Title
Early-life adversity, epigenetics, and visceral hypersensitivity

Journal
Neurogastroenterology & Motility, 29(9)

ISSN
1350-1925

Authors
Liu, S
Hagiwara, SI
Bhargava, A

Publication Date
2017-09-01

DOI
10.1111/nmo.13170

Peer reviewed

HHS Public Access

Author manuscript

Neurogastroenterol Motil. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

Neurogastroenterol Motil. 2017 September ; 29(9): . doi:10.1111/nmo.13170.

Early-life adversity, epigenetics, and visceral hypersensitivity

S. Liu[1], **SI. Hagiwara**[2], and **A. Bhargava**[2,3]

[1]Department of Biology, College of Science and Health, University of Wisconsin-La Crosse, La Crosse, WI 54601, USA

[2]The Osher Center for Integrative Medicine, University of California San Francisco, San Francisco, CA 94143, USA

[3]Department of Ob-Gyn, University of California San Francisco, San Francisco, CA 94143, USA

Abstract

Abdominal pain is associated with many gastrointestinal dysfunctions, such as irritable bowel syndrome (IBS), functional dyspepsia, and inflammatory bowel disease (IBD). Visceral hypersensitivity is a key reason for development of abdominal pain that presents in these gastrointestinal disorders/diseases. The pathogenesis of visceral hypersensitivity is complex and still far from being fully understood. In animal studies, visceral hypersensitivity has been linked to several early-life adverse (ELA) events. In humans, IBD, functional dyspepsia, and IBS can have adult onset, though the adverse events that lead to visceral hypersensitivity are largely uncharacterized. In this issue of the journal, Aguirre et al. report the interesting finding that epigenetics underlies the effects of ELA events on visceral hypersensitivity. This mini-review examines models of ELA events leading to visceral hypersensitivity and the potential role of epigenetics, as reported by Aguirre et al. and others.

Keywords

abdominal pain; functional dyspepsia; IBD; IBS; maternal separation

1 Introduction

Visceral hypersensitivity in response to intestinal inflammation or even in absence of any identifiable pathology is present in many gastrointestinal diseases and disorders that include inflammatory bowel disease (IBD), functional dyspepsia, and irritable bowel syndrome (IBS). Subsets of IBD patients with active disease or in clinical remission report abdominal pain as a major presenting symptom. Stressful episodes often precede disease flare in IBD patients. Stress is also often associated with functional dyspepsia and IBS. Stress-induced symptoms include, but are not limited to, feelings of incomplete evacuation, abnormal stool

Correspondence: Aditi Bhargava, Ph.D., Department of Ob-Gyn, San Francisco, CA 94143-0556, USA. aditi.bhargava@ucsf.edu.

Competing Interests: No competing interest declared.

Author Contribution: SL, SH, and AB searched literature, drafted the manuscript, and critically revised the manuscript.

Addendum: The authors were saddened to learn that Dr. Sushil Sarna, the senior author of the accompanying article in this issue, died unexpectedly on February 27, 2017. His passing will leave a vacuum in this field.

consistency or frequency, straining or urgency of defecation, abdominal bloating, and pain. Although the etiology of abdominal pain remains puzzling, visceral hypersensitivity has been known to cause abdominal pain in functional gastrointestinal disorders.[1] Multiple mechanisms at peripheral, spinal, and supraspinal levels contribute to the sensitization of visceral pain pathways, which leads to increased perception of luminal stimuli, ie, visceral hypersensitivity. Emerging evidence suggests that early-life adverse (ELA) events may predispose to visceral hypersensitivity in adult life. Several clinical observations support a strong correlation between ELA events and adult IBS.[2,3] Although there is generally a consensus on the association of ELA events and IBS development, whether ELA events are a cause or a predisposing factor for abdominal pain later in life is difficult to test in humans.

In the current issue of *Neurogastroenterology and Motility*, Aguirre et al. tested whether ELA events predispose adults to visceral hypersensitivity and possible molecular and epigenetic mechanisms that may be involved.[4] Using an ELA event rat model of intestinal inflammation, the authors demonstrated that adult rats exposed to an intestinal insult showed evidence of visceral hypersensitivity. In light of these interesting findings, this mini-review examines what other models of ELA events have shown and discusses ELA-induced epigenetic mechanisms that may lead to visceral hypersensitivity. The possible involvement of the gut microbiota and gut-brain axis is also discussed and summarized in Figure 1.

2 Animal Models of ELA Events and Visceral Hypersensitivity

A wide range of animal models has been developed to investigate the influence of ELA events on visceral hypersensitivity (summarized in Table 1) and the underlying mechanisms. These models use a variety of stressors that range from mechanical and chemical to psychological as well as environmental stressors.

2.1 Mechanical and chemical stressors

In rats, transient mechanical (eg, colorectal distention) or chemical (eg, mustard oil) irritation in the colon during the neonatal period induced chronic visceral hypersensitivity in adult animals in the absence of clear pathology or tissue damage.[5] In this issue, Aguirre et al.[4] add to the existing body of research by showing that although colonic instillation of trinitrobenzene sulfonic (TNBS) acid alone in the neonates did not induce visceral hypersensitivity in adult rats, it exacerbated visceral hypersensitivity induced by a second insult in adults. This interesting finding suggests that although a given ELA event alone may not be sufficient to cause gastrointestinal disease, it primes one for adult onset and increases vulnerability to other triggering factors.

Mechanical (suction) or chemical irritation of the stomach in the neonatal period has also been linked to visceral hypersensitivity in adults.[6-8] In humans, gastric suction at birth has been shown to be associated with functional gastrointestinal disorders in later life.[6] In a rat model, gastric suction during the neonatal period resulted in chronic visceral and somatic hyperalgesia in adult animals.[8] Rat models of functional dyspepsia also demonstrate a linkage to ELA events.[7] In neonatal rats, transient gastric irritation with iodoacetamide resulted in long-lasting effects on adults, including visceral hypersensitivity to graded gastric distension.[7] In this animal model of functional dyspepsia, rats that experienced gastric

irritation as neonates exhibited depression-and anxiety-like behaviors as adults even in absence of a secondary insult.[9] Neonatal gastric irritation-induced visceral hyperalgesia and depression/anxiety-like behaviors are mediated by corticotropin-releasing factor (CRF)-and vagal nerve-dependent mechanisms.[8,9]

2.2 Maternal involvement

Maternal separation during the neonatal period is another potent cause of visceral hypersensitivity in adulthood. The neonatal period of maternal separation is important; separation during the development-sensitive and stress-hyporesponsive periods (postnatal days 2-14) results in adult visceral hypersensitivity.[10-13] The intensity of visceral sensitivity appears to be enhanced by exposure to an acute psychological stressor later in life, which is accompanied by increased colonic motility.[13] Interestingly, different paradigms of maternal separation also induce different visceral responses in adulthood. Removing all pups from the dam evoked greater visceral hyperalgesia in adult rats than removing only half of the littermates,[12] suggesting that maternal behavior and stress level play a role in visceral sensitivity of the offspring. Maternal separation-induced visceral hypersensitivity can be transferred to the next generation without further exposure of the offspring to maternal separation, and this phenotype transfer depends on maternal care.[14]

Human child neglect in which the parent and/or caregiver is usually present but exhibits improper and abnormal care is another ELA event associated with IBS.[2] In rats, limiting bedding material from postnatal days 2 to 9 without separating the dam from the pups induced abnormal maternal care, mimicking human child neglect.[15] Limiting bedding material caused significant visceral hypersensitivity in adult rats,[16] similar to findings reported for rats with a prior history of maternal separation.[11,12]

2.3 Prenatal stress

Besides the postnatal adverse events, the effects of prenatal adversity on adulthood visceral sensitivity have also been investigated. Winston et al. developed a chronic prenatal stress animal model by exposing the pregnant dams to a heterotypic intermittent stress twice-daily from embryonic day 11 to the time of delivery.[17] They found that chronic prenatal stress induced visceral hypersensitivity in both adult male and adult female rats under basal conditions. When exposed to chronic stress later in life, the female offspring that have experienced prenatal chronic stress showed a greater and prolonged (≥2 wk duration) visceral hypersensitivity than the male offspring.[17] This study suggests that chronic stress during the *in utero* development period is another risk factor for the development of visceral hypersensitivity later in life.

3 Epigenetic Mechanisms in Visceral Hypersensitivity

The early-life period, both before and after birth, is critical for the development of nociceptive pathways and demonstrates great plasticity. The mechanisms by which ELA events induce visceral hypersensitivity remain to be determined. Several recent studies have implicated an important role of aberrant epigenetic modifications in the pathogenesis of visceral hypersensitivity (Table 2).[4,10,17-21]

Epigenetic modification refers to the process where developmental or environmental cues affect gene expression without altering DNA sequence. This results in a stable and potentially heritable phenotypes.[22] Epigenetic mechanisms include post-translational histone modifications and DNA methylation, which can promote or suppress gene transcription.[23] Histone marks such as acetylation of histone 3 (H3) and histone 4 (H4) by histone acetyltransferases (HATs) decrease the affinity between histones and DNA, relax the chromatin, and allow the transcriptional machinery to interact with particular gene promoters to activate gene transcription. On the other hand, reducing acetylation by histone deacetylases (HDACs) stabilizes the chromatin and represses gene transcription.[23] DNA methylation refers to the addition of a methyl group via DNA methyltransferases (DNMTs) to the CpG dinucleotides in the promoter region of a gene, which usually leads to gene silencing.[23]

3.1 Histone acetylation/deacetylation

Aguirre et al. reported in this issue that histone acetylation played a role in augmenting visceral hypersensitivity in adult rats received intestinal immune challenge that also have been exposed to an ELA event (neonatal intestinal immune challenge).[4] Although the neonatal intestinal immune challenge alone did not trigger the epigenetic reprogramming, it increased the susceptibility to an adult immune challenge. Neonatal immune challenge followed by an adult immune challenge caused increased expression of tyrosine hydroxylase in the locus ceruleus and elevated norepinephrine levels in the cerebrospinal fluid. Norepinephrine acting via the adrenergic receptors in the lumbosacral spinal cord induced acetylation at lysine 9 on histone 3 (H3K9) and lysine 12 on histone 4 (H4K12) at the core promoter of brain-derived neurotrophic factor (BDNF), which resulted in increased BDNF gene transcription. Inhibition of histone acetylation by a HAT inhibitor blocked the epigenetic upregulation of BDNF expression in the spinal cord and the visceral hypersensitivity in the neonatal/adult immune-challenged rats.[4] In a previous study, Winston et al. also reported that H3 acetylation and upregulation of spinal cord BDNF expression were involved in the development of visceral hypersensitivity induced by prenatal chronic stress followed by adult chronic stress in female rats.[17]

There have been several studies documenting that histone deacetylation, on the contrary, may promote visceral pain and HDAC inhibitors attenuate visceral pain by increasing histone acetylation levels. A recent study showed that maternal separation-induced visceral pain behavior in rats was negatively correlated with H4K12 acetylation level in the lumbosacral spinal cord.[10] Intraperitoneal administration of a HDAC inhibitor in adulthood normalized neonatal maternal separation-induced reduction of H4K12 acetylation and visceral hypersensitivity.[10] Similarly, local administration of HDAC inhibitors into the rat cerebral ventricles or amygdala attenuated chronic repeated water avoidance stress or corticosteroid-induced visceral hypersensitivity.[20,21] Prolonged exposure of the central nucleus of amygdala (CeA) to elevated corticosteroids, which mimics the effects of chronic stress, reduced H3K9 acetylation at the glucocorticoid receptor (GR) promoter in rats. Silencing of GR gene led to upregulation of CRF expression in the CeA, resulting in visceral hypersensitivity. Bilateral infusion of an HDAC inhibitor into the rat CeA enhanced H3K9 acetylation, increased GR expression, decreased CRF expression, and attenuated

corticosteroid-induced visceral hypersensitivity.[21] Furthermore, intrathecal administration of HDAC inhibitors prevented forced swim stress-induced visceral hypersensitivity in rats.[18] Forced swim stress alone did not alter global histone acetylation in the lumbosacral spinal cord, however, HDAC inhibitors increased H3K9 acetylation at the metabotropic glutamate receptor 2 and 3 (mGluR2/3) promoters and enhanced mGluR2/3 expression in the lumbosacral spinal cord.[18] Activation of mGluR2/3 in the spinal cord has been shown to reduce neuropathic pain in rats,[24] indicating that mGluR2/3 play an analgesic role at the spinal cord level. Data suggest that activation of HAT by certain stressors resulted in increased acetylation of histones in specific positions on pro-nociceptive genes (eg, BDNF in the spinal cord).[4,17] Paradoxically, activation of HDAC by different set of stressors resulted in global deacetylation of histones in the spinal cord.[10] Thus, both histone acetylation and deacetylation appear to be associated with visceral pain.

3.2 DNA methylation

Altered DNA methylation of key genes in the nociceptive pathways has also been implicated in the development of visceral hypersensitivity. Visceral hypersensitivity induced by repeated water avoidance stress is associated with increased DNA methylation of the GR promoter region and decreased DNA methylation of the CRF promoter in the CeA, which in turn decreased expression of GR and increased expression of CRF in the same brain region.[20] Previous studies have demonstrated that stress increased CRF expression both in the brain and the intestine,[25,26] and CRF receptor antagonism both in the brain and in the periphery reversed visceral hypersensitivity induced by stress.[13,27] Another study examining the role of DNA methylation in visceral hypersensitivity showed that chronic water avoidance stress induced DNA methylation of the GR promoter and reduced its mRNA and protein expression in the dorsal root ganglia neurons innervating the pelvic viscera.[19] Chronic water avoidance stress also induced DNA methylation of the antinociceptive cannabinoid receptor 1 promoter and downregulated its expression, which may contribute to stress-induced visceral pain. Chronic water avoidance stress also increased H3 acetylation, which resulted in upregulation of pro-nociceptive transient receptor potential vanilloid 1 expression and function.[19] These findings suggest that visceral hypersensitivity induced by different stressors may involve a combination of post-translational histone modifications and DNA methylation at various levels of the nociceptive pathways. However, the understanding of visceral pain epigenetics is still very much in its early stage, and is mostly based on animal studies. The data from clinical studies are very sparse. Translational research in human tissue may enhance our understanding of epigenetic processes involved in the development of visceral pain in functional gastrointestinal diseases and/or disorders.

4 The Microbiome

The gut microbiota appears to modulate visceral sensory pathways during early life. Overuse of antibiotics in the developed world has resulted in abnormal gut microbiota in humans.[28] Early postnatal perturbation of the gut microbiota by using broad-spectrum antibiotics was associated with visceral hypersensitivity in adult rats.[29] In fact, early-life stress has been shown to alter the composition of gut microbiota in adult rats, neonatal mice, infant monkeys, and humans.[11,30-32] Transfer of fecal microbiota from IBS patients to germ-free

rats induced visceral hypersensitivity, probably through bacterial metabolites such as sulfides.[33] These observations suggest that gut microbiota may also play role in the development of visceral sensory pathways in response to ELA events.

5 Gut-Brain Connection

Winston and Sarna[34] demonstrated that ELA events in neonatal rats re-program and upregulate sympathetic activity, resulting in visceral hypersensitivity and anxiety-like behavior. Rats subjected to neonatal colon inflammation demonstrated higher level of norepinephrine in the plasma, which upregulated nerve growth factor (NGF) expression in the stomach and contributed to gastric hypersensitivity.[34,35] Expression of NGF in stomachs of adult rats with neonatal colon inflammation-induced gastric hypersensitivity was found to be higher compared with the non-responding rats and rats with no ELA exposure.[35] Tyrosine hydroxylase expression in the celiac ganglia was elevated after neonatal colon inflammation, which appears to be responsible for the increased release of norepinephrine into the gastric fundus.[34] Thus, an increase in norepinephrine release from the sympathetic nerve terminals in the stomach upregulates NGF expression, which in turn increases the visceromotor response to gastric distension.

In the accompanying study, Aguirre et al. found that upregulation of sympathetic nervous system activity in the locus coeruleus and increased expression of BDNF in the lumbar spinal cord may additionally underlie the enhancement of visceral hypersensitivity in adult rats with colon inflammation.[4] They found that elevated norepinephrine level in the cerebral spinal fluid triggered epigenetic mechanisms to enhance BDNF transcription in the lumbar spinal cord of adult rats with colon inflammation that have been exposed to ELA events as neonates.[4] These findings suggest that ELA events increase sympathetic outflow, which brings about epigenetic changes and consequently contributes to the development of visceral hypersensitivity in adulthood.

6 Conclusions and Future Direction

Early-life adverse events play a central role and increase the risk of developing visceral hypersensitivity in adulthood (Figure 1). Epigenetic changes that ensue due to ELA events can have profound and long-term effects on the health of an individual and their progeny, as these changes can be inherited. In human gastrointestinal dysfunction, visceral hypersensitivity is one major contributing factor, but other factors also exist. Animal studies are limited by a greater focus on the visceral component of gastrointestinal function. Animal studies also tend to focus on one sex: males. Data from a few animal studies that included both sexes suggest sex-specific responses to inflammatory insults[36] and to maternal separation.[12] Clinical observations also suggest that visceral hypersensitivity is more prevalent in females with IBS[37,38] and functional dyspepsia.[39] Inclusion of both sexes in animal models and examining physiology and mechanisms in an integrated manner will help advance our understanding of gastrointestinal function in a more holistic fashion.

Acknowledgments

The authors would like to acknowledge research grants from the National Institutes of Health R15DK097460-01 to SL and R56-DK080787-06, R01DK097518 to AB.

Funding information: National Institutes of Health, Grant/Award Number: R15DK097460-01, R56-DK080787-06 and R01DK097518

References

1. Farmer AD, Aziz Q. Gut pain & visceral hypersensitivity. Br J Pain. 2013; 7:39–47. [PubMed: 26516496]
2. Bradford K, Shih W, Videlock EJ, et al. Association between early adverse life events and irritable bowel syndrome. Clin Gastroenterol Hepatol. 2012; 10:385–390. e381–383. [PubMed: 22178460]
3. Chitkara DK, Van Tilburg MA, Blois-Martin N, Whitehead WE. Early life risk factors that contribute to irritable bowel syndrome in adults: a systematic review. Am J Gastroenterol. 2008; 103:765–774. quiz 775. [PubMed: 18177446]
4. Aguirre, JE., Winston, JH., Sarna, SK. Neonatal immune challenge followed by adult immune challenge induces epigenetic-susceptibility to aggravated visceral hypersensitivity [published online April 25 2017]. Neurogastroenterol Motil. 2017. https://doi.org/10.111/nmo.13081
5. Al-Chaer ED, Kawasaki M, Pasricha PJ. A new model of chronic visceral hypersensitivity in adult rats induced by colon irritation during postnatal development. Gastroenterology. 2000; 119:1276–1285. [PubMed: 11054385]
6. Anand KJ, Runeson B, Jacobson B. Gastric suction at birth associated with long- term risk for functional intestinal disorders in later life. J Pediatr. 2004; 144:449–454. [PubMed: 15069391]
7. Liu LS, Winston JH, Shenoy MM, Song GQ, Chen JD, Pasricha PJ. A rat model of chronic gastric sensorimotor dysfunction resulting from transient neonatal gastric irritation. Gastroenterology. 2008; 134:2070–2079. [PubMed: 18448102]
8. Smith C, Nordstrom E, Sengupta JN, Miranda A. Neonatal gastric suctioning results in chronic visceral and somatic hyperalgesia: role of corticotropin releasing factor. Neurogastroenterol Motil. 2007; 19:692–699. [PubMed: 17640185]
9. Liu L, Li Q, Sapolsky R, et al. Transient gastric irritation in the neonatal rats leads to changes in hypothalamic CRF expression, depression-and anxiety-like behavior as adults. PLoS ONE. 2011; 6:e19498. [PubMed: 21589865]
10. Moloney RD, Stilling RM, Dinan TG, Cryan JF. Early-life stress-induced visceral hypersensitivity and anxiety behavior is reversed by histone deacetylase inhibition. Neurogastroenterol Motil. 2015; 27:1831–1836. [PubMed: 26403543]
11. O'Mahony SM, Marchesi JR, Scully P, et al. Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses. Biol Psychiatry. 2009; 65:263–267.
12. Rosztoczy A, Fioramonti J, Jarmay K, Barreau F, Wittmann T, Bueno L. Influence of sex and experimental protocol on the effect of maternal deprivation on rectal sensitivity to distension in the adult rat. Neurogastroenterol Motil. 2003; 15:679–686. [PubMed: 14651604]
13. Schwetz I, McRoberts JA, Coutinho SV, et al. Corticotropin-releasing factor receptor 1 mediates acute and delayed stress-induced visceral hyperalgesia in maternally separated long-evans rats. Am J Physiol Gastrointest Liver Physiol. 2005; 289:G704–G712. [PubMed: 15994424]
14. van den Wijngaard RM, Stanisor OI, van Diest SA, et al. Susceptibility to stress induced visceral hypersensitivity in maternally separated rats is transferred across generations. Neurogastroenterol Motil. 2013; 25:e780–e790. [PubMed: 23965154]
15. Gilles EE, Schultz L, Baram TZ. Abnormal corticosterone regulation in an immature rat model of continuous chronic stress. Pediatr Neurol. 1996; 15:114–119. [PubMed: 8888044]
16. Guo Y, Wang Z, Mayer EA, Holschneider DP. Neonatal stress from limited bedding elicits visceral hyperalgesia in adult rats. NeuroReport. 2015; 26:13–16. [PubMed: 25426824]

17. Winston JH, Li Q, Sarna SK. Chronic prenatal stress epigenetically modifies spinal cord BDNF expression to induce sex-specific visceral hypersensitivity in offspring. Neurogastroenterol Motil. 2014; 26:715–730. [PubMed: 24588943]
18. Cao DY, Bai G, Ji Y, Karpowicz JM, Traub RJ. EXPRESS: histone hyper-acetylation modulates spinal type II metabotropic glutamate receptor alleviating stress-induced visceral hypersensitivity in female rats. Mol Pain. 2016; 12:1744806916660722. [PubMed: 27385724]
19. Hong S, Zheng G, Wiley JW. Epigenetic regulation of genes that modulate chronic stress-induced visceral pain in the peripheral nervous system. Gastroenterology. 2015; 148(148-157):e147.
20. Tran L, Chaloner A, Sawalha AH, Greenwood Van-Meerveld B. Importance of epigenetic mechanisms in visceral pain induced by chronic water avoidance stress. Psychoneuroendocrinology. 2013; 38:898–906. [PubMed: 23084728]
21. Tran L, Schulkin J, Ligon CO, Greenwood-Van Meerveld B. Epigenetic modulation of chronic anxiety and pain by histone deacetylation. Mol Psychiatry. 2015; 20:1219–1231.
22. Berger SL, Kouzarides T, Shiekhattar R, Shilatifard A. An operational definition of epigenetics. Genes Dev. 2009; 23:781–783. [PubMed: 19339683]
23. Graff J, Kim D, Dobbin MM, Tsai LH. Epigenetic regulation of gene expression in physiological and pathological brain processes. Physiol Rev. 2011; 91:603–649. [PubMed: 21527733]
24. Simmons RM, Webster AA, Kalra AB, Iyengar S. Group II mGluR receptor agonists are effective in persistent and neuropathic pain models in rats. Pharmacol Biochem Behav. 2002; 73:419–427. [PubMed: 12117597]
25. Aisa B, Tordera R, Lasheras B, Del Rio J, Ramirez MJ. Effects of maternal separation on hypothalamic-pituitary-adrenal responses, cognition and vulnerability to stress in adult female rats. Neuroscience. 2008; 154:1218–1226. [PubMed: 18554808]
26. Liu S, Chang J, Long N, et al. Endogenous CRF in rat large intestine mediates motor and secretory responses to stress. Neurogastroenterol Motil. 2016; 28:281–291. [PubMed: 26611915]
27. Nozu, T., Miyagishi, S., Nozu, R., Takakusaki, K., Okumura, T. Repeated water avoidance stress induces visceral hypersensitivity; role of IL-1, IL-6 and peripheral corticotropin-releasing factor [published online March 15 2017. J Gastroenterol Hepatol. 2017. https://doi.org/10.1111/jgh.13787
28. Ferrer M, Mendez-Garcia C, Rojo D, Barbas C, Moya A. Antibiotic use and microbiome function. Biochem Pharmacol. 2017; 134:114–126. [PubMed: 27641814]
29. O'Mahony SM, Felice VD, Nally K, et al. Disturbance of the gut microbiota in early-life selectively affects visceral pain in adulthood without impacting cognitive or anxiety-related behaviors in male rats. Neuroscience. 2014; 277:885–901. [PubMed: 25088912]
30. Bailey MT, Coe CL. Maternal separation disrupts the integrity of the intestinal microflora in infant rhesus monkeys. Dev Psychobiol. 1999; 35:146–155. [PubMed: 10461128]
31. Jasarevic E, Howerton CL, Howard CD, Bale TL. Alterations in the vaginal microbiome by maternal stress are associated with metabolic reprogramming of the offspring gut and brain. Endocrinology. 2015; 156:3265–3276. [PubMed: 26079804]
32. Zijlmans MA, Korpela K, Riksen-Walraven JM, de Vos WM, de Weerth C. Maternal prenatal stress is associated with the infant intestinal microbiota. Psychoneuroendocrinology. 2015; 53:233–245. [PubMed: 25638481]
33. Crouzet L, Gaultier E, Del'Homme C, et al. The hypersensitivity to colonic distension of IBS patients can be transferred to rats through their fecal microbiota. Neurogastroenterol Motil. 2013; 25:e272–e282. [PubMed: 23433203]
34. Winston JH, Sarna SK. Enhanced sympathetic nerve activity induced by neonatal colon inflammation induces gastric hypersensitivity and anxiety-like behavior in adult rats. Am J Physiol Gastrointest Liver Physiol. 2016; 311:G32–G39. [PubMed: 27151940]
35. Li Q, Winston JH, Sarna SK. Noninflammatory upregulation of nerve growth factor underlies gastric hypersensitivity induced by neonatal colon inflammation. Am J Physiol Regul Integr Comp Physiol. 2016; 310:R235–R242. [PubMed: 26608656]
36. Hasdemir B, Mhaske P, Paruthiyil S, et al. Sex-and corticotropin-releasing factor receptor 2-dependent actions of urocortin 1 during inflammation. Am J Physiol Regul Integr Comp Physiol. 2016; 310:R1244–R1257. [PubMed: 27053649]

37. Heitkemper M, Jarrett M. Irritable bowel syndrome: does gender matter? J Psychosom Res. 2008; 64:583–587. [PubMed: 18501258]

38. Lee OY, Mayer EA, Schmulson M, Chang L, Naliboff B. Gender-related differences in IBS symptoms. Am J Gastroenterol. 2001; 96:2184–2193. [PubMed: 11467651]

39. Flier SN, Rose S. Is functional dyspepsia of particular concern in women? A review of gender differences in epidemiology, pathophysiologic mechanisms, clinical presentation, and management. Am J Gastroenterol. 2006; 101:S644–S653. [PubMed: 17177870]

Key points

- Visceral hypersensitivity is a multifactorial and complex condition associated with many gastrointestinal disorders.
- Early-life adverse events increase the risk of developing visceral hypersensitivity in adulthood.
- Epigenetic changes induced by early-life adversity shape the visceral nociceptive pathways and aggravate visceral sensory responses to insults encountered later in life. These epigenetic processes can have profound and long-term effects on the health of an individual and their progeny, as these changes can be inherited.

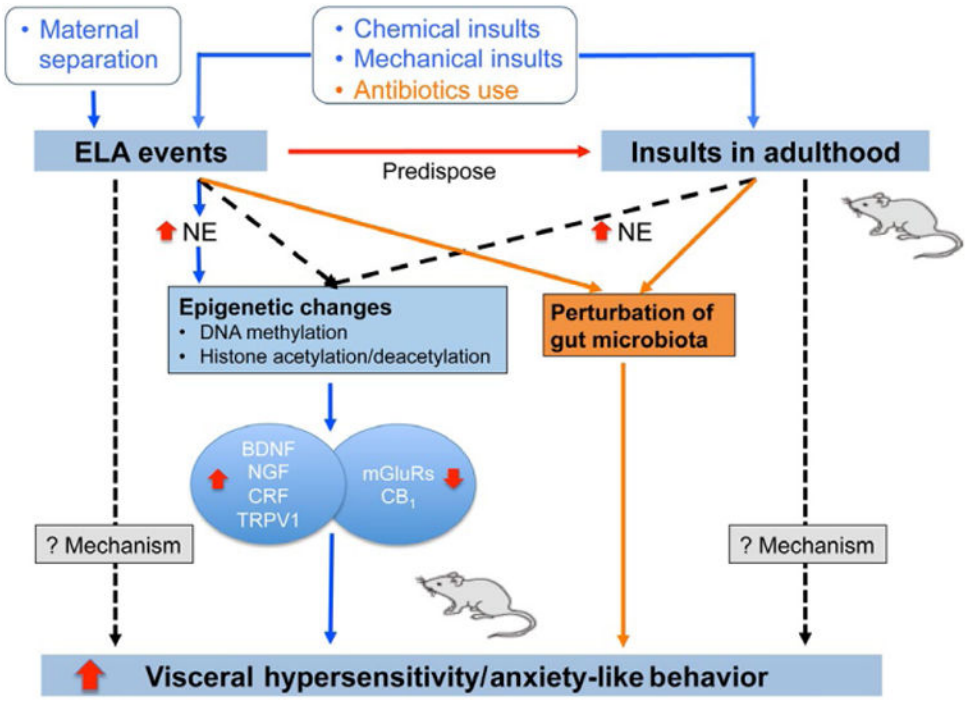

Figure 1.

Early-life adverse events and visceral hypersensitivity in animal models. Early-life adverse (ELA) events that range from physical, chemical, psychological to environmental stressors are linked to visceral hypersensitivity and anxiety- like behavior in later life. Insults encountered in adulthood may also cause visceral hypersensitivity and anxiety-like behavior. Exposure to ELA events predisposes adults and exacerbates the symptoms of visceral hypersensitivity induced by insults in later life. Both ELA events and insults in adulthood increase sympathetic output. Changes in sympathetic output that involve NE release result in epigenetic changes. Epigenetic changes induced by ELA events or insults in adulthood may underlie visceral hypersensitivity. Activating DNA and/or histone epigenetic changes were found in genes involved in the nociceptive pathways (eg, BDNF, NGF, CRF, TRPV1). Repressive epigenetic marks were found in genes involved in the antinociceptive pathways (eg, mGluR, CB1). Perturbation of gut microbiota and other unknown (?) mechanisms may also contribute to ELA events or adult insults-induced visceral hypersensitivity and anxiety-like behavior in later life. BDNF: brain-derived neurotropic factor; CB_1: cannabinoid receptor 1; CRF: corticotropin- releasing factor; mGluR: metabotropic glutamate receptors; NE: norepinephrine; NGF: neurotropic growth factor; TRPV1: transient receptor potential vanilloid 1. Dash line: unknown (?) mechanisms

Table 1
Animal models of early-life adverse events

ELA event	Species/sex	Age of animal when exposed to ELA and frequency of ELA exposure	Does the ELA event lead to adult visceral hypersensitivity?	Reference
Colorectal distention	Male SD rats	Postnatal day 8-21; colorectal distention was applied daily	Yes	5
Intracolonical instillation of mustard oil	Male SD rats	Postnatal day 8-21; mustard oil was applied daily	Yes	5
Intracolonical instillation of TNBS	Male SD rats	Postnatal day 10; TNBS was applied once	No, but the ELA event exacerbates visceral hypersensitivity induced by an adult insult	4
Gastric suction	Male long evans rats	Postnatal day 2-11; gastric suction was applied once daily	Yes	8
Oral gavage of iodoacetamide	Male SD rats	Postnatal day 10-15; iodoacetamide was applied daily	Yes	7, 9
Neonatal maternal separation	Male SD rats	Postnatal day 2-12; pups were separated from their mother daily for 3 h.	Yes	10, 11
Neonatal maternal separation	Wistar rats of both sexes	Postnatal day 1-14; pups were separated from their mother daily for 2 h.	Yes	12
Neonatal maternal separation	Male Long Evans rats	Postnatal day 2-14; pups were separated from their mother daily for 3 h.	Yes	13
Limited bedding	Wistar rats of both sexes	Postnatal day 2-9; everyday for 8 d.	Yes	16
Prenatal chronic stress	SD rats of both sexes	Embryonic day 11 to delivery; pregnant dams were exposed to a random sequence of heterotypic intermittent chronic stress twice-daily	Yes	17

Note: ELA, early-life adversity; SD, Sprague Dawley; TNBS, trinitrobenzene sulfonic acid.

Neurogastroenterol Motil. Author manuscript; available in PMC 2017 September 01.

Table 2

Epigenetic mechanisms in visceral hypersensitivity

	Species/sex	Epigenetic mechanism	Target gene expression	Location	Pharmacology	Reference
Neonatal colon inflammation + adult colon inflammation	Male SD rats	H3K9 and H4K12 acetylation at *bdnf*	Upregulation of BDNF by enhanced sympathetic activity	SC	HAT inhibitor suppresses BDNF expression and visceral hypersensitivity	4
Prenatal chronic stress + adult chronic stress	Male and female SD rats	H3 acetylation at *bdnf*; decrease in HDAC1 association with *bdnf* promoter	Upregulation of BDNF	SC	HAT inhibitors suppresses BDNF expression and visceral hypersensitivity	17
Neonatal maternal separation	Male SD rats	H4K12 deacetylation	Not investigated	SC	HDAC inhibitor restores H4K12 acetylation and attenuates early-life stress-induced visceral hypersensitivity	10
Water avoidance stress	Male F-344 rats	Increased DNA methylation on the GR promoter; and decreased DNA methylation on the CRF promoter	Decreased expression of GR and increased expression of CRF	CeA	HDAC inhibitor normalizes chronic water avoidance stress-induced visceral hypersensitivity	20
Corticosteroid injection into the amygdala	Male F-344 rats	H3K9 deacetylation at the GR promoter	Decreased expression of GR and increased expression of CRF	CeA	HDAC inhibitors enhances H3K9 acetylation. increases GR expression, decreases CRF expression, and attenuates corticosteroid-induced visceral hypersensitivity	21
Forced swim	Female SD rats	Forced swim alone does not alter global histone acetylation; however, HDAC inhibitor increases H3K9 acetylation at the mGlur2/3 promoters	HDAC inhibitor increases mGluR2/3 expression	SC	HDAC inhibitor increases H3K9 acetylation and attenuates forced swim-induced visceral hypersensitivity	18
Water avoidance stress	Male SD rats	Increased DNA methylation of GR and cannabinoid receptor promoters; increased histone acetylation of *Trpv1* promoter	Reduced expression of GR and cannabinoid receptor; increased expression of TRPV1	DRG		19

BDNF, brain-derived neurotrophic factor; CeA, central nucleus of the amygdala; CRF, corticotropin-releasing factor, DRG, dorsal root ganglia; GR, glucocorticoid receptor; H3K9, histone 3 lysine 9; H4K12. histone 4 lysine 12; HAT, histone acetyltransferase; HDAC1, histone deacetylase 1; mGluR2/3, metabotropic glutamate receptor 2/3; SC, spinal cord; SD, Sprague Dawley; TRPV1, transient receptor potential vanilloid type 1.