

Traumatic Brain Injury and the Gastrointestinal Tract: The Role of Female Sexual Hormones

Zakieh Keshavarzi^{a, b}, Amir R. Afshari^c, Nasibeh Mohammadzadeh^d, Masoud Mohebbi^{e, f},
Moein Mohebbi^e, Hamid Mollazadeh^{a, b, g}

Abstract

Traumatic brain injury (TBI) is an important public health problem which can lead to several complications like gastrointestinal dysfunction. Patients with TBI often suffer from gastrointestinal dysfunctions such as enteral feeding intolerance. Gastric ulceration is induced by various forms of stress like surgery, ischemia and trauma. TBI causes a delayed but significant decrease in intestinal contractile activity in the ileum leading to delayed transport. The association between severity of brain injury and enteral feeding intolerance suggests a strong link between the central nervous system and the non-functional gut. The results of recent basic and clinical studies revealed the beneficial effects of estrogen and progesterone hormones in the treatment of gastrointestinal dysfunction. Females have more resistance to stress and fewer gastrointestinal lesions occur in females as compared to males. Sex steroid hormones have sparked interest as possible neuroprotective agents after traumatic injury and many studies have been done on this subject. This article reviews the literature related to some possible physiological effects of female sexual hormones on the gastrointestinal tract following TBI.

Keywords: Female sexual hormones; Traumatic brain injury; Gastrointestinal tract; Estrogen; Progesterone

Introduction

Traumatic brain injury (TBI) is a noteworthy general medical

problem which is regularly joined by hemorrhagic shock. TBI continues to be the most common cause of death for young people and is considered as a significant source of morbidity and death for all ages in developed countries [1]. Current estimates suggest that as many as 5.3 million Americans live with long-term disabilities related to TBI [2]. TBI-induced biomechanical and neurochemical mediated damage, often lead to deficit in cognitive, neuropsychiatric, and physical functions [3-5]. Various forms of traumatic injury are seen worldwide and represent an epidemic condition affecting people of different countries regardless of their level of economic development. Among patients with TBI, gastrointestinal (GI) dysfunction occurs frequently. The association between the severity of brain injury and the intolerance of enteral feeding suggests a strong link between the central nervous system and the non-functional gut [6, 7]. More than 50% of patients with severe head injuries do not tolerate enteral feedings [8]. The intolerance is presented by vomiting, abdominal distention, delayed gastric emptying [9], esophageal reflux [10], and decreased intestinal peristalsis indicating that GI dysfunction is a common phenomenon following TBI [11].

Usually, acute gastric dilation and postponed gastric emptying are commonly seen in patients with intracranial hypertension, and correction of these gastric abnormalities can help the patients with brain injuries [3]. GI, includes motility abnormality and mucosal alterations that can lead to ulceration, inflammation, and increased gut permeability [12, 13].

It is now apparent that sex alters the incidence and outcome of ischemic and traumatic brain injury. Several studies on TBI patients have demonstrated that female sex steroids play neuroprotective roles such as reducing cerebral edema, preventing neuronal loss, and improving functional outcomes [14-16].

Sex hormones, especially estrogens, play a significant role in GI physiology and pathology including regulation of motor and sensory function [17, 18]. In some studies, it has been reported that steroid hormones, especially progesterone and estrogen, have noticeable effects on the gastric motility and secretions [19] and are also involved in the pathogenesis of some functional disorders of the gut [20].

In recent three decades, numerous researchers have tried to discover the effects of sexual hormones on GI tract following TBI. Based on the female predominance as well as the connection between irritable bowel syndrome (IBS) symptoms and hormonal status, several models have been used to examine the role of sex hormones in GI tract functions including differences in GI symptoms during different phases of the menstrual cycle, in pre- and post-menopausal women, during pregnancy,

Manuscript submitted October 31, 2017, accepted November 15, 2017

^aDepartment of Physiology and Pharmacology, School of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran

^bNatural Products and Medicinal Plants Research Center, North Khorasan University of Medical Sciences, Bojnurd, Iran

^cDepartment of Pharmacology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

^dNeuroscience Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

^eDepartment of Internal Medicine, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran

^fEndocrine Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

^gCorresponding Author: Hamid Mollazadeh, Department of Physiology and Pharmacology, School of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran. Email: hamidmollazadeh1984@gmail.com

doi: <https://doi.org/10.14740/jem466w>

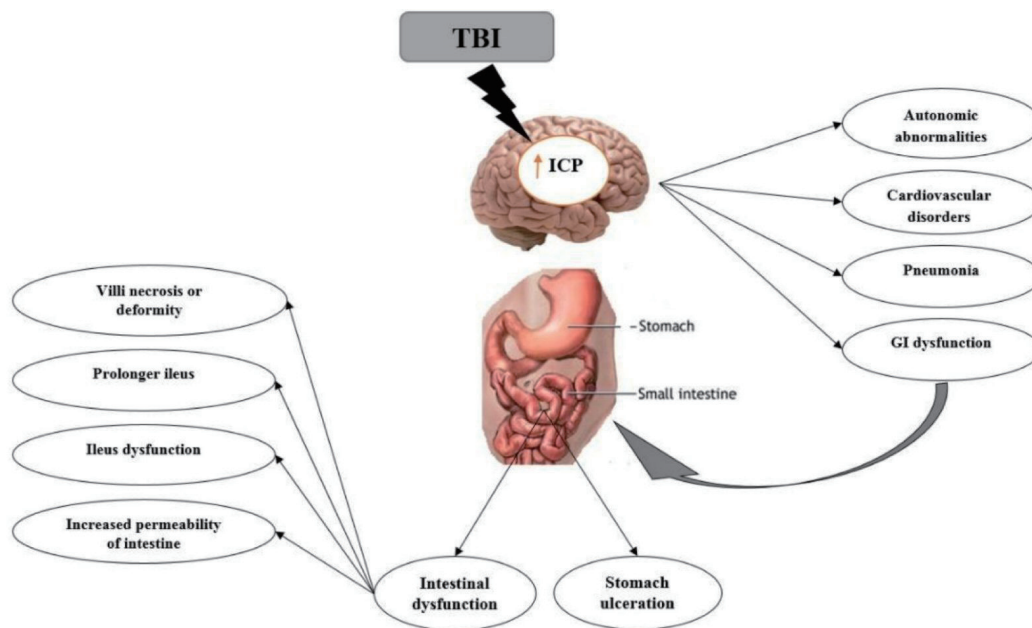


Figure 1. Brain-gut interactions. Some gastrointestinal dysfunction following TBI declared.

and following hormonal treatment or oophorectomy. Consequently, a considerable deal of research was done and compelling evidence indicates sex and gender contribute to the epidemiology, symptomatology, pathophysiology, and treatment outcome. Here, the effects of female sexual hormones on GI tract following TBI were reviewed.

Methods

Online scientific databases including Medline, PubMed, Science Direct, Scopus, and Google Scholar websites were checked using the terms TBI, cerebral ischemia, GI dysfunction, sex hormones, estrogen and progesterone to identify studies about the effects of female sexual hormones on GI tract following TBI.

TBI and GI Problems

TBI can lead to significant clinical sequel including pneumonia, cardiovascular disorders, autonomic abnormalities, intestinal dysfunction, multi-system organ failure [21, 22] (e.g. stomach ulceration and gastritis (Cushing's ulcer), prolonged ileus and other motility problems) and most significantly, impairment of gut barrier function [9, 23]. GI dysfunction frequently occurs in patients with TBI and some GI tract disorders experienced during acute stages of stroke are usually considered as stress-induced injuries [24].

Bowel dysfunction is a common complaint among patients with brain damage due to stroke and TBI [25]. Injuries in the brain and its connections can modify individuals' intestinal functioning. Examples of these injuries comprise stroke (cerebrovascular attack (CVA)) and TBI. Brain injury can affect fecal peristalsis and deletion. Immobility, spasticity, muscle

weakness, loss of independent bathroom use and the use of some drugs can contribute to bowel dysfunction [25-27].

In one study, the terminal ileum was removed 6 h following both TBI and sham operation for histologic analysis using hematoxylin and eosin staining. Sham-operated animals had normal-appearing villi with consistent villous height. The histologic appearance of intestinal specimens from TBI animals was notable for marked blunting of intestinal villi with architectural deformity and intestinal villi necrosis [28].

Increased intracranial pressure (ICP) induces immense increases in sympathetic activity, which is responsible for several of the peripheral systemic and GI symptoms [4]. Increased ICP may cause changes in GI motility, water and electrolyte absorption. Studies have examined different means of feeding to brain injured patients as strategies to decrease GI symptoms [29, 30].

GI disturbances such as mucosal alterations and motility abnormalities can cause ulceration, inflammation, and increased gut permeability [9, 13]. The majority of patients with temperate to severe TBI have upper GI intolerance in the first few weeks after injury [31, 32]. Feighery et al have demonstrated blunting of intestinal villi and increased intestinal permeability, 6 h following TBI in rats [23] (Fig. 1).

Motility disorders in brain injured patients include gastroesophageal reflux related to reduced tone in the lower esophageal sphincter and deferred gastric emptying [8, 9]. Some studies showed that moderate TBI with no substantial mucosal damage causes a delayed significant decrease in intestinal contractile activity that occurs primarily in the ileum due to decreased contraction amplitude. In addition, intestinal transit was decreased after TBI [33]. Also, studies demonstrated that TBI induces a decrease in both intestinal contractility and transit and an increase in inflammation in the intestinal smooth muscle suggesting that motility is inhibited in the small intes-

tine due to inflammatory damage secondary to the brain injury. Inflammation of the mucosal layer of the small intestine, leading to increased permeability, has been demonstrated suggesting inflammatory damage to the small intestine [13, 34]. Hang et al have also shown histopathologic changes and increased permeability in gut as early as 2 h, peaking at 24 h following TBI [13].

In a study, contractile activity was examined in ileal segments of the small intestine in sham and TBI groups 1, 3 and 7 days post surgery. This study showed that motility in the small intestine is also affected by TBI. Contractile dysfunction was mainly limited to the distal small intestine. Contractile activity was considerably decreased in the TBI group 7 days post injury compared to the sham group. TBI was scanned using a computed tomography (CT) scanner and volume loss due to TBI was calculated. Following TBI, there is neuronal loss due to necrosis and apoptosis in the damaged area. This is followed by a delayed secondary loss of neurons in the area surrounding the injury site due to apoptosis [33].

Decreased intestinal contractile activity may contribute to the symptoms of vomiting and abdominal distension described in TBI patients. Altered contractile activity and motility in the small intestine were associated with increased inflammation in the intestinal smooth muscle [33].

Sex Hormones and TBI

The majority of available data suggest that 17 β -estradiol (E2) protects against apoptotic cell death, and this is maybe mediated through mitochondrial anti-apoptotic mechanisms, as some studies investigating estrogen in central nervous system (CNS) trauma have reported favorable modulation of Bcl family proteins [35]. Sex steroid hormones have sparked interest as possible therapeutic agents following TBI. Estrogen or progesterone alone or a combination of these two hormones, reduces brain edema following TBI [36, 37]. E2 or G-protein coupled estrogen receptor 1 (GPER)-specific agonist, G-1, increases cell survival and decreases neuronal degeneration, apoptosis, and astrogliosis. The anti-inflammatory properties of estrogen or progesterone alone or in combination reduce brain edema and permeability of the blood-brain barrier following TBI [36], and these effects were associated with changes in pro-inflammatory cytokines concentrations [38, 39]. Among numerous interactions between sex hormones and other neurotransmitters, estrogen interactions and serotonin and corticotropin-releasing factor (CRF) signaling systems play a pivotal role [40, 41]. Estrogens can also modulate neuro-immune interactions triggered by stress via the brain-gut axis [42].

TBI, GI Tract and Sex Hormones

Numerous studies have suggested the protection role of estrogen and progesterone in the development of a variety of diseases, including cardiovascular diseases [43], cerebral damage, fatality [44], and osteoporosis [43, 45, 46]. Also, previous studies have shown that peptic ulcer is more common in men

than women. Therefore, it is rational to infer that, similar to other organs, E2 and progesterone may have protective effects in GI tract, and E2 plays a protecting role against acid-peptic duodenal injury in females [47]. Steroid hormones, in particular progesterone and estrogen, have effects on the gastric motility and secretions [19], and are also involved in the pathogenesis of some functional disorders in the gut [20]. This might provide a sensible explanation for the clinically observed gender difference in the prevalence of duodenal ulcer (Table 1 [48-62]).

Keshavarzi et al have shown that protective effect of estradiol and a combination of E2 and progesterone (P4) against mucosal damage after TBI might be mediated by inhibition of pepsin secretion. In this study, gastric pepsin levels were increased in sham-operated animals as compared to intact group. Gastric pepsin levels were considerably lower in E2 alone and E2 and P4-treated rats as compared to vehicle-treated group. These results suggest that the possible protective effect of estradiol and E2-P4 combination against mucosal injury after TBI might be mediated by inhibition of pepsin secretion [63].

The results demonstrated that a reduction of pepsin secretion in pregnancy, when the concentration of ovarian hormones is high [64], a decrease in pepsin secretion induced by ovarian hormones in rats [65], inhibition of pepsin secretion in ovariectomized (OVX) rats by estradiol [66], and an increase in pepsin secretion followed by gastric mucosal inflammation after stress [67].

Peptic duodenal and gastric ulcers raise serious health problems and significant economic burden worldwide [1]. Gender differences in duodenal ulcer have been clinically observed for many years; however, little is known about the causes and underlying mechanisms [68-70]. Due to the fact that estrogen is a hormone mainly present in the female body and, in comparison to men, women of reproductive ages also experience a significantly lower occurrence of duodenal ulcer [71, 72]. Studies have shown that pregnant women or women taking oral contraceptive pills (estrogen/progesterone compounds) exhibited a reduced frequency of duodenal ulcer [73]. Furthermore, duodenal ulcer runs a more serious course in postmenopausal than premenopausal women [47]. Finally, clinical observations showing that pregnant women with high estrogen levels of placental origin hardly develop ulcers and women taking oral contraceptives experience a significantly decreased incidence of ulcers [73], strongly support the protective role of estrogen in the duodenum [3].

Keshavarzi and Khaksari examined the alteration of gastric function and barrier function of GI tract following diffuse brain injury in different ovarian hormone status. In this study, diffuse TBI was induced by Marmarou's method. Rats were randomly assigned into 10 groups: Intact, sham + ovariectomized female (OVX), TBI, TBI + OVX, vehicle, estradiol (E2), progesterone (P), E2 + P, estrogen receptor alpha agonist and estrogen receptor beta agonist (DPN). Endotoxin levels were measured using enzyme-linked immunosorbent assay method. They found that pretreatment with sexual steroids is not useful in the treatment of GI dysfunction induced by TBI and treatment with all sexual female hormones worsened gastric tissue condition. Furthermore, the applied weight was not enough for releasing of endotoxin. It seems that estrogen re-

Table 1. The Relationships Between Traumatic Brain Injury, Sex Hormones Status and Gastrointestinal Tract and Their Underlying Mechanisms

| Compound of interest | Model of study | Underlying mechanisms of the observed results | References |
|--------------------------------|---|---|------------|
| ICH | Change in gastric volume, following an ICP increase to 20, 40 and 60 mm Hg, respectively. | ICH decreases the gastric volume by increasing gastric tonus in anesthetized rats. | [48] |
| ICH | Amplitude and frequency of gastric contractions after ICH. | An increase in ICP increases the strength of gastric contractions. Increased amplitudes, without frequency changes. | [49] |
| IBS | Measurement of lower level of luteinizing hormone in middle-aged men & elevated level of sex hormone-binding globulin in young men. | Generally more prevalent diarrhea (compared to women with IBS). | [50, 51] |
| Hormone replacement therapy | Check the estrogen and progesterone supplementation | Increased prevalence of IBS in postmenopausal women during HRT, Prolongation of IBS symptoms to a later. | [52] |
| Late luteal phase (pre menses) | Evaluation of estrogen and progesterone levels | Exacerbation of bowel symptoms. Increased bloating. | [53, 54] |
| Menstruation (menses) | Study of lowest levels of estrogen and progesterone | Exacerbation of bowel symptoms. Increased abdominal pain/discomfort. | [55-57] |
| Pregnancy | Physiological hyper- estrogenemia and hyperprolactinemia | Decreased pain sensitivity and alleviation of many chronic pain syndromes. Exacerbation of constipation (prolonged gastrointestinal transit). | [58, 59] |
| Menopause | Measurement of reduction in ovarian hormones | High prevalence of constipation and somatic discomfort syndromes. | [60-62] |

IBS: irritable bowel syndrome; HRT: hormone replacement therapy; ICH: intracranial hypertension; ICP: intracranial pressure.

duced endotoxin levels via estrogen beta receptor [74].

The role of gonadal hormones, in symptomatology and pathophysiology of IBS is being recognized based on the female predominance as well as the relation between IBS symptoms and hormonal status during menstrual cycle phases, pregnancy or menopause [75]. IBS is a GI sensory-motor disorder characterized by abdominal pain or discomfort linked with changes in bowel habits [59]. Li et al noted that the expression of 5-HT₃ receptor mRNA was considerably decreased in rats after E₂ + P treatment as compared to sham-treated ovariectomized rats that often coexist with IBS [76]. Women with IBS are likely to experience an increase in abdominal pain and bowel symptoms at a time of declining or low ovarian-hormone levels. Dourado et al demonstrated that, in patients with brain injury because of stroke and TBI, bowel dysfunction is frequent, especially in patients with motor difficulties communication impairment and memory disorder [25]. Furthermore, it was shown that the prevalence of IBS subtypes vary according to gender [77]. Women with IBS, compared to male patients, are more likely to report constipation, bloating, severe abdominal pain, and feeling of incomplete evacuation, while men with IBS more often complain of diarrhea-associated symptoms [77-79]. The results of epidemiological studies and clinical views confirm significant effect of sex and gender differences on IBS prevalence and symptomatology. Moreover, a growing number of clinical and experimental studies strongly support the crucial role of sex hormones in the regenerative mechanisms of the brain-gut-microbiota axis involved in

the pathophysiology of IBS. Sex hormones may influence on the peripheral and central regulatory mechanisms such as contributing the alterations in stress reaction, visceral sensitivity and motility, intestinal barrier function, and immune activation of intestinal mucosa [63].

The relationships between gonadal hormones and somatic and visceral pain sensibility in humans are complex. E₂ and progesterone may play both anti-nociceptive and pro-nociceptive roles, depending on their relative density as well as the duration of presentation. The results of a study done by Khaksari et al have shown that progesterone has no effect on intestinal cytokines, and when used in combination with estradiol, the effect of estradiol was also eliminated. They concluded that progesterone may interfere with the action of estrogen on the levels of intestinal cytokines [74].

Research analyzing post-TBI intestines and serum has shown the importance of a local inflammatory reaction, mediated in part by an increase in intestinal concentrations of cytokines such as tumor necrosis factor (TNF)- α and interleukin (IL)-6 [80]. Studies have shown that increased levels of TNF- α as well as IL-1 β and IL-6 production [81] associated with higher intestinal permeability following TBI [82, 83]. It is now obvious that gender alters the outcome of TBI.

Previous studies showed that pregnancy can decrease the symptoms of rheumatoid arthritis and inflammatory bowel disease [84], and estradiol can reduce the production of inflammatory cytokines such as IL-6 and TNF- α [85]. Estradiol has been found to have anti-inflammatory activity in GI, through

reduction of neutrophil leakage and cytokine production in colitis [86]. Estradiol can also inhibit cytokine production via an NF κ B-dependent mechanism [87]. Mizushima et al have reported that administration of estradiol to rats after a period of shock/hemorrhage decreased plasma levels of IL-6 and improved cardiac and liver function [88]. Also, estradiol has been shown to reduce intestinal levels of IL-6 following trauma-hemorrhage [89]. TNF- α and IL-6 form a complete feedback loop whereby TNF- α induces IL-6 synthesis and IL-6, in turn, inhibits TNF- α production.

Telleria et al reported that progesterone can efficiently inhibit the expression of IL-6 in the corpus luteum [90]. Lan et al revealed that progesterone reduced the consistency of IL-1 β mRNA [91], and Pioli et al reported that estradiol decreased IL-8 production in monocytes. It has been also shown that estrogen increased intestinal levels of IL-6 and IL-1 β following TBI [85]. Hang et al have shown that intestinal levels of TNF- α and IL-6 considerably increased after brain trauma [80]. Also, Brzozowski et al have shown that serum IL-1 β increased after ischemia-reperfusion damage [92]. The results of Khaksari et al have shown that estradiol decreased intestinal levels of TNF- α , progesterone decreased serum levels of TNF- α and estrogen influenced intestinal levels of pro-inflammatory cytokines, especially TNF- α , which is probably mediated through estrogen receptor [93]. Chen et al found that intestinal levels of TNF- α , IL-1 β , and IL-6 significantly increased following brain trauma [82]. Khaksari et al have shown that TBI induced an increase in intestinal-1 β , IL-6, and TNF- α levels as well as serum levels of IL-1 β [93].

Other studies have shown that levels of TNF- α in intestinal segments exposed to acidosis and hypoxia are higher in men than women. Also, menopause is thought to be linked with increased production of inflammatory cytokines like ILs and TNF- α , as increased levels of inflammatory cytokines have been seen in postmenopausal women [94].

Some studies have shown that the beneficial effects of 17 β -estradiol on inflammatory cytokine production following trauma hemorrhage are dependent on the tissue compartment as this effect is mediated by endoplasmic reticulum (ER) in Kupffer cells and splenic macrophages and by ER- β in alveolar macrophages [95].

Some of the possible mechanisms underlying the activity of these hormones against ulcerative effects of traumatic brain injuries are: maintaining calcitonin gene relevant peptide (CGRP) level, that has the protective role in mucosal injuries [96], over-production of mucosal secretion by gastric mucosal [17], the increase of bicarbonate secretion from gastric mucosal like to the increased secretion of bicarbonate from duodenum mucosal by estrogen [47], alteration of hypothalamic pituitary axis (HPA) is response to stress [86], the reduction of vascular epidermal growth factor (VEGF) secretion in stomach [97], inhibition of oxidative stress [98], modulation of nitric oxide (NO) production [99], regulation of autonomic nervous system activity [100], interaction with melatonin in gastric mucosal level [101], promotion of angiogenesis [102], reduction of gastric inflammation by decreasing TNF- α release [103], and inhibition of apoptosis due to ischemia [104].

In the present review, we studied the effects of estrogen and progesterone on GI tract following TBI. The results of

epidemiological and clinical studies showed the significant role of female sexual hormones in sex and gender differences. Furthermore, a growing number of clinical and experimental studies strongly support the crucial role of sex hormones in regulation of the brain-gut axis [105]. Some discrepancies in the results may result from different experimental conditions or heterogeneous groups of patients (e.g. different age, different status), but they also reflect the very complex nature of sex hormone actions.

Conclusions

In summary, TBI can lead to several physiological complications including chronic GI dysfunction and may cause a delayed but significant reduction of intestinal contractile activity mainly in the distal intestine. Specifically, TBI can induce an increase in intestinal permeability, which may lead to bacterial translocation, sepsis, and finally multi-system organ failure. However, the exact mechanism of increased intestinal permeability following TBI is unknown.

According to the available data, that administration of estrogen alone or co-administration of estrogen and progesterone has an inhibitory effect on the pepsin production. These results suggest that the possible protecting effect of ovarian hormones against mucosal injury induced by TBI is mediated by inhibition of pepsin secretion and not via acid secretion. However, the real fluctuations in ovarian hormones may influence peripheral and central regulatory mechanisms of the brain-gut axis involved in the pathophysiology of IBS contributing to the alterations in visceral sensibility motility, intestinal barrier function, and immune activation of intestinal mucosa.

Therefore, female sexual hormones can have some effects on the GI tract following TBI. However, further investigations (both clinical and experimental) are required to reveal the exact perspectives of their constituents effects.

Acknowledgments

This study was partially supported by the North Khorasan University of Medical Sciences.

Conflict of Interest

The authors declare no conflict of interest.

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