Emerging neuropeptide targets in inflammation: NPY and VIP

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Chandrasekharan B, Nezami BG, Srinivasan S. Emerging neuropeptide targets in inflammation: NPY and VIP. Am J Physiol Gastrointest Liver Physiol 304: G949–G957, 2013.—The enteric nervous system (ENS), referred to as the “second brain,” comprises a vast number of neurons that form an elegant network throughout the gastrointestinal tract. Neuropeptides produced by the ENS play a crucial role in the regulation of inflammatory processes via cross talk with the enteric immune system. In addition, neuropeptides have paracrine effects on epithelial secretion, thus regulating epithelial barrier functions and thereby susceptibility to inflammation. Ultimately the inflammatory response damages the enteric neurons themselves, resulting in dereregulations in circuitry and gut motility. In this review, we have emphasized the concept of neurogenic inflammation and the interaction between the enteric immune system and enteric nervous system, focusing on neuropeptide Y (NPY) and vasoactive intestinal peptide (VIP). The alterations in the expression of NPY and VIP in inflammation and their significant roles in immunomodulation are discussed. We highlight the mechanism of action of these neuropeptides on immune cells, focusing on the key receptors as well as the intracellular signaling pathways that are activated to regulate the release of cytokines. In addition, we also examine the direct and indirect mechanisms of neuropeptide regulation of epithelial tight junctions and permeability, which are a crucial determinant of susceptibility to inflammation. Finally, we also discuss the potential of emerging neuropeptide-based therapies that utilize peptide agonists, antagonists, siRNA, oligonucleotides, and lentiviral vectors.

ENS; inflammation; neuropeptides; neurogenic inflammation

The enteric nervous system (ENS) is organized into two main plexi that innervate the submucosa (submucosal plexus/Meissner’s plexus) and the muscularis propria (myenteric plexus). The neural networks of the plexi regulate the secretory and motor functions of the gastrointestinal tract via multiple neurotransmitters. In inflammatory diseases of the gut such as inflammatory bowel disease (IBD), the neural morphology, circuitry, and physiology are adversely affected (36). Inflammation induces abnormalities like neuronal hyperplasia, ganglion and axonal degeneration, and necrosis, alterations in the synthesis and release of neurotransmitters and/or their receptor systems, leading to impairment of secretory and motor gastrointestinal functions (82). These adaptive changes in the enteric neurons lead to significant neuronal remodeling that underlies the plasticity of the ENS.

In addition to being a target of inflammation, the neurotransmitters produced by the ENS also play a pivotal role in orchestrating the inflammatory processes in the gastrointestinal tract via effects on gut-associated lymphoid tissue (GALT), the largest immune repertoire in the body (77). GALT recognizes the “self/commensal” bacterial flora and maintains tolerance in a normal state. Considering the proximity to immune cells, it is not surprising that neuropeptides from the ENS can modulate immune cell functions like neutrophil chemotaxis (42), histamine release from mast cells (22), phagocytosis, chemokine expression (12, 79), and immunoglobulin production (51).

Extensive research in the past decade has demonstrated the significance of enteric neuroenteric immune interactions in potentiating or dampening the inflammatory responses.

Neurogenic Inflammation

In late 1980, peripheral nerves were first recognized to play an active role in modulating immune responses and disease pathology of inflammatory diseases (17). Neuropeptides released from small-diameter sensory nerves were observed to regulate mast cell activation and vascular responses (14, 22), chemotaxis of neutrophils (42), and differentiation of T helper cells (63). Collectively, the responses evoked by neuropeptides, which were analogous to the inflammatory responses, were characterized as “neurogenic inflammation.” However, the effects of neuropeptides last longer because of the feedback regulation between neuropeptide expression and cytokine release from immune cells, compared with vasodilation and plasma extravasation, which are acute and rapid responses. Recently it was demonstrated that enteric hyperinnervation can actively drive intestinal inflammation, thus emphasizing the relevance of neurogenic inflammation in the gut (57). Since
dysregulated immune signaling is central to IBD (18) and changes in neuropeptides have been associated with IBD (33, 59), understanding the role of enteric neuropeptides and neurogenic inflammation would help gain better insights into the pathophysiology of inflammatory diseases like IBD.

**Mechanisms Mediating Neurotransmitter Release**

Various mechanisms that mediate neurotransmitter release from sensory neurons include voltage-gated calcium channels (65) (capsaicin, heat, and protons), protein kinase C (PKC) (bradykinin) (83), and tryptase (via proteinase activated receptors, PAR-2) (84). It has been demonstrated recently that the activation of Toll-like receptor (TLR)-4 on enteric and sensory neurons can induce neuronal excitability, calcium signaling, and neuropeptide release (56).

**Neuropeptide Effects on Inflammation**

Neuropeptides may have anti-inflammatory [vasoactive intestinal peptide (VIP) and galanin] or proinflammatory effects [neuropeptide Y (NPY), substance P], serotonin, and neuropeptide Y. Various mechanisms that mediate neurotransmitter release from sensory neurons include voltage-gated calcium channels (65) (capsaicin, heat, and protons), protein kinase C (PKC) (bradykinin) (83), and tryptase (via proteinase activated receptors, PAR-2) (84). It has been demonstrated recently that the activation of Toll-like receptor (TLR)-4 on enteric and sensory neurons can induce neuronal excitability, calcium signaling, and neuropeptide release (56).

NPY is a 36-amino acid peptide produced abundantly in the central and peripheral neuronal systems. NPY modulates anxiety (91), appetite (32), blood pressure, and nociception (11). In the gut, NPY is abundantly produced in the sympathetic nerves and is coreleased with norepinephrine (45), where it induces colonic relaxation. Of the five receptors, NPYY1 receptor is critical to inflammatory signaling as Y1 receptor activation has been shown to exert negative effects on T cell responses, but activates antigen-presenting cells (87). Thus NPY producing neurons in the gut are potent modulators of immune responses during inflammation.

**NPY Is an Immunomodulator**

NPY potentiates inflammation by modulating key immune cell functions via Y1/Y2 receptors. Several studies have been instrumental in understanding NPY actions on immune cells. Interestingly, NPY is produced from T cells, macrophages, and dendritic cells during inflammation (88). NPY effects on immune and inflammatory responses are regulated by tissue-specific expression of different receptor subtypes that belong to the family of 7-transmembrane G protein-coupled receptors (GPCRs) (72). It is documented that NPY modulates inflammation by regulating key immune cell functions like neutrophil chemotaxis (42), granulocyte oxidative burst and nitric oxide production (29), T helper cell differentiation (12), natural killer cell activity (74), suppression of lymphocyte proliferation (58), and activation of antigen-presenting cells (APC) (88). The NPYY1 receptor plays a crucial role in immunomodulation as attenuation of inflammation has been noted in Y1-receptor knockout mice (43). In addition, elegant studies have delineated the bimodal role of Y1 receptor in the immune system, where it has been demonstrated that NPY exerts negative regulation on T cells but activates APC functions (88). NPYY1 receptors have been also found to mediate µ-opioid receptor (MOR)-induced reductions of natural killer cell activity (74). MORs are widely expressed in the central and peripheral neurons (68). Cytokines enhance MOR expression in mucosal immune cells and myenteric neurons during experimental inflammation (68). Hence NPY-MOR interactions in immune cells may have profound effects in modulating inflammatory signaling. The Y1 receptor is rapidly internalized by clathrin-dependent events (suggesting interactions with ß-arr3) and is also recycled rapidly (85).

NPY Y2 receptor is localized on immune cells (30) and plays a significant role in migration and adhesion of leukocytes. Contrary to the Y1 receptor, Y2 binds N-truncated fragments of the NPY peptide generated by activity of the enzyme dipeptidyl peptidase 4 (DPP4 or CD26) (30). NPY is a substrate for DPP4, a serine-endopeptidase that is highly expressed on T cells and other immune cells. DPP4 is crucial because it terminates the action of the NPY (1-36) on Y1 receptor by cleaving it into NPY (3-36) peptide. Studies using DPP4 inhibitors, synergistic with NPY, are suggestive of potentiation of inflammation by NPY-Y1 axis. Studies on knockout murine models of DPP4 have revealed attenuation of disease activity in CD26+/− mice with significant upregulation of macrophages (28).

A schematic representation of interaction between enteric immune cells and NPY is summarized in Fig. 1. As depicted in Fig. 1, NPY can activate macrophages leading to production of...
cytokines like IL-12, TNF-α, nitric oxide, and IL-4. Interestingly NPY inhibits T cell cytokines like IFN-γ. It is therefore suspected that Y1 receptor expression on T cells is induced only after T cell activation, thus maintaining a negative feedback loop that prevents sustained or hyperactivation of T cell responses (87).

**NPY Activation of Intracellular Signaling Pathways in Immune Cells Mediates Cytokine Secretion in the Gut**

NPY binding to the Y1/Y2 receptors activates various signaling pathways that mediate immunity and inflammation. These include adenylate cyclase-cAMP, NF-κB, COX-2, protein kinases (MAPK), protein kinase A (PKA), phospholipase C, PKC, and phosphatidyl inositol-3-kinase.

The transcription factor NF-κB is a key regulator of cellular response to various stressors and mediates secretion of proinflammatory cytokines (8). NPY has been shown to inhibit nuclear translocation of NF-κB in microglia challenged with IL-1β, thus inhibiting IL-1β-induced nitric oxide release (35). In addition, the presence of potential binding sites for NF-κB has been identified in the human and murine NPY-Y1 receptor gene (80). Interestingly, inflamed mucosa from IBD patients display increased NF-κB activity in macrophages and epithelial cells, which correlates significantly with the severity of inflammation (61). Accordingly, downregulation of inflammation has been shown by administration of antisense oligonucleotides to the p65 subunit of NF-κB (49). Recent studies using NPY antisense oligonucleotides in mouse model of DSS colitis also revealed a reduction in TNF-α and phosphorylation of NF-κB (67). Thus NF-κB is a potent regulator of NPY-induced inflammatory signaling that could be targeted for therapy. NPY via PKC modulates intracellular Ca²⁺ mobilization and thus plays a significant role in controlling the excitability of submucosal neurons and hyperexcitability after inflammation (69). In addition, NPY modulates macrophage functions like oxidative burst via PKC (30).

All NPY receptor subtypes activate MAPK pathways, and as a consequence influence the control of gene expression and cell fate. NPY via activation of c-Jun NH₂-terminal kinase (JNK) and p38 kinase play a significant role in the innate and adaptive immune systems as activation of TLRs can activate MAPK. MAPK activation in sensory neurons can also regulate inflammatory pain (64).

**Stress and NPY**

Recent studies have demonstrated that perceived stress, negative mood and major life events can significantly trigger the flare of inflammatory diseases (5). Stress response involves mainly the glucocorticoids and catecholamines (norepinephrine and epinephrine) and is mediated by hypothalamic-pituitary axis and sympathoadrenomedullary system. NPY may or may not be coreleased with catecholamines during stress. Stress-induced NPY release through Y2 receptors can inhibit...
production of catecholamines or cortisol presynaptically and thus modulate the overall magnitude of stress response (62). Recently it has been demonstrated that stress exaggerates diet-induced obesity via NPY and its receptor (NPY2R) up-regulation in the white adipose tissue. NPY upregulation in turn induced a metabolic syndrome-like condition involving angiogenesis, macrophage infiltration, adipocyte proliferation, and differentiation, resulting in abdominal obesity. Elegant studies demonstrated that these effects were reversed by pharmacological inhibition or adipose-specific knockdown of NPY2R, thus opening new treatment options for treatment of metabolic syndrome focused on inhibition of NPY receptors (53).

Effects of NPY on Epithelial Permeability

The maintenance of the integrity of the intestinal epithelium is crucial in preventing inflammatory processes. Barrier integrity within intestinal epithelia is mediated by desmosomes, adherens junctions, and tight junctions. Tight junctions are composed of at least 20 transmembrane proteins embedded across the plasma membrane, with extracellular domains joining one another directly and intracellular domains linked to the actin cytoskeleton of the cell (4). A compromised epithelial barrier adversely affects the phagocytosis of pathogens, secretion, and nutrient uptake, thus disturbing epithelial homeostasis and increasing the susceptibility to diseases like IBD (86).

As submucosal neurons innervate the epithelium, various coculture models of neuronal and epithelial cell lines have been utilized to better understand the neuronal modulation of epithelial barrier functions. It has been recently shown that dysfunction of tight junctions can also induce activation of the immune system in experimental colitis (78). Stress has been postulated to play a significant role in causing active flares of diseases like IBD and irritable bowel syndrome leading to disorders in epithelial secretion and permeability (3).

NPY, abundantly produced by submucosal neurons, is released within the lamina propria of both crypts and villi. The effects of NPY on epithelial cells are mainly mediated by G protein-coupled receptors Y1 and Y2 (72, 81). These receptors regulate epithelial secretory function and hence contribute to changes in permeability. Recently it has been demonstrated that NPY via stimulation of Erk/MAPK-dependent pathways can stimulate Cl−/HCO3− (OH−) exchange activity, and alterations in the association of Cl−/HCO3− (OH−) exchanger with lipid rafts might contribute to proabsorptive effects of NPY (73). In addition to its direct effect on epithelial permeability via its receptors, NPY can also have indirect effects on epithelia via regulation of cytokine production.

Direct Effects of NPY on Intestinal Epithelium via Y1 Receptors

A schematic representation of mechanism of NPY regulation of epithelial permeability is given in Fig. 2. NPY peptide via Y1 receptors exerts an antisecretory role via attenuation of cytoplasmic cAMP (81), thereby reducing the activity of the PKA-sensitive chloride channels (CFTR) and basolateral K+ conductance (21). As CFTR-mediated chloride secretion modulates secretory diarrhea phenotype, it is probable that stable Y1 agonists could be therapeutically beneficial as novel antidiarrheals. However, in experimental colitis, antisecretory effects are observed to be diminished as reported recently because of reduction in Y1 receptor expression (52).

Indirect Effects of NPY on Intestinal Epithelium via Modulation of Immune Cell Cytokine Release

NPY can also modulate epithelial permeability by regulating TNF-α release from immune cells or histamine from mast cells as depicted in Fig. 2, resulting in chloride secretion (66). Binding of histamine to H2 receptors on enteric neuronal cell bodies can elevate excitability of submucosal secretomotor neurons, increasing the volume of mucosal secretions of electrolytes and H2O, thus causing neurogenic secretory diarrhea commonly observed in IBD (20). The diarrhea may be helpful in expulsion of pathogenic bacteria and thus beneficial to the organism.

Vasoactive Intestinal Peptide

VIP is a 28-amino acid, inhibitory neuropeptide that induces colonic relaxation like NPY. Unlike NPY, VIP promotes secretory effects on the colonic epithelia and is proven to have anti-inflammatory role. VIP downregulates proinflammatory cytokines and mediators like IL-6, TNF-α, IL-12, nitric oxide, and chemokines (26, 54, 75). Recent research has demonstrated that VIP is also produced by type 2 T lymphocytes (Th2), raising the possibility of viewing it as a Th2 cytokine (24, 70).

VIP Is an Immunomodulator

VIP has potent anti-inflammatory effects due to varied effects on immune cell function particularly by favoring T helper (Th) cell differentiation toward a “Th2” phenotype (25). In addition, VIP also stimulates regulatory T cell production and inhibits macrophage proinflammatory actions. All these effects contribute to downregulation of inflammation. Since VIP administration has demonstrated downregulation of chemokine production and expression of chemokine receptors (34), VIP has been successfully administered in several models of neurodegenerative disorders (39). VIP also exerts its protective effect via stimulation of T cells to produce neurotrophic factors such as brain-derived neurotrophic factor to compensate for inflammation-induced neuronal loss (71).

Alterations in VIP Levels During Inflammation

Despite the well documented anti-inflammatory effects of VIP, there has not been consistency in linking VIP expression to pathophysiology of intestinal diseases. Differential changes in VIP expression has been noted in the submucosal and myenteric plexi of pediatric Crohn’s patients (15). A positive association between plasma levels of VIP and active flares of IBD have been demonstrated (31). On the contrary, recent studies also demonstrate decreased binding and epithelial downregulation of VIP and its receptor (VPAC1) in patients with ulcerative colitis (48, 90). These observations suggest that VIP production from neuronal and nonneuronal cell types (inflammatory cells and epithelia) differ during normal and inflammatory conditions.
VIP Attenuates Inflammation by Modulating Key Immune Cell Functions via VPAC1/VPAC2

VIP maintains immunological tolerance and homeostasis in the gut mainly by regulation of T cell responses and TLR-mediated innate immune responses. The effects of VIP are mediated by the receptors VPAC1 and VPAC2, the GPCRs expressed on T cells. VPAC1 are constitutively expressed on T cells whereas VPAC2 expression is induced by inflammation (25). VIP promotes Th2-like responses and inhibits Th1 immune responses via VPAC2 as VPAC2 gene depletion leads to increased Th1-type responses (46). In this study short-deletion splice variant of VPAC2 was utilized, which, despite having similar affinity to VIP, failed to induce chemotaxis, T cell adenylate cyclase signaling, and inhibition of IL-2 production (41). Intraperitoneal administration of VIP has been shown to downregulate the Th1-driven responses, including the systemic levels of proinflammatory cytokines like TNF-α, and IL-6. Another mechanism of VIP-mediated protection is by promoting regulatory T cell function via increased expression of Foxp3 and TGF-β (6). In addition, VIP regulates innate and adaptive immunity by downregulation of TLR-2 and TLR-4 expression, and chemokine CXCL1 production (7, 44). On the contrary TLR ligands (TLR-2, 4) can effectively downregulate the VPAC2 receptor in macrophages via MAPK kinase signaling pathway (44). Thus VIP is a potent regulator of T cell- and TLR-mediated responses and plays a significantly role in gut homeostasis.

VIP Activation of Intracellular Signaling Pathways via VPAC1/VPAC2 Mediates Anti-Inflammatory Effects

Several studies have examined the signaling pathways activated by VIP on immune cells. Mainly, anti-inflammatory effect of VIP is ascribed to anti-inflammatory cytokine IL-10 synthesis via PKA-mediated phosphorylation of cAMP response element binding (54). Also VIP downregulates TNF-α expression by inhibiting downstream phosphorylation of MEK4, JNK, and c-Jun mediated through the specific VPAC1 receptor and the cAMP/ PKA pathway (50). VIP also reprograms macrophages to produce Th2-type cytokines by favoring the development of bone marrow-derived tolerogenic dendritic cells via VPAC1 receptor and PKA, which involves NF-κB inhibition (37, 55). VIP also exerts its anti-inflammatory effects via downregulation of NF-κB-dependent gene activation of the COX-2 promoter (38).
A schematic representation of interaction between enteric immune cells and enteric neuropeptide VIP is summarized in Fig. 1.

**VIP Exerts Direct and Indirect Effects on Epithelial Permeability**

VIP also regulates epithelial barrier function, thereby determining the susceptibility to inflammation. VIP-ergic neurons in the submucosa directly innervate intestinal epithelial crypt cells and promote intestinal ion and fluid secretion via VPAC1-cAMP (10, 20). In addition, VIP indirectly modulates epithelial permeability via regulation of epithelial tight junction proteins. VIP-ergic pathways have been recognized to mediate increased expression of the tight junction protein zona occludens in the human submucosal neuronal layer and reduce paracellular epithelial permeability in Caco2 and HT29-C1.16E monolayers (60). VIP has also been demonstrated to attenuate barrier dysfunction associated with *Citrobacter rodentium*-induced colitis in mice via reduction of paracellular permeability by prevention of translocation of tight junction proteins (19).

**Therapeutic Potential**

Neuropeptides and their receptor agonists or antagonists can be exploited as powerful therapeutic tools to attenuate inflammation. This is because neuropeptides modulate various aspects of inflammatory signaling as well as epithelial permeability via their receptors localized on immune and epithelial cells. A change in the content of neuropeptides and their receptor expression during pathological states induces a state of neuronal remodeling that can tip the balance of neuroimmune and neuroepithelial interactions. Hence administration of neuropeptide receptor agonists, antagonists, antisense oligonucleotides, or silencing the neuropeptide expression (using siRNAs) offers promise in attenuating or improving some of the pathological manifestations in inflammatory diseases.

**NPYY1 Receptor Antagonists**

NPYY1 antagonists may be exploited for treating inflammatory signaling as Y1 receptor is widely expressed on immune cells and promotes inflammatory signaling. Several peptide and nonpeptide agonists and antagonists have been synthesized for the Y1 receptor, and studies in rodent models have explored the effects of these compounds on orexigenic and vasoconstrictor responses. Peptidic antagonists of NPY are mainly the N-truncated NPY analogs. The first nonpeptide antagonist developed was BIBP-3226, i.e., (R)-N-2-(diphenylacetyl)-N-[(4-hydroxyphenyl) methyl]-arginimamide, which is very potent and highly selective for Y1 receptor (2).

Another significant role of NPY is in bone homeostasis. As many as 30 to 60% of people with IBD report osteoporosis or bone abnormalities due to steroid therapy, inflammation, or vitamin D deficiency (47). These conditions occur more frequently in people with Crohn’s disease than in those with ulcerative colitis and are more common in women than in men (www.ccf.org). NPYY1 knockout mice have greater bone mass and formation, and Y1 receptors have been observed on osteoblasts (76). Current pharmacological treatments for osteoporosis that utilize bisphosphonates that incorporate into bone and prevent bone reabsorption by osteoclasts are not successful in case of advanced osteoporosis. NPYY2 antagonists can inhibit osteoclast activity via a hypothalamic mechanism and also lead to reduced NPYY1 function that in turn would lead to increased osteoblast function and increased bone density (9).

Under normal conditions, NPY regulates water absorption in the colonic epithelia via Y1 (antisecretory) and Y2 receptors (promotes secretion). NPY also induces colonic relaxation and modulates colonic motility. Hence NPY receptors may be targeted to treat motility disorders like constipation or diarrhea. For example, a Y1 agonist would promote water absorption, which could be used to curb diarrhea, and a Y1 antagonist may also be utilized to treat constipation. On the other hand, enteric inflammation can skew the normal functions of NPY, resulting in loss of antiserotory effects of NPY, which is attributed to the downregulation of NPYY1 receptor mRNA and protein in the colonic epithelia (52). Inflammation also induces extensive damage to neurons in the gut, causing impaired gut motility. Moreover, the limited availability of receptor ligands coupled with the lack of studies to validate their efficacy and side effects on gut health are also decisive factors that restrict their therapeutic potential. Hence, considering the relevance and multifaceted roles of NPY in various human diseases like inflammation, pain, cancer, obesity, epilepsy, alcoholism, cardiovascular diseases, anxiety, bone metabolism, etc., more research is needed to exploit the full potential of these receptor agonists and antagonists in novel treatment strategies.

**VIP Vectors**

Despite the well-documented anti-inflammatory potential, VIP-based drug design has not been successful because of the peptide instability and limited bioavailability. Recent advances in the field include synthesis of lipophilic analogs of VIP, peptide derivatives that mimic the activity of VIP (40), and lentiviral vectors in a model of autoimmune arthritis (27). Administration of the peptide itself in mouse models of colitis have been shown to improve the clinical score and gastrointestinal inflammation (1).

**Challenges in Therapy**

Despite the well-documented recognition of the role of neuroimmune interactions in the pathology of several inflammatory diseases, there has not been a corresponding success in the application of neuropeptides in therapy. A key factor that limits the usage of peptide agonists or antagonists in therapy is their multiple cellular targets. Hence the targeted delivery of the neuropeptide or its receptor agonists or antagonists via nanoparticles is a desirable option. Another approach would be to utilize gene therapy to maintain a desired level of expression of the neuropeptide or its receptor via a tissue-specific promoter. Here again, the adverse effects of commonly used viral vectors like toxicity, immune activation, and complications due to interference with other genes are undesirable side effects. Hence combining a nonviral approach in a nanoparticle-based delivery system may represent an attractive option to exploit the therapeutic potential of neuropeptides.

**Summary**

In summary, neuropeptides NPY and VIP, via their receptors on immune cells, can activate or dampen inflammatory signaling. The expression of a specific neuropeptide and its receptor can vary during active inflammatory and latent phases of the
disease. This can significantly alter immune cell responses and production of cytokines. On the other hand, inflammation can alter the neuropeptide milieu in the gut (inflammation-associated neuronal remodeling), which in turn can have drastic paracrine effects on immune and epithelial functions.

Conclusions

Enteric neuropeptides NPY and VIP, and their receptors, play a significant role in modulating immune cell functions and epithelial barrier functions. Thus they are important to the predisposition, propagation, and sustainability of inflammation. Hence further understanding of their role and receptors in inflammatory signaling and epithelial barrier functions can help develop new therapeutic targets to treat inflammatory diseases.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

B.C. and S.S. conception and design of research; B.C., B.G.N., and S.S. prepared figures; B.C. drafted manuscript; B.C. and S.S. edited and revised manuscript; B.C. and S.S. approved final version of manuscript.

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