in animals with TNBS-induced colitis provide evidence for the production of pro-inflammatory cytokines and chemokines, alterations in T-cell activation and apoptosis [33] and actions similar to those of cholecystokinin-B agonists and β 3-antagonists [34]. Using the same TNBS-based experimental model of colitis, however, anti-inflammatory properties of leptin have also been detected [35]. As for spontaneous colitis in IL-10 deficient mice, no associations with leptin, could be identified other than a modulation of intestinal lymphocyte survival [36].

Apart from the animal models already described, others with a close proximity to UC have also been used, showing that leptin may be a mediator of inflammation. Reduced production of pro-inflammatory cytokines and chemokines, alterations in T-cell activation and apoptosis as well as a lack of activator of transcription 3 (STAT3) phosphorylation were identified as potential mechanisms responsible for reduced intestinal inflammation in ob/ob mice with dextran sulfate sodium (DSS)- induced colitis [33,37]. Interestingly, these parameters were inverted with white adipose tissue (WAT) transplantation [31]. The administration of oxazolone in mice, another experimental model of UC, revealed that leptin-deficient mice were protected from developing colitis through decreased expression of transcription factors for T helper 1 and 2 polarization, both *in vitro* and *in vivo* [38]. On the contrary, the administration of leptin in rats receiving acetic acid ameliorated colitis, through mechanisms dependent on tissue neutrophils, the release of glucocorticoids [39] and capsaicin-sensitive vagal afferent fibers [40].

The role of leptin in IBD: evidence from studies in humans

Studies in humans have revealed that leptin mRNA in the mWAT was significantly upregulated in IBD patients compared to controls while no significant difference was observed among CD and UC patients [32]. Its levels in colonic lavages from IBD patients were extremely elevated possibly due to an up-regulation by IFN- γ [1]. The results, however, originating from studies assessing serum leptin levels are controversial [41-44]. In a study by Karmiris *et al*, serum leptin levels were significantly decreased in UC patients compared to CD patients or controls and associated only with body mass index (BMI) [45]. Valentini *et al*, on the other hand, showed that circulating levels of leptin were similar in IBD patients as compared to controls and well correlated with fat mass, but not with inflammatory parameters or actual disease activity [46]. On the contrary, higher leptin levels recorded in patients

with active UC in the study of Tuzun et al, were attributed to anorexia and subsequent weight loss [43].

In CD patients, due to the inflammation-mediated hypoxia affecting adipocytes, there is an increased production of leptin in the inflamed mWAT [47]. Leptin also stimulates C-reactive protein (CRP) production, which is predominantly elevated in CD compared to UC [48]. In UC, leptin, produced by the epithelial cells and intraepithelial and lamina propria T-cells, results in enhanced function of increased numbers of natural killer (NK) cells [49]. In addition, leptin levels were significantly higher in those with total involvement than in those with left-sided colitis or proctitis, while this was not the case for either the leukocyte count or CRP levels [43]. Interestingly, leptin values were higher in UC patients experiencing disease relapse within 90 days than in those without, an association that was not observed in CD [46].

Patients suffering from IBD face various complications, such as osteoporosis, anorexia and delay in puberty. It is possible that an IBD-induced weight loss leading to a decrease in circulating leptin may be an important contributor for bone mass reduction through a leptin-NF- κ B-bone resorption/formation axis [50]. Besides, leptin concentration has been shown to modulate the loss in total and femoral neck bone mineral density values in physically active, healthy, older women [51]. As far as anorexia is concerned, leptin has been associated with prolonged anorexia in IBD patients [43,52], although there is lack of unanimity on the subject as the rate of weight loss in these patients represents a major confounding factor [42]. An association between leptin, anorexia and weight loss was also observed in animals with TNBS-induced, CD-like colitis [53,54], but not in IL-2 deficient mice with a UC-like colitis [55]. Finally, as shown by a recent study in mice with DSS-induced colitis, a UC-similar animal model, the delay in puberty observed in IBD is beyond what would be expected from decreases in leptin levels [56].

In IBD, increased levels of TNF α are present and this is why anti-TNF α agents have been successfully used for therapeutic purposes. Although TNF α is a crucial contributor to leptin's dysregulation through the NF- κ B pathway [57], the impact in its post-treatment levels remains obscure. Once a neutralizing monoclonal antibody against TNF α was administered to IL-2 deficient mice, an animal model that resembles UC, elevated serum leptin concentrations dropped to levels that were similar or greater to those recorded in control mice [58]. In humans, serum leptin was not affected by infliximab therapy [59]. In another study, treatment of CD patients with infliximab significantly increased leptinaemia [60]. As far as the use of immunosuppressant medicine in IBD treatment is concerned, methotrexate seems to reduce the production of leptin by mWAT in rats with TNBS-induced colitis [61]. Although the impact of corticosteroid treatment for IBD in leptin levels has not been assessed directly, it was found that corticotropin-releasing hormone deficiency is associated with elevated leptin serum levels in TNBS-induced colitis [62]. Finally, exclusive enteral feeding reduces inflammation and improves well being, nutrition and growth in children with

active CD, but serum leptin as a marker of fat storage shows no sustainable change [63].

Ghrelin's role in IBD: evidence from experimental studies

The mechanism through which ghrelin is involved in IBD is far from clear. Hypotheses regarding its implication in IBD have relied on its role as an antagonist of leptin's effects on the immune system. In this direction several studies have combined *in vitro* experiments with observations on animal models. Some studies describe a pro-, while others an anti-inflammatory effect.

As far as CD-similar colitis is concerned, Zhao et al found that ghrelin and ghrelin receptor mRNA expression were up-regulated in TNBS-induced colitis in mice and that its participation in colonic inflammation may be through the activation of the NF- κ B pathway and the induction of IL-8 production, as shown *in vitro* [64]. Conversely, Gonzalez-Rey et al reported that after the administration of ghrelin in TNBS colitis, the clinical and histopathologic severity of the disease was ameliorated. This therapeutic effect was also associated with a suppression of inflammatory response and a raise in IL-10 levels [65]. These data are in agreement with those reported by Konturek et al who found that exogenous ghrelin in TNBS-induced colitis accelerated healing of colonic lesions via increased release of NO and prostaglandin E2 (PGE2) [66]. Furthermore, in rats with indomethacin-induced colitis, a decrease in central neurons, projecting to the enteric nervous system, was accompanied by an increase in ghrelin levels [67]. According to the authors this increase represented a compensatory mechanism since *in vitro* ghrelin could induce a marked proliferation of these neurons [67].

Regarding UC-similar colitis, De Smet et al reported that absence of ghrelin decreased the disease activity index and delayed neutrophil infiltration in chronic DSS-induced colitis in comparison with controls [68]. Besides, endogenous ghrelin enhanced the inflammatory process, while its exogenous administration aggravated DSS-induced colitis [69]. On the other hand, in *Citrobacter rodentium*-induced colitis a raise in ghrelin's expression was reported in the peak and late stages of the infection accompanied by an induction of regulatory T-cell pathways in protection from the inflammation [70].

Ghrelin's role in IBD: evidence from human studies

CD patients bear T-cells over-expressing ghrelin receptor mRNA, with a lower reactivity. Similarly, colonic mucosa in active CD has been found to express high levels of ghrelin receptor compared to controls. In addition, colonic mucosal and serum ghrelin mRNA levels seem to be higher in IBD patients compared to controls [71]. In three separate studies [72-74], circulating ghrelin was higher in patients with active IBD compared to patients in remission and healthy controls, while in the study of Karmiris et al no correlation with disease activity could be established [45]. Based on recent data,

however, the low obestatin/ghrelin ratio has been proposed as a more reliable candidate marker of disease activity, in IBD [72]. Interestingly, the levels of ghrelin are higher in male than female patients, higher in ileal compared to colonic CD and correlate positively with lower leptin levels in IBD patients compared to controls [45]. Furthermore, the upregulated ghrelin showed a negative association with IGF-1 and bioelectrical impedance analysis, body composition, and anthropometric assessments [73]. As for des-acylated ghrelin, its assessment in IBD might be more beneficial, compared to the acylated form [75].

Ischemic colitis

Ischemic colitis has much in resemblance with lesions that occur after gut ischemia-reperfusion (I/R) injury. In absence of human studies, the use of animal-models can lead to helpful guidance in research.

Leptin in I/R injury

Leptin has a time-dependent response to intestinal I/R injury and it may participate as anti-inflammatory cytokine [76]. Its levels in serum and WAT, as well as its mRNA expression in WAT, vary according to different post-I/R injury time points. The release of leptin is decreased at an early stage during reperfusion, in contrast to other inflammatory cytokines [77], due to the destructive action of free radicals on circulating proteins. As reperfusion progresses, serum leptin levels increase and the WAT expresses more leptin mRNA, under the control of a possible feedback mechanism for compensation and protection. This mechanism is capable of causing a significant increase in WAT leptin levels, which is also suggestive of a slow but constant protective role for leptin against inflammatory damage in the whole process of intestinal I/R injury [78]. In addition, pre-treatment with leptin prevents gut mucosal damage and improves intestinal regeneration following intestinal I/R [79]. The underlying mechanism could be the modification of lipid peroxidation, since administration of leptin results in significantly decreased tissue malondialdehyde (MDA) levels, increased NO production and release in mesenteric vessels, all playing a significant role in the maintenance of mucosal integrity. Based on these observations, some authors suggested the use of leptin in mesenteric occlusive diseases, as it appears to act protectively against I/R injuries [80].

Ghrelin in I/R injury

Ghrelin levels were significantly reduced after I/R in rats, which had undergone artery occlusion, while its intravenous administration inhibited pro-inflammatory cytokine release, reduced neutrophil infiltration, ameliorated intestinal barrier dysfunction, attenuated organ injury, and improved overall

survival after gut I/R. Its intra-cerebroventricular injection also exerted a similar protective effect. Besides, the administration of a ghrelin receptor antagonist worsened gut I/R-induced organ injury and mortality. Moreover, it was shown, by means of vagotomy, that these effects of ghrelin are mediated by activation of the cholinergic anti-inflammatory pathway [81]. As a result; ghrelin seems to exhibit a protective role against this animal model of ischemic colitis.

Drug-induced colitis

Several drugs have been incriminated for the induction of persistent colitis. An example that has been investigated in accordance with leptin is methotrexate-induced acute colitis in Sprague-Dawley rats. Luminal leptin could act as an intestinal chloride secretagogue, particularly when present at elevated concentrations in the setting of colonic inflammation. Responsible for this phenomenon are, at least in part, the activation of mitogen-activated protein kinase (MAPK) and the phosphorylation of extracellular signal regulated kinase (ERK) and Akt1. Apical leptin induces chloride secretion by intestinal epithelial cells resulting in secretory diarrhea after administration of chemotherapeutic agents [82].

Miscellaneous colitis

An animal model, combining ischemic and infectious phenomena, is that of cecal ligation and puncture (CLP). Small animals, mainly mice and rats, are operated and their cecum is ligated below the ileocecal valve and then punctured with selected gauge needle. This technique causes ischemia of the cecum and, finally, sepsis [83].

Leptin and CLP

In animals subjected to CLP, it was found that leptin-deficient and leptin-resistant mice exhibited more intense inflammatory and thrombogenic responses in the gut microcirculation during sepsis compared to WT mice [84]. Besides, leptin decreased sepsis-induced intestinal injury by controlling the tissue levels of heart-type fatty acid-binding protein, a useful marker for organ dysfunction [85].

Ghrelin and CLP

In an animal study applying the CLP technique, it was shown that although ghrelin levels decreased during early and late stages of sepsis, its receptor was markedly elevated and, as a result, the vascular sensitivity to ghrelin stimulation was increased in the hyperdynamic phase of sepsis [86]. In the same hyperdynamic phase the administration of exogenous ghrelin

was found to improve organ blood flow by down-regulating endothelin-1, through a NF- κ B-dependent pathway [87], and to ameliorate gut barrier dysfunction by a central ghrelin receptor-mediated vagus nerve activation [88,89]. A study combining CLP with radiation proposed a beneficial role for ghrelin, through rebalance of the deregulated sympathetic/parasympathetic nervous systems [90].

Conclusions-directions for future studies

The major goal of the present review was the collection and classified presentation of available data on the role of leptin and ghrelin in different types of colitis. The motivation for this kind of research originated mainly from the fact that these hormones are tightly and functionally linked not only with each other but also with the immune system. In particular, leptin –the most studied adipokine- and ghrelin -its “partner in crime”- seem to play an important role in the inflammatory downstream and the angiogenetic cascade [91-93]. Since both phenomena are exerted in colitides, several

studies have emerged attempting to examine the role of both hormones in different types of colitis [Tables 3 and 4], using different approaches i.e. *in vitro* research, studies in animal or human populations. Due to the great diversity of the available studies, a mosaic of often conflicting evidence has emerged, thus raising confusion regarding the actual role of leptin and ghrelin in colitis. For this reason, in the present review attempt has been made so that common patterns, gaps and loose ends could be identified in the associated literature, in order to allow critical comparison and evidence-based conclusion.

In infectious colitis, available data are suggestive of interplay between leptin, ghrelin and microorganisms, although the results from related studies are controversial. As far as leptin is concerned, the controversy may be due to the diversity of pathogens and their ability to induce inflammation and immune responses of different extent and severity. As for ghrelin, although its role seems to be protective as it attenuates excessive inflammation caused by endotoxins from enteric pathogens, more studies are required to consolidate this single study-based observation.

In view of the IBD-associated leptin or ghrelin-focused studies, they represent the vast majority of the literature on

Table 3 Studies investigating the association of leptin and ghrelin with different types of colitis either in experimental settings (*in vitro/animal*) or in humans

Type of colitis	Leptin		Ghrelin	
	<i>in vitro/ animal</i>	human	<i>in vitro/ animal</i>	human
Infectious colitis	√	√	√	-
<i>Pseudomembranous colitis †</i>	√	-	-	-
IBD	√	√	√	√
Ischemic colitis	√	-	√	-
Drug-induced colitis	√	-	-	-
Miscellaneous colitis	√	-	√	-
CMV-induced colitis	-	-	-	-
Diversion colitis	-	-	-	-
Eosinophilic colitis	-	-	-	-
GVHD-associated colitis	-	-	-	-
Laxative-induced colitis	-	-	-	-
Mastocytic colitis	-	-	-	-
Microscopic colitis	-	-	-	-
Plasmacytoma-associated colitis	-	-	-	-
Radiation colitis	-	-	-	-
Segmental colitis	-	-	-	-

√/-, available/non-available data; †, mentioned separately due to its distinct characteristics; IBD, Inflammatory Bowel Disease; CMV, Cytomegalovirus; GVHD, Graft-Versus-Host Disease

Table 4 The “tasks” of leptin and ghrelin with respect to the cause of colitis

Cause of colitis	Leptin	Ghrelin
Ischemia	P	P
Infection	D	P
Auto-immunity	A	A
Immunosuppression	A	NAD

P, Protective; NAD, Non-Available Data D, Diverse; A, Aggravating

the two hormones and colitides. In an effort to specify the role played by leptin and ghrelin in the pathogenesis of IBD and IBD-associated manifestations such as weight loss and anorexia, different animal models have been used [Table 5]. The results from these experimental models although lacking unanimity may represent different IBD subpopulations [94], bearing different characteristics (i.e., different trigger pathogen, presence of genetic predisposition, different disease duration, natural history, different therapy). Similarly, data obtained from human studies are rather conflicting, with the majority, however, favoring an aggravating role for both hormones in IBD. At this point, it has to be underlined that more attention should be drawn into the impact of different agents used for therapeutic purposes in IBD, as available data are either conflicting (i.e. anti-TNF α therapy) or scarce, as in the case of corticosteroids.

To simulate ischemic colitis in humans, the experimental model of intestinal I/R injury has been applied in animals. Interestingly the use of this animal model has revealed a protective as well as therapeutic potential of both leptin

Table 5 The role of leptin and ghrelin in different models of IBD colitis

IBD Colitis	Leptin	Ghrelin
DSS	A	A
TNBS	P/A	P/A
transfer of CD4+CD45RB	A	NAD
Oxazolone	A	NAD
acetic acid	P	NAD
Indomethacin	NAD	A
IL-10-deficiency	NS	NAD
IL-2-deficiency	A	NAD
Citrobacter rodentium	NAD	P
Human IBD	A	A

IBD, Inflammatory Bowel Disease; TNBS, 2,4,6-Trinitrobenzene Sulfonic acid; DSS, Dextran Sulfate Sodium; IL, Interleukin; P, Protective Role; A, Aggravating Role; NS, Non Significant Role; NAD, Non-Available Data

and ghrelin, as the initial damage of intestinal mucosa, corresponding to low leptin and ghrelin levels, is fully reversed after administration of either hormone. Based on this observation, it would perhaps be helpful to assess the levels of leptin and ghrelin in patients with ischemic colitis or those undergoing surgery during which, intestinal blood flow is temporarily blocked.

Another experimental model combining the onset of both ischemic and inflammatory phenomena in the colon, is CLP. The variations of leptin and ghrelin as well as the effect of these variations upon other substances are once more indicative of a protective effect during CLP, thus offering additional evidence regarding the tasks performed by these hormones during each individual disorder –inflammatory, ischemic.

In all, it seems that the available literature on leptin, ghrelin and colitides, is supportive of the notion that both hormones are key components of the biological pathways, triggered during the onset of such disorders. Interestingly, the actual biological effect of leptin and ghrelin varies depending on the type of colitis and this is why research should be expanded so as to also include types of colitis that have not been previously investigated [Table 3]. Ongoing research should also clarify the underlying mechanisms through which leptin and ghrelin exert their effects and at the same time look for potential implications for the diagnosis and therapy of colitis.

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