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Irritable bowel syndrome may be induced by decreased neuroplasticity

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Abstract

Neuroplasticity is the nervous system's ability to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function and connections. And the nervous system monitors and coordinates internal organ function. Thus neuroplasticity may also be associated with the pathogenesis of other diseases besides neuropsychiatric diseases, such as cardiovascular disease. The digestive system is controlled by the nervous system, mainly by the autonomic nervous system. Stress may lead to depression/anxiety and irritable bowel syndrome (IBS). IBS is commonly comorbid with depression/anxiety, which are disorders of decreased neuroplasticity. And the mechanisms of depression/anxiety and IBS are related. The hypothalamo-pituitary-adrenal axis, hippocampus, amygdala and stress-related factors and hormones, such as corticotropin-releasing factor, glucocorticoids and brain-derived neurotrophic factor are involved in both neuroplasticity and the pathogenesis of depression/anxiety and IBS. So we conclude that decreased neuroplasticity causes the comorbidity of depression/anxiety and IBS, and increased neuroplasticity may be beneficial against the development of IBS. This theory provides another angle that can explain some of the reported phenomena related to IBS and neuropsychiatry, and provide a potential treatment to protect against IBS.

Abbrevations:

ANS	- Autonomic nervous system
BDNF	- Brain derived neurotrophic factor
BLA	- Basolateral amygdala
CeA	- Central nucleus of the amygdala
CNS	- Central nervous system
CRF	- Corticotropin-releasing factor
CRF1	- CRF subtype 1 receptors
FGID	- Functional gastrointestinal disorder
GR	- Glucocorticoid receptor
HPA	- Hypothalamus-pituitary-adrenal
IBS	- Irritable bowel syndrome
MS	- Maternal separation
PND	- Postnatal days
PVN	- Paraventricular nucleus
SSRI	- Selective serotonin reuptake inhibitor

REVIEW ARTICLE

INTRODUCTION

Irritable bowel syndrome (IBS) is a prevalent functional gastrointestinal disorder (FGID) with an estimated prevalence of 10–20% (Philpott *et al.* 2011), which is characterised by chronic abdominal pain, discomfort, bloating, and alteration of bowel habits. As a prototypic and representative disorder of FGIDs, its origin cannot be linked to structural, organic, or metabolic diseases detected by routine examinations in current clinical practice (Drossman 2006). Although not life-threatening, it is a heavy economic burden due to increased work absenteeism and impaired quality, and increased use of health care services (Saunders *et al.* 2002). The etiology of IBS is multifactorial, involving altered gut reactivity and motility, altered pain perception, and alteration of the brain-gut axis.

Neuroplasticity refers to the capacity of the nervous system to modify its organization such that the nervous system can be shaped by environmental input (Bavelier & Neville 2002). Individuals show different degrees of neuroplasticity due to their different courses of growth (Zheng & Xu 2012). Evidence has documented that even monozygotic twins may develop different neural structure and function though having an identical genetic background (Fraga *et al.* 2005; Zheng & Xu 2012). The nervous system monitors and coordinates internal organ function and neuroplasticity is the ability of the nervous system to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function and connections (Cramer *et al.* 2011). Thus neuroplasticity may be also associated with the pathogenesis and the treatment of other diseases besides neuropsychiatric diseases. For example, increased neuroplasticity may protect against cardiovascular disease (Zheng *et al.* 2013b). The digestive system is controlled by the nervous system, mainly by the autonomic nervous system (ANS). IBS is associated with depression/anxiety, which is closely related to neuroplasticity. In this review, we focus on some mood disorders, such as depression and anxiety, to discuss the relation between neuroplasticity and IBS, and provide a potential treatment to protect against IBS.

IBS IS A STRESS-RELATED DISORDER

Exposure to chronic stress may disrupt the normal, adaptive stress response (de Kloet *et al.* 2005). IBS is repeatedly reported as a stress-related disorder (Whitehead *et al.* 1992; Farmer *et al.* 2010). In IBS patients, stress is strongly associated with symptom onset and symptom severity (Drossman *et al.* 1996). Experimental and clinical data indicate that stress strongly influences gastrointestinal motility and sensitivity (Monnikes *et al.* 2001). Advanced methods using a barostat have detected a fine increase in colonic wall tone under psychosocial stress in IBS patients (Fukudo 2013).

Maternal separation (MS), which is a well-established model of early life stress and induces depressive-like behavior and long-term changes in cognition in rats, is also a suitable model of IBS (Freund *et al.* 2013; Couto *et al.* 2012; van den Wijngaard *et al.* 2013). MS induces life-long hyperactivity of the hypothalamus-pituitary-adrenal (HPA) axis response to stress and an abnormal central CRFergic system (corticotropin-releasing factor (CRF) and its receptors) (Lippmann *et al.* 2007; Plotsky *et al.* 2005). MS predisposes adult rats to stress-induced visceral hypersensitivity, dysfunction of intestinal barrier, hyperdefecation, increased HPA axis response, and anxiety (Coutinho *et al.* 2002; Gareau *et al.* 2006). Additionally, repeated water avoidance stress, a validated model of chronic psychological stress, leads to heightened visceral pain behaviors in rodents that resemble IBS sequelae (Tran *et al.* 2012).

Stress related-psychiatric disorders, especially major depression, anxiety, and somatoform disorders, occur among 20 to 50% of IBS patients (Garakani *et al.* 2003). Depression is the most common psychiatric diagnosis in IBS patients (Creed *et al.* 2005; Surdea-Blaga *et al.* 2012). IBS patients have higher scores of depression than healthy controls (Savas *et al.* 2009; Graham *et al.* 2010), but lower than the psychiatric population (Surdea-Blaga *et al.* 2012). However, depression is more common in IBS patients compared to patients with similar symptoms and organic gastrointestinal diseases and compared to healthy controls (Henningsen *et al.* 2003; Surdea-Blaga *et al.* 2012). Anxiety is more common in IBS patients than in the general population (Lee *et al.* 2009). Anxiety tends to precede IBS onset, particularly if diarrhea predominates. This indicates that the psychiatric disorder cannot be regarded as a response to IBS. It seems more likely that the psychiatric symptoms, especially anxiety, play a role in the development of IBS (Sykes *et al.* 2003). Somatization is frequently associated with anxiety and depression, and explains the frequent extra-intestinal symptoms, such as musculoskeletal complaints, urinary symptoms, sexual symptoms, headaches, and constant fatigue observed in IBS patients (North *et al.* 2004; Zimmerman 2003).

IBS IS CAUSED BY DYSFUNCTION OF THE BRAIN-GUT AXIS

IBS has been generally considered to be caused by alterations in the brain-gut axis, which constitutes the enteric nervous system and the gut wall in the periphery, the central nervous system (CNS), and the HPA axis (Fichna & Storr 2012). Brain-gut interactions play crucial roles in the pathophysiology of most pain-related FGIDs, especially in IBS (Mayer & Tillisch 2010). The bi-directional communication between the gut and the CNS is based on the neural, endocrine, and neuroimmune pathways (Fichna & Storr 2012). The neural network for control of digestive functions forms a hierarchic four-level integrative organization: (1) the enteric nervous system; (2) the pre-vertebral sympathetic ganglia, where peripheral reflex pathways are

induced by preganglionic sympathetic fibers from the spinal cord; (3) the ANS (parasympathetic and sympathetic systems); and (4) higher brain centers. Disturbances occurring at every level of this neural control, affect not only modulation of gastrointestinal motility, secretion, and immune functions, but also perception and emotional response to visceral events (Mulak & Bonaz 2004).

The responsiveness of the CNS is altered in IBS patients (Mayer & Tillisch 2010). The gut has the capacity to function as an autonomous organ. However, in normal conditions, the gut and the CNS talk to each other through the ANS, represented by the sympathetic and parasympathetic nervous system. A particular role in modulating gut functions is played by the emotional motor system, which consists of the limbic system and some paralimbic structures (Mulak & Bonaz 2004). The brain receives a constant stream of interoceptive input from the gastrointestinal tract, integrating this information with other interoceptive information from the body, as well as with contextual information from the environment, and then sends an integrated response back to various target cells within the gastrointestinal tract. This system is optimized to assure homeostasis of the gastrointestinal tract during physiological perturbations, and to adapt gastrointestinal function to the overall state of the organism. In health, the majority of interoceptive information reaching the brain is not consciously perceived, but serves primarily as input to autonomic reflex pathways. In patients with functional abdominal pain syndromes, conscious perception of interoceptive information from the gastrointestinal tract or recall of interoceptive memories of such input, can occur in the form of constant or recurrent discomfort or pain. This is often related to alterations in ANS output and with emotional changes (Mayer & Tillisch 2010).

As noted above, IBS is a stress-related disorder. Actually it is evidenced that the components of the stress response system, some of which are also components of brain-gut axis, such as hippocampus, amygdala, ANS and HPA axis, play important roles in the pathogenesis of IBS.

The hippocampus, amygdala, and prefrontal cortex undergo stress-induced structural remodeling, which alters behavioral and physiological responses (McEwen 2007). When vertebrates are exposed to chronic stress, a dichotomy appears in the morphology of different brain regions. Stress and depression are related to aberrant neuroplasticity in the amygdala: there is increased volume as well as increased dendritic arborization and synaptogenesis, maybe explaining the increased anxiety and fear that are often apparent in depressed patients (Khaleel *et al.* 2013; Tebartz van Elst *et al.* 2000). In contrast, chronic stress results in decreased volume and trophic and functional alterations as well as a loss of spines and dendritic branch points in the hippocampus (Frodl *et al.* 2002; Bremner *et al.* 2000; Vyas *et al.* 2002; Radley *et al.* 2006; Bergstrom *et al.* 2008; Bravo *et al.* 2009; Hageman *et al.* 2008; Magarinos *et al.* 1996; Magarinos *et al.* 1997; Hajszan *et al.* 2005), suggesting hypofunction of this structure.

The ANS and HPA axis are commonly regarded as the major components of the stress response system in the vertebrates. Alterations of this complex system have been associated with a variety of anxiety-related psychiatric disorders and stress-sensitive pain syndromes (Arborelius *et al.* 1999; Fichna & Storr 2012).

The ANS is a major mediator of the visceral response to central influences, such as psychological stress (Tougas 2000). Central and psychological factors, which are well known to be linked to functional gut symptoms, are capable of altering autonomic balance as well. Depression and anxiety have been shown to be associated with lower parasympathetic activity, both in female IBS patients and healthy controls (Jarrett *et al.* 2003).

The amygdala is involved in regulating the ANS. The functions of the central nucleus of the amygdala (CeA) and medial nucleus amygdala are related to the ANS (Swanson 2000). The CeA facilitates the autonomic response to stress (Applegate *et al.* 1983). Anatomical studies indicate that the CeA provides major output to autonomic regions which mediate not only fear and anxiety-related behaviors but also enteric processes such as gastric emptying and colonic motility (LeDoux *et al.* 1988; Lyubashina 2004). Furthermore, the hippocampus also has a role in regulating the ANS (Zheng *et al.* 2013b; Kim & Yosipovitch 2013; Holsen *et al.* 2012).

Regulation of the HPA axis is critical for adaptation to environmental changes. The hippocampus and amygdala play key roles in regulating the HPA axis (Miller & O'Callaghan 2002). The HPA axis controls the stress response through interactions among the relevant factors and hormones, which are discussed in the next section. These responses regulate some important body processes such as digestion, immunity, and mood. The evidence has demonstrated increased HPA axis responses in IBS (Chang *et al.* 2009). Inhibitory inputs from the amygdala and excitatory inputs from the hippocampus project to inhibitory neurons in the paraventricular nucleus (PVN) and hypothalamus (Herman *et al.* 2002; Herman *et al.* 2004). Thus it is implied that increasing input from the amygdala or decreasing input from the hippocampus, as occurs during chronic stress, enhances the net activity of the HPA axis. This dysregulation of the HPA axis is responsible for many negative effects of chronic stress on brain functioning and behavior (Chrousos & Gold 1998; Chrousos 2000).

It is showed in animal models that there is a link between the central pathways mediating stress and anxiety and the mechanisms regulating the gastrointestinal sensitivity. A key component of this link is the amygdala, specifically the CeA, which is known for its role in the regulation of emotional behavior and the expression of fear and anxiety (Greenwood-Van Meerveld *et al.* 2001).

The hippocampus may also be involved in several aspects relevant to the IBS symptom atology, such as pain, anxiety, and stress (Bannerman *et al.* 2004; Kwan *et al.* 2005; McEwen 2007; Niddam *et al.* 2011). Chronic stress leads to alterations of the glutamatergic system, which may lead to dendrite retraction in hippocampal subfields (Christian *et al.* 2011; McEwen *et al.* 2002). It was observed abnormal hippocampal glutamatergic neurotransmission in IBS patients, and inverse correlation between glutamate-glutamine concentrations and emotional stress indicators (Niddam *et al.* 2011). It is possible that the observed hippocampal glutamatergic hypofunction could due to a generally impaired HPA axis tone, or it could represent compensatory mechanisms of adaption to increased glucocorticoid feedback. Glutamatergic dysfunction is also an underlying cause of depression (Kallarackal *et al.* 2013).

IBS has been demonstrated to be associated with autonomic dysfunction, both cholinergic and adrenergic (Mulak & Bonaz 2004). The correct function of the ANS and its cross-talk with CNS are important factors preventing from IBS. An abnormal functioning of these brain-gut interactions has been described in IBS classically considered as a biopsychosocial model where stress plays a promoting role (Bonaz 2013). Disturbances at the ANS level, indicated by decreased parasympathetic and increased sympathetic activity and altered autonomic reflexes, often occur in IBS patients and account for the level of perception to gastrointestinal stimuli (Azpiroz 2002; Jarrett *et al.* 2003; Spaziani *et al.* 2008). Vagal dysfunction is obvious in the constipation-predominant IBS subgroup (Liu *et al.* 2013), and IBS patients have an abnormal autonomic response to painful stimuli to the colorectum (Fukudo 2013). Autonomic dysfunction may also represent the physiological pathways accounting for many of the extra-intestinal symptoms present in IBS patients (Tougas 2000). In addition, autonomic responses can also directly or indirectly modulate gut permeability, thereby changing the access of luminal factors, such as antigens and bacteria, to the gut immune system (Black 2002; Wood 2002).

The visceral organs, including that of the digestive and cardiovascular system, are mainly controlled by the ANS. Therefore gastrointestinal function is associated with cardiac function. For instance, heart rate variability is now commonly used in gastrointestinal physiology to assess autonomic imbalances (Pellissier *et al.* 2010; Mazurak *et al.* 2012). IBS patients show an impaired cardiac sympathetic and vagal response to colonic stimulation in response to flexible sigmoidoscopy (Cheng *et al.* 2013). Much evidence suggests that robust sympathetic arousal is a normal feature of the cardiac autonomic response to colorectal distention (Fukudo 2013). It is also showed that cardiovagal dysfunction is specifically associated with the constipation-predominant subgroup of IBS patients, whereas patients with diarrhea-predominant symptoms have evidence of sympathetic adrenergic dysfunction (Aggarwal *et al.* 1994).

NEUROPLASTICITY RELATED-FACTORS AND HORMONES ARE IMPORTANT FOR IBS AND MOOD DISORDERS

HPA axis plays a critical role in neuroplasticity, which is closely associated with mood disorders, by its related factors and hormones, such as CRF, glucocorticoids and BDNF. The principle regulator of the HPA axis is CRF, which is produced in the PVN in response to stress and is an important target of negative feedback by glucocorticoids, functions as a neurotransmitter in the integration of behavioral and autonomic responses to stress (Jeanneteau *et al.* 2012; Koob 1999). Neuroplasticity underlies our ability to adapt to stress. However, excessive exposure to stress can lead to maladaptive plasticity. Together with other important components of the stress system, such as glucocorticoids, which will be discussed later, CRF plays a central role in these neuroplastic changes (Regev & Baram 2014).

In the hypothalamic system, CRF stimulates the secretion of adrenocorticotropin, which stimulates the secretion of glucocorticoids from the adrenal cortex. Corticosteroids reach every organ through the circulatory system, thus enabling coordination between brain and body functions aimed at management of stress, recovery and adaptation (Ulrich-Lai & Herman 2009). CRF also responds to stress in the extra-hypothalamic systems (Cratty *et al.* 1995; Bao *et al.* 2008; Dunn & Swiergiel 2008; Fernandez Macedo *et al.* 2013). At the extra-hypothalamic level, CRF is present in different neuronal circuits and acts as a neuroregulator in the behavioral and emotional integration of environmental and endogenous inputs related to stress (Swanson *et al.* 1983; Fernandez Macedo *et al.* 2013). The basolateral amygdala (BLA) that contains CRF-synthesizing neurons and participates during periods of stress, where an increment in CRF immunoreactive neurons during stress is observed, forms part of this extra-hypothalamic circuit together with the hippocampus (Falco *et al.* 2009; Becker *et al.* 2007; Fernandez Macedo *et al.* 2013). Early life stress can change methylation patterns in the genomic DNA, leading to permanent changes in gene expression in the brain. Hypomethylation of a critical cAMP response element in the CRF promoter, a region essential for CRF transcriptional activation, favors increased transcriptional responses to stress in MS rats (Chen *et al.* 2012), which is a model of IBS.

CRF plays a particular role in the stress-related alterations of gastrointestinal motility and sensitivity (Collins 2001). CRF released into the PVN activates colonic motility, enhances visceral perception, and evokes negative emotion mainly through CRF subtype 1 receptors (CRF1) (Fukudo 2013). CRF in the brain and possibly in the gut is a plausible key molecular mediator of the pathophysiology behind stress-induced exacerbation of IBS symptoms (Fukudo 2013). It was observed that the intravenous injection of CRF in IBS patients led to exaggerated motility of the colon and increased visceral

pain sensitivity compared to healthy controls (Fukudo *et al.* 1998), whereas administration of a non-selective CRF receptor antagonist ameliorated these responses (Lembo *et al.* 1996; Sagami *et al.* 2004).

Dysregulation of CRF plays a very important role in the depression genesis and development, sustained elevation of CRF induced by stress may be the chief factor for depression (Gao *et al.* 2009). Depression is characterized by the HPA axis, which is thought to participate in the development of depressive symptoms (Nemeroff 1996; Pariante & Miller 2001). The HPA axis changes are believed to be secondary to the hypersecretion of the CRF. Depressed patients show increased concentrations of CRF in the cerebrospinal fluid, with elevated CRF mRNA and protein expression in the PVN of the hypothalamus being revealed in postmortem studies and elevated levels of circulating cortisol (Arborelius *et al.* 1999; Nemeroff 1996). Besides the hypothalamic system, it is evidenced that there is a relationship between dysregulation of CRF/CRF1 extra-hypothalamic signaling and depression (Fernandez Macedo *et al.* 2013). The hippocampus and the BLA are important brain regions of CRF action in depression (Fernandez Macedo *et al.* 2013). Considerable evidence suggests that CRF is hypersecreted in depression (Nemeroff 1996; Nemeroff 1992; Keck 2006; Arborelius *et al.* 1999), and central (intracerebroventricular) administration of CRF to laboratory animals leads to a spectrum of behaviours strikingly similar to those of the depressive syndrome (Nemeroff 2002). Since depression is a manifestation of decreased neuroplasticity (Zheng *et al.* 2014), the link between CRF and depression implies the relationship between CRF and decreased neuroplasticity.

The dysregulation of CRF and the decreased corticosteroid function in depressed patients may be corrected by antidepressant treatment (Holsboer 2000; Pariante & Miller 2001; Kim *et al.* 2006). For example, increased concentrations of CRF in cerebrospinal fluid have been reported in depressed patients (Banki *et al.* 1987). Additionally, the normalization of elevated CRF concentrations in cerebrospinal fluid has been reported after successful treatment of depression by fluoxetine (De Bellis *et al.* 1993).

Although categorised as different nosological entities, depression and anxiety frequently co-occur. Jacob *et al.* even concluded that mixed conditions are more common than pure depression or pure anxiety (Jacob *et al.* 1998). Besides depression, alterations in central CRF signaling pathways have also been implicated in the pathophysiology of anxiety (Keck 2006; Binder & Nemeroff 2010). CRF has a critical role in the comorbidity of anxiety/depression and IBS. Some research showed that involvement of the CRF1 in both the colonic and anxiogenic responses to stress may have clinical relevance in the comorbidity of anxiety/depression and IBS (Monnikes *et al.* 2001). The CRF-dependent involvement of the amygdala in the induction of anxiety-like behavior, visceral hypersensitivity, altered bowel habits and other common feature of IBS has been confirmed in animal studies (Tache *et al.* 2002; Myers & Greenwood-Van Meerveld 2007; Myers & Greenwood-Van Meerveld 2010; Venkova *et al.* 2010). Both the hypothalamic and extra-hypothalamic CRF systems play important roles in both psychiatric disorders and IBS (Lowry & Moore 2006; Bravo *et al.* 2011).

Glucocorticoids, the final product of HPA activation, are also key regulators of stress responses. The CeA indirectly activates the HPA axis and increases glucocorticoid secretion via subcortical regions, which relay on PVN (Feldman & Weidenfeld 1998). Interestingly, the amygdala is an important target for glucocorticoids. Glucocorticoids increase expression of CRF in the CeA and potentiate autonomic responses to chronic stress. Glucocorticoid infusion into the CeA does not affect HPA activation acutely but may play a feed-forward role to potentiate HPA responses to stress (Smith & Vale 2006). Evidence showed that elevated corticosterone level affected the amygdala and significantly increased brain activation in response to colorectal distension in rats (Johnson *et al.* 2010), and cortisol was elevated in all IBS subgroups (diarrhea predominant, constipated, and alternators) in humans (Dinan *et al.* 2006).

Glucocorticoid receptor (GR) is believed to be important in the regulation of the response to stress when endogenous levels of glucocorticoids are high (Juruena *et al.* 2004). Stress significantly reduced expression of GRs in the amygdala, hippocampus, prefrontal cortex, and nucleus accumbens (Abush & Akirav 2013). It is demonstrated that methylation of the GR gene is increased following water avoidance stress, a new model for sustained visceral hyperalgesia in rats that resemble IBS sequelae, while expression of the GR gene is decreased in the amygdala (Tran *et al.* 2012). Deficient maternal care in rats increases GR promoter methylation leading to decreased expression in the hippocampus, a recognized target for glucocorticoid feedback (Meaney *et al.* 2007).

Glucocorticoids play an important role in the etiology of depression. It is broadly accepted that stress triggers the activation of the HPA axis and induces the brain to be exposed to corticosteroids, affecting neurobehavioral functions with a strong downregulation of hippocampal neurogenesis, which is a major risk factor for depression (Zheng *et al.* 2013b).

Brain derived neurotrophic factor (BDNF), a stress- and activity-dependent factor, is a critical cytokine in neuronal survival, morphogenesis, and plasticity. Environmental conditions guide neural networks to better adapt to the environment through BDNF regulation. BDNF secretion can be regulated by stimuli related to neuroplasticity change. BDNF is involved in many activities modulated by the HPA axis. For example, BDNF expression is regulated by stress-responsive corticosteroids, and increased glucocorticoid exposure induces a reduction in BDNF level. The interaction

between BDNF and corticosteroids plays a key role in the environmentally mediated vulnerability to psychopathology (Zheng *et al.* 2013b). Additionally, recent studies have shown a role for CRF in this regard. It seems that CRF does have a role to play in determining BDNF control of dendritic spines (Bennett & Lagopoulos 2014). BDNF is important for ANS function (Zheng *et al.* 2013b).

Most of the circulating BDNF is produced in the brain and passes through the blood-brain barrier (Zheng *et al.* 2013b). Chronic restraint stress leads to decreases in BDNF mRNA and protein in some regions of the brain such as the CA3 region of the hippocampus, but increases in other regions such as the BLA. The most likely cause of these changes is provided by the stress initiated release of glucocorticoids, which readily enter neurons and alter gene expression of BDNF (Zheng *et al.* 2013b; Bennett & Lagopoulos 2014; Gray *et al.* 2013). Nevertheless, many studies have shown that peripheral BDNF could be used as a biomarker of mood states, and that serum BDNF level is a biomarker for depression (Zheng *et al.* 2013b). Decreased serum and hippocampus BDNF levels, reduced hippocampal volume and neurogenesis, CA3 dendritic retraction and decrease in spine density, as well as amygdala neuron hypertrophy, constitute latent vulnerability traits to depression (Blugeot *et al.* 2011). This suggests that BDNF level in the serum is consistent with that in the hippocampus, and contrary to that in the amygdala, in stress response. Incensole acetate was demonstrated to exhibit an antidepressive-like effect. This effect was concomitant to reduced serum corticosterone levels, dose-dependent down-regulation of CRF and up-regulation of BDNF transcripts IV and VI expression in the hippocampus (Moussaieff *et al.* 2012).

Although one report showed that anxious patients with recent trauma had significantly higher BDNF levels (Hauck *et al.* 2010), some other reports showed that BDNF levels in anxious patients were lower than in participants without anxiety (Dell'Osso *et al.* 2009; Maina *et al.* 2010; Strohle *et al.* 2010; Dos Santos *et al.* 2011; Wang *et al.* 2011). The elevated BDNF levels may result from stress generating for fear extinction modulators which act or may act through BDNF (Andero & Ressler 2012). And in the long run, BDNF levels may be reduced in anxiety. Although it would be useful to clarify the relationship further, BDNF is also a potential biomarker of anxiety (Suliman *et al.* 2013).

Though some findings are inconsistent (Yu *et al.* 2011; O'Sullivan *et al.* 2011), it is evidenced that BDNF level in IBS resembles that in depression, where serum and hippocampus BDNF levels are decreased. For example, besides IBS, MS is also a model of depression (El Khoury *et al.* 2006), suggesting that BDNF level in IBS resembles that in depression. BDNF level is significantly decreased in the hippocampus of MS rats (Aisa *et al.* 2009; Lippmann *et al.* 2007). Wistar rats were separated from their mothers for 3h per day during postnatal days (PND) 10 to 15. By PND60, the expression levels of BDNF and its receptor TrkB in the cerebral cortex were attenuated (Lee *et al.* 2012).

NEUROPLASTICITY IS DECREASED IN IBS

Depression is a disorder of decreased neuroplasticity (Zheng *et al.* 2013b). Besides depression, some other psychological disorders which IBS is commonly comorbid with, such as anxiety and somatization, are also associated with decreased neuroplasticity (Domingos da Silveira da Luz *et al.* 2013; Bhang *et al.* 2012). Thus it is suggested that decreased neuroplasticity leads to the comorbidity of depression/anxiety and IBS, and IBS is closely associated with decreased neuroplasticity.

There is much evidence for this theory. Although increased gray matter density in the hypothalamus of IBS patients (Blankstein *et al.* 2010), increasing evidence supports the association of chronic pain with accelerated gray matter atrophy in IBS (Robinson *et al.* 2011). In a previous study in IBS patients, the decreased gray matter density in the anterior/medial thalamus in IBS patients may have been related to subclinical levels of anxiety or depression (Davis *et al.* 2008). Physiological analysis of IBS patients revealed decreased gray matter density (thickness) in widespread areas of the brain, such as the medial prefrontal cortex, ventrolateral prefrontal cortex, and left dorsolateral prefrontal cortex (Seminowicz *et al.* 2010). Another study showed that female IBS patients have lower volumes in bilateral superior frontal gyrus, bilateral insula, bilateral hippocampus, bilateral amygdala, bilateral middle orbital frontal gyrus, left cingulate, left gyrus rectus, brainstem, and left putamen, while higher volume was found for the left postcentral gyrus (Labus *et al.* 2014). A research result indicates that neural degeneration in the myenteric plexus connected with inflammatory changes may play a role in the pathogenesis of IBS (Tornblom *et al.* 2002).

CONCLUSIONS

Though the pathophysiology of IBS is complex and multifactorial, neuroplasticity may have a role in it. The digestive system is controlled by the nervous system, mainly through the ANS. On the basis of the above discussion, it is concluded that: (1) stress influences the HPA axis by increasing CRF, and then leads to increased glucocorticoid, which decreases BDNF; (2) this pattern of increased glucocorticoid and deceased BDNF induces decreased neuroplasticity; and (3) decreased neuroplasticity influences the ANS, and then may lead to IBS. Figure 1 presents an integrative pathophysiologic model that shows the possible association between depression/anxiety and IBS. This model is not intended to be complete, but is rather meant to emphasize and connect certain interesting evidence pointing to this association. In addition, some studies

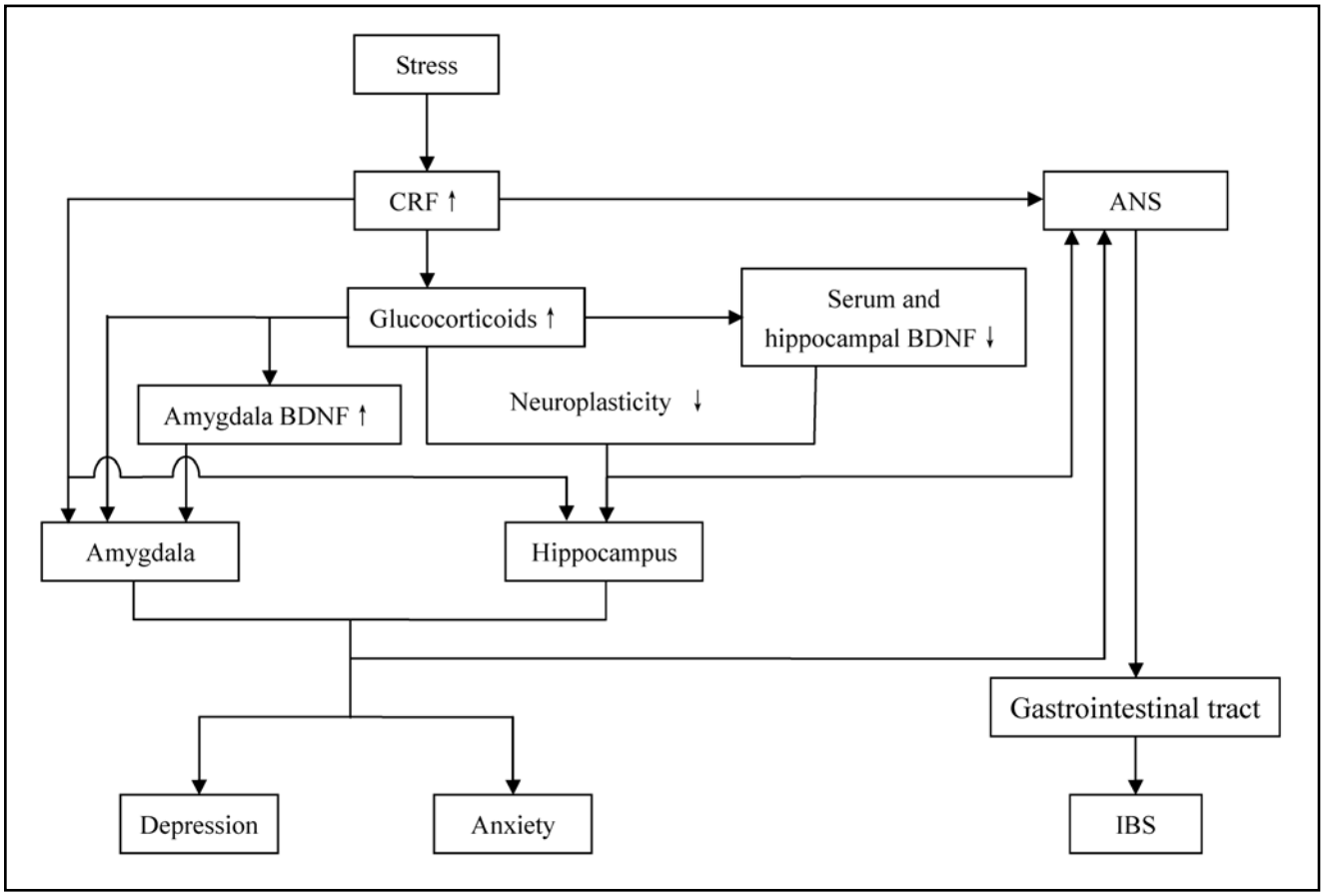

Fig. 1. An integrative pathophysiologic model that associates depression/anxiety with IBS. Decreased neuroplasticity plays a role in pathogenesis of the comorbidity of depression/anxiety and IBS. Abbreviations: CRF, corticotropin-releasing factor; ANS, autonomic nervous system; BDNF, brain-derived neurotrophic factor; IBS, irritable bowel syndrome.

pointed out that CRF is also play an important role in neuroplasticity (Regev & Baram 2014). Neuroplasticity is a fundamental mechanism of the adaptation of the nervous system to intrinsic or extrinsic stimuli, and the digestive system is controlled by the nervous system. Thus, increased neuroplasticity may also be beneficial against the development of IBS.

Since increased neuroplasticity represents enhancement of the nervous system, as well as the adaptation of the digestive system to intrinsic or extrinsic stimuli, non-neuropsychiatric symptoms patients with IBS may benefit from treatments that can increase neuroplasticity. For example, IBS patients may benefit from cognitive therapy, relaxation exercise, and treatment with centrally targeted medications such as anxiolytics, selective serotonin reuptake inhibitors (SSRIs), and low doses of tricyclic antidepressants in the treatment of IBS (Mulak & Bonaz 2004). Although the effect of benzodiazepines on neuroplasticity is complex (Zhao *et al.* 2012), cognitive therapy, exercise, and medication of SSRIs and tricyclic antidepressants increase neuroplasticity (Boku *et al.* 2013; Zheng *et al.* 2013b; Park & Bischof 2013).

In order to improve IBS treatment, more research on the role of the factors and mechanisms related to neuroplasticity should be conducted. Some common factors, such as microRNA-132, may play roles in both neuroplasticity and cardiovascular function (Zheng *et al.* 2013a). Similarly, the factors and mechanisms involved in IBS and neuroplasticity could be a promising field for further study.

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