Published in final edited form as:
Front Biol (Beijing). 2014 June ; 9(3): 216–224. doi:10.1007/s11515-014-1304-4.

Neurotrophin signaling and visceral hypersensitivity

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Abstract

Neurotrophin family are traditionally recognized for their nerve growth promoting function and are recently identified as crucial factors in regulating neuronal activity in the central and peripheral nervous systems. The family members including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3) are reported to have distinct roles in the development and maintenance of sensory phenotypes in normal states and in the modulation of sensory activity in disease. This paper highlights receptor tyrosine kinase (Trk) -mediated signal transduction by which neurotrophins regulate neuronal activity in the visceral sensory reflex pathways with emphasis on the distinct roles of NGF and BDNF signaling in physiologic and pathophysiological processes. Viscero-visceral cross-organ sensitization exists widely in human diseases. The role of neurotrophins in mediating neural cross talk and interaction in primary afferent neurons in the dorsal root ganglia (DRG) and neurotrophin signal transduction in the context of cross-organ sensitization are also discussed.

Keywords

neurotrophin; signal transduction; visceral hypersensitivity; cross-sensitization

Introduction

Visceral hypersensitivity refers to increased sensation of stimuli to the visceral organs. It is a major source of abdominal pain which is attributable to abnormal responses of the sensory reflex pathways that govern the viscera. Information arising from the visceral organ project to extrinsic sensory neurons located in the dorsal root ganglia (DRG) and/or the nodose ganglia where information are organized and passed along to the central nervous system (CNS) in the spinal cord and brainstem. Descending nerves carrying excitatory or inhibitory neurotransmission in turn regulate the functionality of the organs. Neuronal tracing dye techniques have allowed identifying the spinal segmental distribution patterns of visceral sensory pathways and provide a powerful tool in study of the phenotypes of specifically labeled primary afferent neurons that innervate a particular organ. For example, neuronal

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Compliance with ethics guidelines

Li-Ya Qiao declares that she has no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant insitutional review board or ethics committee.

tracing studies demonstrate that primary afferent neurons with projection to the distal colon, the urinary bladder or a small number of neurons with dichotomizing projection to both bladder and colon are located in thoracolumbar (T10-L2) and lumbosacral DRG (L6-S1) (Applebaum et al., 1980; Morgan et al., 1981; Keast and Degroat, 1992; Christianson et al., 2007; Qiao and Grider, 2007). DRG neurons are of the pseudo-unipolar type. They have an axon with two branches referred to as a distal process in the periphery and a proximal process at the terminals in the dorsal horn of the spinal cord. Primary afferents synapse at the dorsal gray of the spinal cord with the efferent neurons located in the lateral horn of the spinal cord, and lead to changes in the efferent pathways and ultimately in the function of visceral organs.

The primary afferent neurons exhibit extensive plasticity in response to a variety of conditions and innocuous/noxious stimuli of the viscera, resulting in alterations in neurochemical, structural, organizational and electrophysiological properties of the neurons. One of the driving forces that lead to sensory neuronal plasticity under pathophysiologic conditions arises from the visceral organs which demonstrate increased levels of endogenous factors including growth factors, cytokines, chemokines, cannabinoids, adenosines, etc. (Dinis et al., 2004; Theiss et al., 2004; Nazif et al., 2007; Saini et al., 2008). The large number of mediators that are identified in the viscera during organ inflammation or injury not only play significant roles in mediating inflammatory process in the organs but also can lead to increases in the excitability of the axonal terminals located in the organ, resulting in sensory hypersensitivity (Nazif et al., 2007). The increases in the axonal terminal excitability in turn lead to neuropeptide expression in and release from primary afferent neurons at the peripheral terminals through multiple pathways and ion channel activation, which result in an increase in local blood flow exacerbating the inflammatory process and dysfunction of the visceral organ (Donnerer et al., 1992; Donnerer and Stein, 1992; Tonra et al., 1998; Roza and Reeh, 2001). Among the numerous factors generated by the viscera, nerve growth factor (NGF) has a prominent role in regulating sensory sensitivity. Exogenous NGF injected into the normal rat bladder (Lamb et al., 2004; Zvara and Vizzard, 2007) or intrathecal NGF to rat spinal cord (Yoshimura et al., 2006) result in bladder hyperactivity; conversely treatment with NGF inhibitor attenuates visceral hypersensitivity and organ hypertrophy as results of inflammation (Tyagi et al., 2006; Chung et al., 2010; Matricon et al., 2013). NGF is produced in and released from the epithelial cells and mast cells during visceral inflammation, where it acts in a paracrine manner to regulate the cytological changes and the sensitivity of the viscera (Skaper et al., 2001; Stanzel et al., 2008). Within the NGF family, other members including brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) also have critical roles in modulating sensory activity in diseases (Obata and Noguchi, 2006; Tender et al., 2011). Distinct receptors and signal transduction mediated by these neurotrophins endow them unique roles in the sensory reflex pathway that govern the visceral organs.

Neurotrophin signal transduction

The mammalian neurotrophins consist of four secreted small proteins, NGF, BDNF, NT-3, and NT-4/5. The high affinity receptors for each distinct neurotrophin are tyrosine kinase A (TrkA) binding to NGF, TrkB binding to BDNF or NT-4, and TrkC binding to NT-3. Under

some circumstances, NT-3 can also bind to TrkA and TrkB. The general neurotrophin receptor (NTR) p75 that was originally cloned and identified as a receptor for NGF binds to each of the neurotrophins with low affinity ($K_d \sim 10^{-9}$M) when present in cells alone or with high affinity ($K_d \sim 10^{-11}$M) when co-expressed with Trk by which the cell responsiveness to neurotrophins is further enhanced (Zampieri and Chao, 2004; Wehrman et al., 2007). The unprocessed precursor of the neurotrophins, the proneurotrophins, can also bind to p75NTR in the present of sortilin. Sortilin recognizes the pro-domain of the proneurotrophins, which upon dimerization with p75NTR, transmits signals through the intracellular docking protein to the intracellular domain of p75NTR. The cellular responses to Trk/p75NTR complex verse sortilin/p75NTR complex are often leading to opposite and antagonistic effects, with the former enhancing survival and growth promoting signals and the latter causing apoptosis (Wehrman et al., 2007; Skeldal et al., 2012). These are due to that interaction of p75NTR and Trk can increase the specificity and affinity of Trk for specific ligands thereby enhancing cell growth and survival through activation of the phosphoinositide 3-kinase (PI3K)/Akt pathway or the mitogen-activated protein kinases (MAPK)/extracellular signal-regulated kinases (ERK) pathway, while interaction of p75NTR with sortilin often activates the c-Jun N-terminal kinases (JNK), nuclear factor κ-B (NFκB), or Rho pathways which contribute to inflammatory responses and/or apoptosis. Neurotrophins influence cell biologic function through two mechanisms: 1) activation of signal transduction cascades at the nerve terminals, and 2) retrogradely transport of signaling molecules or signal from the nerve terminals to the neuronal cell body. The PI3K/Akt and ERK5 pathways are involved in the target-derived neurotrophin retrograde signaling cascades (Watson et al., 2001). The phospholipase C gamma (PLCγ) pathway activated by neurotrophins leads to Ca^{2+} and Na^{+} influx through the activation of ion channels and contributes prominently to long-term potentiation (LTP) and neuronal plasticity in CNS (Gruart et al., 2007). Another feature of neurotrophin transport involves anterograde transport of neurotrophins and receptors away from the neuronal cell body toward axonal terminals (Tonra et al., 1998; Wang et al., 2002; Ng et al., 2007; Ha et al., 2008).

Neurotrophin signaling in the viscera

NGF was discovered by Rita Levi-Montalcini, 1986 Nobel Laureate in Medicine, who found that NGF released from malignant tumors caused nerve fibers to grow rapidly. Subsequent studies have revealed that NGF is a target-derived trophic factor that promotes neuronal innervation and axonal terminal branching during development and has roles in the maintenance of neural homeostasis in adult. In the visceral organs, NGF and its receptor TrkA are found for their expression in neuronal and non-neuronal structures of the gut (Lin et al., 2005; Barada et al., 2007; Stanzel et al., 2008; Qiao and Grider, 2010), and NGF and TrkA are also expressed by the urinary bladder epithelial cells and detrusor muscle (see review (Cruz, 2014)). Pancreatic β cells are able to synthesize and secrete NGF (Rosenbaum et al., 1998) which can lead to selective hyperinnervation of the islets when NGF is overexpressed (Edwards et al., 1989). When the visceral organs are inflamed or dysfunctional by diseases, NGF levels are often elevated in the viscera which then become a strong chemical cue acting on cells within the organ via a paracrine manner and/or act on the nerve terminals and sensitize the nervous system (Nazif et al., 2007; Yu et al., 2012; Qiao et

al., 2013). In inflammatory states, NGF is a critical contributor in promoting excessive collagen production and deposition thereby resulting in poor compliance and stiffness of the organ (Chung et al., 2010; Kilic et al., 2011). In the urinary bladder with inflammation, endogenous NGF promotes type I collagen production through the MAPK and PI3K/Akt pathways (Chung et al., 2010). In chronic allergic airway inflammation, the increased NGF production contributes to type III collagen expression and deposition in the subepithelial compartment of the airways (Kilic et al., 2011). The novel role of NGF in regulating non-neuronal structure morphology is also suggested by transgenic overexpression of NGF in the organ which leads to excessive collagen deposition resulting in altered visceral physiology (Allen and Saban, 2010; Schnegelsberg et al., 2010; Kilic et al., 2011). NGF-regulated collagen production is mediated by the MAPK pathways involving the activation of ERK and p38, however, is independent of the traditional pathway involving the transforming growth factor beta (TGF-β)1/mothers against decapentaplegic homolog (SMAD) pathway (Kilic et al., 2011; Zhang and Qiao, 2012).

In addition to the non-neuronal tissue, overexpression of NGF in the smooth muscle cells under the control of the smooth muscle alpha-actin promoter results in robust sprouting of sympathetic axons in the colon and bladder (Elliott et al., 2009). Overexpression of NGF in the urothelium under the control of the uroplakin II promoter results in a marked increase in the density of sensory afferent fibers positive to calcitonin gene-related peptide (CGRP), substance P, and neurofilament 200, as well as sympathetic nerve fibers positive to tyrosine hydroxylase (Schnegelsberg et al., 2010). Inhibition of NGF action *in vivo* by NGF antiserum or Trk inhibitor K252a reverses peripheral mechanical hypersensitivity as a result of bladder inflammation suggesting Trk-mediated NGF action in the regulation of sensory activity (Guerios et al., 2006). This may be due to an action of NGF on receptors localized at the sensory nerve terminals in the viscera. NGF receptors TrkA and p75NTR are both expressed in the neuronal and non-neuronal structures in the primary afferent pathways. These transmembrane proteins are generally embedded in the plasma membrane of the cells in the visceral organ or nerve terminals of innervating neurons. TrkA is also found to be expressed in the mitochondrial compartment (Carito et al., 2012) and is likely to be involved in the process of oxidation stress (Podratz and Windebank, 2005; Ersahin et al., 2012; Valdovinos-Flores and Gonsebatt, 2013).

BDNF, which has about 50% amino acid identity with NGF, was first isolated from pig brain (Barde et al., 1982). BDNF is also found to express in non-neuronal tissues such as gut mucosa, adipocytes, liver, lung, pancreas and the urinary bladder (Lommatzsch et al., 1999; Bonini et al., 2001; Lucini et al., 2003; Lommatzsch et al., 2005; Grider et al., 2006; Steinkamp et al., 2012; Yu et al., 2012; Cruz, 2014). Its role in peripheral tissues is less studied. In addition to its ability in affecting neuronal function via retrograde fashion, BDNF and receptor TrkB more likely undergo antergrade transport away from neuronal cell bodies (Tonra et al., 1998; Ng et al., 2007; Ha et al., 2008). NT-4, which is often interchangeable with BDNF in initiating TrkB-mediated signal transduction, also has a role in the periphery in sensitizing peripheral innervation and sensory sensitivity (Krimm et al., 2006; Aven et al., 2014; Huang and Krimm, 2014).

Neurotrophin signaling in primary afferent neurons

The primary afferent pathways such as the vagal pathway and the spinal pathway contain primary afferent neurons that convey normal and aberrant sensation of the visceral organs. Primary afferent neurons are composed of a variety of cells in terms of their size, genotype and function. The spinal afferent pathways projecting via DRG at different levels of the spinal cord support the visceral reflexes including both nociceptive and nonnociceptive signals. Nociceptive signals from primary afferents enter the spinal cord through Lissauer's tract, a thin tract of small axons capping the dorsal horn, and terminate in laminae I of the dorsal horn gray matter, where ascend one or two segments before crossing to the contralateral side.

The distribution and expression level of each neurotrophin or Trk in primary afferent pathways are affected by many factors and dependent on the region, cell type and developmental stage. In adult DRG, TrkA, TrkB and TrkC mRNA are specifically expressed in functionally distinct neurons at a similar level ranging from 10% to 35% of the total number of neurons (Kashiba et al., 2003), with TrkA in nociceptive and thermoceptive small sensory neurons sensing temperature and noxious stimuli, TrkB in less specifically characterized touch neurons, and TrkC in proprioceptive neurons that sense body position (Huang and Reichardt, 2003). The phenotypic formation of DRG sensory neurons is largely dependent on the expression of certain Trks in these neurons (Wright and Snider, 1995). During development, all nociceptive neurons initially expressed TrkA, which mediates target-dependent cell survival. In mice lack of TrkA activation, 70% – 85% of sensory neurons are lost (Silossantiago et al., 1995); however, when mice are engineered to express TrkC protein from the TrkA genomic locus, overexpression of TrkC rescues the DRG neurons from apoptosis, but turns these DRG neurons from TrkA-containing nociceptive and thermoceptive phenotype to TrkC-containing proprioceptive-like neurons (Moqrich et al., 2004). TrkA also plays a role in sensory neuron diversification and maturation. During the first 2 to 3 postnatal weeks, a fraction of nociceptive neurons switch their neurotrophic factor dependence by downregulating expression of TrkA and upregulating the expression of Ret, the GDNF receptor, turning the nociceptive sensory neurons from TrkA-containing peptidergic to Ret-containing non-peptidergic subtypes (Molliver et al., 1997; Chen et al., 2006; Lopes et al., 2012). Activation of Trks in sensory neurons is mediated by retrograde or autocrine/paracrine neurotrophin signals (Korsching, 1993; Delcroix et al., 2003). NGF synthesis in the peripheral tissue and TrkA expression in the sensory neuronal soma do not begin until the fibers reach their peripheral targets (Davies et al., 1987). BDNF, on the other hand, is synthesized in the afferent neuronal cell body and released synaptically or extrasynaptically to induce pre- or post-synaptic efficacy, or maintain sensory neuronal survival (Swanwick et al., 2004; Obata and Noguchi, 2006; Qiao et al., 2008; Vaz et al., 2011; Xia et al., 2012). BDNF protein is expressed in small- and medium-sized sensory neurons that also express TrkA but not TrkB (Kashiba et al., 1997; Michael et al., 1997; Mannion et al., 1999; Qiao et al., 2013). Within the DRG, BDNF acts on TrkB-expressing neurons via a paracrine manner (Obata and Noguchi, 2006; Qiao and Grider, 2007; Xia et al., 2012).

Neurotrophin signaling in visceral sensory activity

The expression of neurotrophins in sensory neurons at physiologic state keeps at a low level. In normal healthy rats, less than 10% of DRG neurons express BDNF (Qiao et al., 2008; Lin et al., 2011; Yu et al., 2012). The level of BDNF dramatically increases with inflammation (Mannion et al., 1999; Obata and Noguchi, 2006; Qiao et al., 2008; Lin et al., 2011; Yu et al., 2012). The mechanism underlying BDNF upregulation in sensory neurons has been suggested showing an involvement of NGF-mediated ERK and PI3K/Akt pathways (Michael et al., 1997; Obata et al., 2003; Qiao and Grider, 2010; Yu et al., 2012; Qiao et al., 2013). Changes in the level of neurotrophins in sensory neurons with inflammation also contribute to the upregulation of a series of sensory markers thereby enhancing the activity of pronociceptive receptors and ion channels. CGRP is one of the most prominent sensory markers that labels peptidergic nociceptors and has a key role in mediating visceral sensory hypersensitivity (Plourde et al., 1997; Delafoy et al., 2006). In DRG, CGRP is co-expressed with TrkA and partially TrkB and its expression is regulated by NGF and BDNF (Patel et al., 2000; Ruiz and Banos, 2005; Qiao and Grider, 2007; Yu et al., 2012). In cultured DRG neurons, NGF, BDNF and NT-3 regulate CGRP expression with a different magnitude and time course (Mulderry 1994; Sterne et al., 1998; Qiao and Grider, 2007). NGF induces CGRP expression with an acute to prolonged effects (Ruiz and Banos, 2005); while acute BDNF treatment has no effects on CGRP expression but prolonged BDNF treatment is able to enhance CGRP expression (Qiao and Grider, 2007); in contrast, CGRP is unable to be regulated by NT-3 (Sterne et al., 1998). In an animal model of bladder inflammation, NGF-induced CGRP expression in DRG is regulated by the ERK5 but not the PI3K/Akt pathway (Yu et al., 2012). It is suggested that NGF-induced Akt activation participates in the expression, activation and trafficking of vaniloid receptor TRPV1 (Zhang et al., 2005; Stein et al., 2006; Zhu and Oxford, 2007). In DRG, TRPV1 is expressed in both peptidergic and non-peptidergic neurons and 60% of CGRP DRG neurons contain TRPV1 immunoreactivity, however, there is scarce overlap of TRPV1 and CGRP fibers in the dorsal horn of the spinal cord (Guo et al., 1999). NGF-induced TRPV1 expression also involves the activation of Ras-mediated MAPK (Bron et al., 2003; Zhu and Oxford, 2007), and Rac-mediated p38 MAPK (Puntambekar et al., 2005), which upregulates TRPV1 expression and increases pain perception (Ji et al., 2002). Other ion channels that participate in visceral pain perception, e.g. the tetrodotoxin-resistant (TTX-R) sodium channel α subunits Nav1.8 and Nav1.9, are also co-expressed with TrkA in sensory neurons and is regulated by NGF (Benn et al., 2001). Conversely, intrathecal infusion of NT-3 reduces the levels of Nav1.8 and Nav1.9 mRNA and proteins in DRG neurons (Wilson-Gerwing et al., 2008). This is consistent with an antagonistic role of NT-3 in suppressing thermal hyperalgesia associated with neuropathic pain (Wilson-Gerwing et al., 2005).

The axon terminals of primary afferent neurons are located in the dorsal horn of the spinal cord. Afferent input received by the sensory cell bodies in DRG pass along to the spinal cord where the signals are organized and in turn affect the physiological function of peripheral organ through efferent output. The spinal plasticity is initiated by the neurotransmitters produced in the afferent cell body and released at the terminal. These neuroactive compounds include glutamate, substance P, somatostatin, VIP, CGRP, neurotrophins, etc.

Electrophysiological recording of C-fiber evoked field potentials in spinal dorsal horn shows that exogenous BDNF is able to induce a LTP-like activity, which is blocked by antagonists of TrkB, N-methyl-D-aspartate (NMDA) receptor, ERK, p38MAPK, NF-κB, but not by JNK inhibitor (Zhou et al., 2008). Upregulation of BDNF in the DRG during visceral inflammation may also release at the central axonal terminals located in the spinal cord and regulates spinal central sensitization by activating the MEK/ERK pathway (Qiao et al., 2008). CGRP is able to induce the activation of cAMP-responsive element binding protein (CREB), a molecular switch of neuronal plasticity, in the spinal cord through signal convergent of PI3K/Akt and NMDA receptor-mediated pathways (Kay et al., 2013) and contribute to cystitis-induced bladder hyperactivity (Kay et al., 2013).

Neurotrophin signaling in cross-organ sensitization

Inter-organ cross-talk has been identified between visceral organs, such as the distal colon and the urinary bladder. Clinical evidence has shown sensory cross-sensitization between the urinary bladder and the distal colon (Alagiri et al., 1997; Ben-Ami et al., 2002). Patients with bowel dysfunction such as inflammatory bowel disease (IBD) are more likely to experience nocturia and some forms of urinary urge incontinence compared to the non-IBD population (Ben-Ami et al., 2002). Case studies show that 50% of patients with bowel dysfunction have evidence of bladder dysfunction including detrusor instability (Whorwell et al., 1986), suggesting the necessity of periodic urologic evaluation in the management of patients with bowel problems. Vice versa, individuals with interstitial cystitis are 100 times more likely to have IBD in comparison to the general population (Alagiri et al., 1997). In the past years, rigorous studies have been initiated to increase the understanding of the underlying mechanisms and pathways by which cross-organ sensitization is regulated (Malykhina, 2007; Brumovsky and Gebhart, 2010; Daly et al., 2013). In regard to the role of neurotrophins, strong evidence suggests that NGF elevated in one visceral organ such as the distal colon may lead to activation of the primary afferent neurons projecting to this organ and cross-activation of the nearby afferent neurons projecting to a different viscus such as the urinary bladder (Qiao and Grider, 2010; Xia et al., 2012). In an animal model involving visceral-somatic cross-sensitization, injection of NGF to the urinary bladder causes enhanced sensitivity to mechanical and thermal stimulation of both hind paws (Bielefeldt et al., 2006). Overexpression of NGF in the urinary bladder also triggers hypersensitivity of the distal colon (Bielefeldt et al., 2006). This suggests that excess of NGF at the nerve terminals may induce neuronal alterations in the primary afferent pathway that receives afferent input from multiple organs. NGF signaling can undergo retrograde transport to the DRG and regulate a paracrine effect within the DRG to facilitate neuron-neuron interaction (Qiao and Grider, 2010; Xia et al., 2012), or may act on dichotomizing DRG neurons that project to both organs (Christianson et al., 2007; Qiao and Grider, 2007). NGF signal can also activate the ERK pathway and lead to neuropeptide expression (Li et al., 2008; Berger, 2009). As for BDNF, its paracrine action on nearby TrkB-containing DRG neurons or perineuronal satellite cells may lead to inter-cell interaction and neuronal cross-sensitization (Lee et al., 1999; Qiao and Grider, 2007; Xia et al., 2012). Cross-organ sensitization can also be regulated at the spinal level (Qin et al., 2005). It is not known whether BDNF release to the spinal cord regulates this process. The increases in mast cells are suggested to have a role in

cross-organ sensitization (Fitzgerald et al., 2013). In the periphery, TrkB/BDNF binding can acutely sensitize nocireceptive pathway that require the presence of mast cells (Huang and Reichardt, 2001). Activation of ion channels such as TRPV1 and TTX-R sodium channels in the DRG are involved in viscera-visceral cross-organ sensitization (Malykhina et al., 2006; Chaban, 2008; Pan et al., 2010; Lei and Malykhina, 2012). The ability of neurotrophins in regulating the activity of these channels (Benn et al., 2001; Natura et al., 2005; Zhang et al., 2005; Stein et al., 2006; Zhu and Oxford, 2007; Zhang et al., 2008) may underlie the mechanisms of DRG neuronal cross - activation.

Conclusions

Neurotrophins are traditionally known for their roles in inducing the survival, differentiation, and growth of neurons. With each neurotrophin binding to a specific receptor and facilitate unique signaling pathways, the family members, NGF, BDNF and NT-3 as mostly studied, have distinct roles in mediating neuronal physiology especially in visceral hypersensitivity. Target-derived NGF acts on sensory nerve terminals leading to sensory activation and neuropeptide production in the primary afferent neurons that innervate the visceral organ. BDNF generated by the primary afferent neurons acts in a paracrine manner within the DRG leading to neuron-neuron cross-activation, and also releases to the nerve terminals peripherally to the target organ where reinforcing terminal sensitization in the presence of mast cells and/or centrally to the spinal cord leading to central sensitization. NT-3 often has antagonistic role in sensory hypersensitivity. Although supporting documents suggest the role of neurotrophins in regulating cross-organ sensitization, the underlying mechanisms and signaling pathways by which neurotrophins regulating neuropeptide expression and ion channel activity is unknown. Tanezumab, a humanized monoclonal antibody against NGF, has been tested in reducing pain arising from inflammation of the urinary bladder (Evans et al., 2011), however it shows unfavorable side effects. In March 2012 the FDA Committee voted in favor of a continuation of Anti-NGF testing as long as certain safety precautions were made. A better understanding of neurotrophin action and signal transduction in visceral hypersensitivity and pain may provide strategies for an alternative target in the neurotrophin cascades.

Acknowledgments

This work was supported by National Institutes of Health (Grant suppot: NIH DK077917).

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