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MINI-REVIEW | *Neurogastroenterology and Motility*

Novel transmitters in brain stem vagal neurocircuitry: new players on the pitch

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Bülbül M, Travagli RA. Novel transmitters in brain stem vagal neurocircuitry: new players on the pitch. *Am J Physiol Gastrointest Liver Physiol* 315: G20–G26, 2018. First published March 29, 2018; doi:10.1152/ajpgi.00059.2018.—The last few decades have seen a major increase in the number of neurotransmitters and neuropeptides recognized as playing a role in brain stem neurocircuits, including those involved in homeostatic functions such as stress responsiveness, gastrointestinal motility, feeding, and/or arousal/wakefulness. This minireview will focus on the known physiological role of three of these novel neuropeptides, i.e., apelin, nesfatin-1, and neuropeptide-S, with a special emphasis on their hypothetical roles in vagal signaling related to gastrointestinal motor functions.

apelin; nesfatin; neuropeptide S; stomach; stress

INTRODUCTION

Vagal pathways originating in the brain stem provide a means by which gastric functions can be modulated with a high degree of precision. At the most basic level, the cell bodies of vagal efferent inputs innervating the stomach are regulated by an array of visceral sensory inputs that arrive primarily, although not exclusively, from afferent fibers in the vagus nerve. The cell bodies for this afferent pathway originate from the bipolar neurons of the nodose ganglia; these fibers carry information about the physiological status of the gut directly to brain stem circuits regulating visceral functions in general and gastric functions in particular. Vagal afferent inputs impinge upon and are integrated by neurons in the nucleus tractus solitarius (NTS) that, in turn, regulate the activity of efferent parasympathetic preganglionic vagal projections to the stomach that arise from the spontaneously firing cholinergic neurons of the dorsal motor nucleus of the vagus (DMV). Postganglionic parasympathetic neurons are located in the myenteric ganglia, which form a dense structural network embedded between the longitudinal and circular smooth muscle layers of the stomach. Myenteric neurons inhibit gastric motility via either the activation of a nonadrenergic noncholinergic (NANC) pathway or the withdrawal of the tonic cholinergic input (93).

Both NTS and DMV neurons are connected to, among other areas, hypothalamic and limbic nuclei (9), which play significant roles in the processing of neuroendocrine, behavioral, and autonomic functions (1, 82–84). In particular, the DMV and NTS provide reciprocal inputs to the paraventricular nucleus of the hypothalamus (PVN) and contribute to maintaining homeostatic balance in response to stress (60).

Within the past several decades, a number of novel peptide molecules have been identified as modulators of brain stem neurocircuits. Among these peptides, apelin, neuropeptide-S (NPS), and nesfatin-1 projections, neuronal expression patterns, and the location of their specific receptors suggest a central regulatory role of autonomic functions.

APELIN

Apelin was identified initially in bovine stomach extracts as the endogenous ligand for the G protein-coupled APJ receptor (91). The apelin gene encodes the 77-amino acid preproapelin precursor molecule that, upon selective enzymatic cleavage, gives distinct forms of apelin, including apelin-36, -26, -19, -17, -13, and -12 (46, 91). Among these mature peptides, the pyroglutamyl form of apelin-13 (pGlu-apelin-13) has been shown to be the most abundant and, in rats, exhibits a greater affinity for APJ than the other cleavage products of the precursor (24, 54).

The APJ receptor is expressed robustly in hypothalamic nuclei [PVN and supraoptic nucleus (SON)] (54, 64, 73) and brain stem structures, including rostral ventrolateral medulla (RVLM), NTS (15, 64), DMV, and hypoglossal nucleus (HGN) (15).

In the rodent brain, apelin-producing cells have been detected in several hypothalamic structures, including the PVN, preoptic, ventromedial (VMN), dorsomedial (DMN), and arcuate (ARC) nuclei, the reticular tegmental pontine nucleus, lateral reticular nucleus, spinal trigeminal nucleus, HGN, nucleus ambiguus (NA), and retrofacial nucleus (46, 54, 77). Apelinergic projections have been found to innervate the periaqueductal gray matter, locus coeruleus (LC), Barrington's

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nucleus, medial and lateral parts of the parabrachial nucleus, and circumventricular structures, including the organum vasculosum of the lamina terminalis, the subfornical organs (SFO), the subcommissural organ, and the area postrema (AP) (13, 15, 77).

The apelin/APJ receptor system has been demonstrated to play a role in hypothalamic regulatory functions such as food intake (90), drinking behavior, fluid homeostasis (59, 65, 76, 90), neuroendocrine control (38, 61, 62, 90), and autonomic/visceromotor signaling, including cardiovascular, gastrointestinal motor, and respiratory functions (4, 12, 13, 15, 27, 52, 53, 59, 85, 101, 102, 104). A growing body of evidence suggests the central apelinergic system is involved in the regulation of gastrointestinal motor functions. In rodents, for example, central (icv) administration of apelin inhibits solid gastric emptying (4, 13, 52), colonic transit (13, 101), and postprandial colonic contractions (13) and increases the antral interdigestive migrating motor complex (51). More importantly, microinjection of apelin-13 in the DMV inhibits gastric tone and motility in anesthetized rats (15). In fact, the APJ receptor is known to be expressed in a subgroup of gastric-projecting DMV neurons, and the gastroinhibition resulting from fourth-ventricular application of apelin is abolished by vagotomy and atropine pretreatment, suggesting that, in the rat, apelin inhibits gastric motor functions through withdrawal of the vagally dependent cholinergic postganglionic pathway (4, 15).

In mice, conversely, pretreatment with the μ-opioid receptor antagonist naloxone abolished the apelin-13-induced inhibitory action on gastrointestinal motor functions (52, 101). One of the most common adverse effects of therapeutic opioid use is severe constipation, most likely because of activation of colonic μ-opioid receptors (11, 34, 43, 70, 89). Similarly, activation of central opioid receptors induces gastric relaxation, most likely via an effect, at least in part, on vagal brain stem neurocircuits (7, 8). Interestingly, some studies suggest the involvement of apelin in central opioid signaling (48, 79, 80). Indeed, central administration of apelin-13 has been shown to potentiate morphine-induced analgesia, and the effects of apelin-13 were reversed by the opioid receptor antagonist naloxone (97). Moreover, the APJ receptor forms a heterodimer with the κ-opioid receptor; activation of this heterodimer increases protein kinase C and decreases protein kinase A activity (48). Despite awaiting confirmation, therefore, central opioid receptors appear to mediate, at least in part, the apelin- and APJ receptor-induced gastroinhibitory responses.

The dense expression of the APJ receptor in the PVN (24, 54, 64) and amygdala (54) suggests that endogenous apelin may be involved in stress responsiveness within central neurocircuitry. In rats, the response to acute and chronic stress increases APJ mRNA expression in PVN (64), and apelin stimulates the release of the prototypical stress hormones, arginine vasopressin (AVP) and corticotropin-releasing factor (CRF), from the hypothalamus (62, 90). The increase in plasma corticosterone that follows central administration of apelin is blocked, in part, by pretreatment with the CRF antagonist α-helical CRF-(9–41), suggesting the involvement of CRF-producing neurons in apelin-induced hypothalamic-pituitary-adrenal axis stimulation (38, 62). Indeed, exposure to either acute restraint or chronic heterotypic stress increased hypothalamic production of both apelin and CRF in rats (13), whereas central administration of an APJ receptor antagonist reversed the gastric and colonic dysmotility induced by acute restraint stress. Likewise, the alterations in gastric emptying and colonic transit induced by intercerebroventricular administration of apelin-13 were abolished by pretreatment with α-helical CRF-(9–41) (13).

There is evidence indicating that apelin also stimulates the release of AVP from the hypothalamus (90, 92). In rats, restraint or water immersion stress for 60 min activates 10% of DMV neurons, the majority of which express the AVP receptor V1b, suggesting that these apelin-responsive AVP-containing hypothalamic neurons may alter gastrointestinal motility via direct projections to DMV neurons (105). Moreover, in rats, daily administration of the V1b receptor antagonist SSR-149415 abolishes the delayed gastric emptying induced by acute or chronic heterotypic stress (14).

Overall, increasing evidence suggests that apelin plays a significant role in stress-related gastric dysfunctions via both direct interactions with DMV neurons and indirect effects through hypothalamic AVP and CRF release (Fig. 1).

NESFATIN-1

Nesfatin-1 was identified in 2006 as an anorexigenic peptide present in rat cerebrospinal fluid and hypothalamic extracts (66). Nesfatin-1 is processed from the 396-amino acid calcium and DNA-binding precursor protein nucleobindin-2 and exhibits over 85% sequence homology between humans and other mammalian species (3, 68).

Nesfatin-1-immunoreactive cells are found in several cortical areas, including the piriform, insular, and cingulate cortexes, the hippocampus, the PVN, ARC, SON, and lateral hypothalamic area (LHA), as well as in brain stem nuclei, including the Edinger-Westphal nucleus, raphe nuclei, DMV, and NTS (29, 86). Within the dorsal vagal complex (DVC, i.e., NTS, DMV, and AP), expression of nesfatin-1 was demonstrated in acetyltransferase- and tyrosine hydroxylase-positive cells (5). Although nesfatin-1 agonists and/or antagonists are not yet available, nesfatin-1 appears to exert its biological effects by interacting with an as yet unidentified G protein-coupled receptor, resulting in an increase in cytoplasmic calcium (5, 95). A recent report used autoradiography in rats to demonstrate the presence of ^{125}I-nesfatin-1 in the cortex, cerebellum, PVN, AP, and DMV, suggesting that nesfatin-1 may play a pivotal role in regulation of several autonomic/homeostatic functions (75). In rats, an anorexigenic effect resulted from nesfatin-1 injection in the ventral tegmental area (19), third ventricle (66), lateral and fourth ventricles, or the cisterna magna (88, 96).

The distribution of nesfatin-1 immunoreactivity in stress-related central neurocircuits, including hypothalamic, limbic, and hindbrain systems, suggests a role for this peptide in the integration of stress responses (28). In fact, in rats, central injection of nesfatin-1 increases both ACTH and corticosterone levels (44) and induces c-Fos expression in the PVN, LC, raphe nuclei, and NTS (103), suggesting nesfatin-1 may be an endogenous modulator of stress responses via both forebrain and brain stem neurocircuits. Indeed, after acute restraint stress, activated nesfatin-1-immunoreactive neurons were detected in well-characterized stress-related structures such as PVN, RVLM, LC, and NTS in rats (30, 103).

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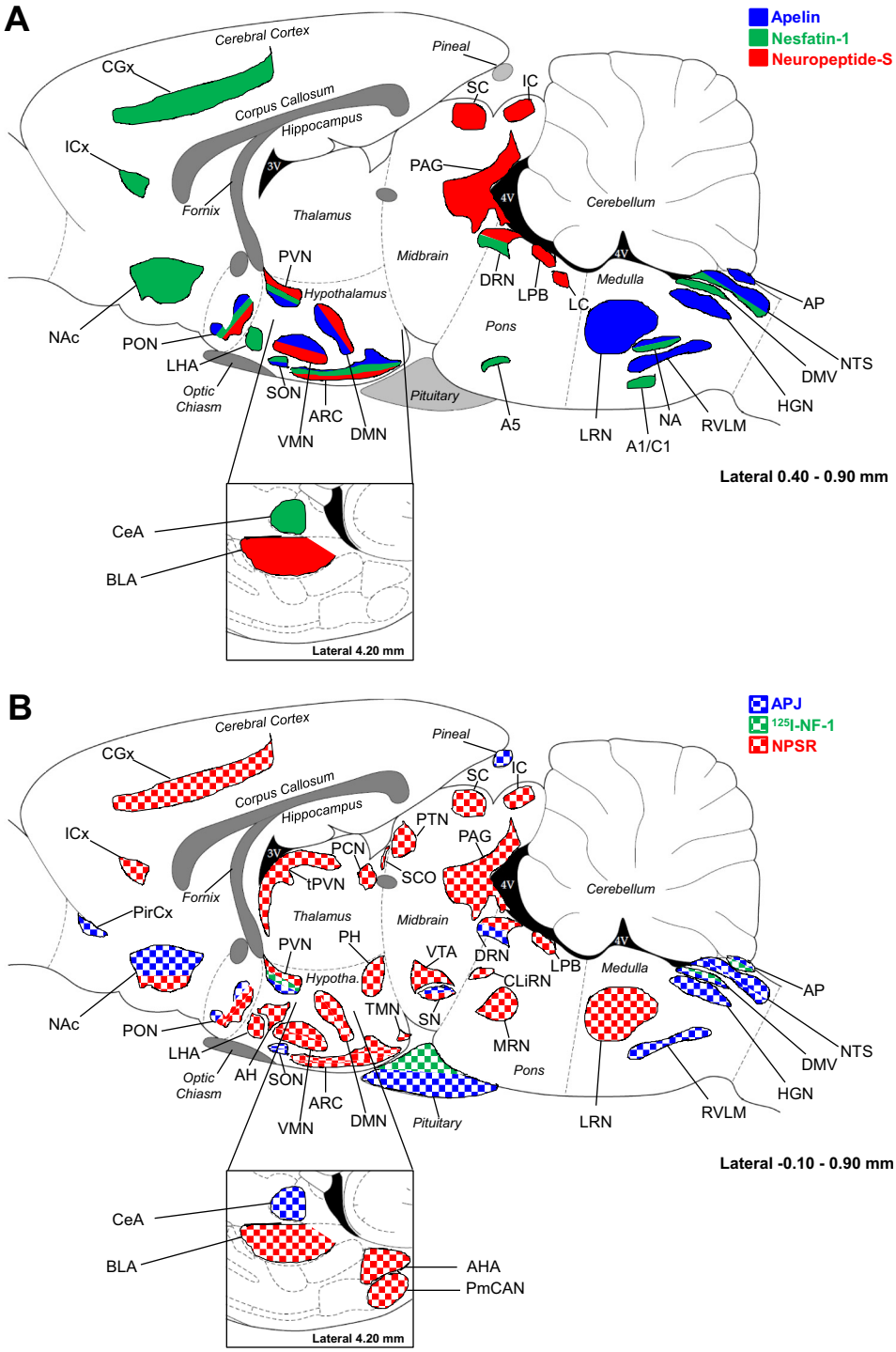


Fig. 1. The distribution of apelin (blue), nesfatin-1 (green), and neuropeptide-S (red) (*A*) and their receptors (*B*) in brain. Schematic representation is summarized from the data of the rodent studies (see text). 3V, third ventricle; 4V, fourth ventricle; A1/C1, catecholaminergic cell groups of the ventrolateral medulla; A5, pontine adrenergic cell group; AH, anterior hypothalamus; AHA, amygdalohippocampal area; AP, area postrema; ARC, arcuate nucleus; BLA, basolateral amygdaloid nucleus; CeA, central amygdaloid nucleus; CGx, cingulate cortex; CLiRN, caudal linear raphe nucleus; DMN, dorsomedial nucleus; DMV, dorsal motor nucleus of vagus; DRN, dorsal raphe nucleus; HGN, hypoglossal nucleus; ICx, insular cortex; IF, inferior colliculus; LC, locus coeruleus; LHA, lateral hypothalamic area; LPB, lateral parabrachial nucleus; LRN, lateral reticular nucleus; MRN, median raphe nucleus; NA, nucleus ambiguus; NAc, nucleus accumbens; NTS, nucleus tractus solitarius; PAG, periaqueductal gray matter; PCN, precommissural nucleus; PH, posterior hypothalamus; PirCx, piriform cortex; PmCAN, posteromedial cortical amygdaloid nucleus; PON, preoptic nucleus; PTN, pretectal nucleus; PVN, paraventricular nucleus of hypothalamus; RVLM, rostral ventrolateral medulla; SC, superior colliculus; SCO, subcommissural organ; SN, substantia nigra; SON, supraoptic nucleus; TMN, tuberomamillar nucleus; tPVN, thalamic paraventricular nucleus; VMN, ventromedial nucleus; VTA, ventral tegmental area.

Other recent studies have outlined potential key roles of nesfatin-1 in the modulation of autonomic functions via actions at the level of the PVN and NTS (56–58, 74). In fact, electrophysiological recordings from brain stem slices demonstrated that nesfatin-1 increased the excitability in 42% of NTS neurons, whereas microinjection of nesfatin-1 in the NTS increased heart rate and blood pressure (58).

Recent rodent studies have additionally suggested that nesfatin-1 may also be an endogenous regulator of gastrointestinal motor functions regulating both afferent and efferent vagal signaling. Nesfatin-1 treatment was shown to act via N-type calcium channels to increase cytosolic calcium levels in isolated nodose ganglion neurons, suggesting nesfatin-1 may increase vagal afferent signaling to brain stem NTS neurons (37). Further support for the modulatory role of nesfatin-1 in vagal afferent responsiveness was provided by an in vitro study demonstrating the increased mechanosensitivity of gastric afferent mucosal tension receptors upon its application (42).

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Central (4th-ventricular) administration of nesfatin-1 increases c-Fos expression in the rat DMV and induces a dose-dependent increase in calcium influx in the overwhelming majority of cultured DMV neurons, suggesting a direct regulatory action on vagal outflow (96). Indeed, central (icv) administration of nesfatin-1 inhibited the antroduodenal motility of mice in a dose-dependent fashion (2) and reduced gastric emptying of rats (88, 100). In addition to its actions to modulate gastric motor functions, nesfatin-1 has also been shown to inhibit secretory functions, including both basal and vagally stimulated (2-deoxy-D-glucose-induced) gastric acid production (96, 100).

The gastromodulatory effects of nesfatin-1 may not be restricted to actions at vagal neurocircuits, however. In agreement with previous studies of Guo et al. (32), Wang and colleagues demonstrated that injection of nesfatin-1 in the central amygdala, an important region in the regulation of anxiety and fear responses (25, 26, 55), reduced gastric motility in rats (94). Furthermore, microinjection of nesfatin-1 in rat PVN decreased gastric motility, an effect attenuated in part by central pretreatment of the oxytocin antagonist H-4928. Additionally, administration of an anti-nesfatin-1 antibody in the PVN increased gastric motility, suggesting an ongoing tonic nesfatin-1-mediated inhibition of gastric motility, possibly via an oxytocin-dependent pathway (32). Oxytocin is known to act on GABAergic neurons at the central amygdala through a rapid and reversible increase of inhibitory postsynaptic currents (35). DMV neurons are known to receive robust inhibitory GABAergic inputs originating in the NTS (93); these inhibitory circuits are highly plastic, and the responsiveness is modulated significantly by ongoing homeostatic demand, including stress, to alter gastrointestinal motor functions via vagally dependent pathways (6, 10, 39). Therefore, the possibility that the observed nesfatin-1-induced gastroinhibition is mediated by an oxytocin-dependent pathway cannot be excluded.

Although the postsynaptic pathways involved in the actions of nesfatin-1 are still under investigation, the modulatory effect of nesfatin-1 on digestive motor functions appears to be dependent mainly on its direct actions on vagal parasympathetic outflow.

NEUROPEPTIDE-S

NPS is a 20-amino-acid neuropeptide identified initially as the endogenous ligand of the orphan G protein-coupled receptor GPR154, also known as NPS receptor (NPSR) (99). NPS derives its name from the serine residue present at its NH_2-terminus, which is conserved across mammalian species and is essential for its biological actions (81, 99).

The NPSR is coupled to either G_s or G_q; by consequence, and ligand binding increases intracellular calcium and/or cAMP levels and leads to activation of the mitogen-activated protein kinase (MAPK) signaling pathway (78). In the central nervous system, NPS precursor mRNA has been detected exclusively in clusters of neurons located between the LC and Barrington's nucleus, between the sensory portion of the rostral trigeminal nucleus and the lateral parabrachial nucleus, and in several hypothalamic nuclei (PVN, DMN, ARC) and, to a lesser extent, the amygdala (47, 98, 99). Unlike its ligand, NPSR is expressed widely in numerous cerebral regions such as the thalamus, hypothalamus, amygdala, cortical areas, and brain stem structures, including periaqueductal gray matter and dorsal and median/pontine raphe nucleus (47, 98).

The distribution of NPS-immunoreactive positive fibers within the thalamus and the hypothalamus overlaps with NPSR mRNA expression; conversely, the immunoreactive pattern of NPSR does not appear to overlap in hippocampal, olfactory, and cortical regions (20).

In rodents, central (icv) NPS administration promotes arousal and wakefulness and reduces anxiety-related behaviors (40, 67); such anxiolytic effects were also obtained in both rats and mice following intranasal NPS application (36, 50). A modulatory role for NPS in fear signaling within the amygdala has also been shown in rodents (69, 106). Because the amygdala possesses bidirectional connections with a wide array of structures, including cortical structures, hypothalamic nuclei, and brain stem, by implication it influences a wide variety of processes from autonomic and motor control, to memory formation and neuromodulation (69, 72). Within the amygdala itself, local GABAergic interneurons connect to projection neurons of the basolateral amygdala. Microinjection of NPS in the basolateral amygdala complex, where NPSR expression is dense, produced an anxiolytic-like effect. Furthermore, in the mouse amygdala, NPS application increases glutamatergic transmission to GABAergic interneurons via presynaptic sites of action, suggesting the brain NPS system may be an important potential pharmacological avenue for the treatment of anxiety disorders (40).

Central administration (icv) of NPS inhibits distal colonic transit, an effect abolished by pretreatment with an NPSR antagonist, but not by tachykinin or opioid receptor antagonists (33). Moreover, intercerebroventricular administration of NPS reduced the increased fecal output induced by restraint stress but had no significant effect on either gastric emptying or fecal output under nonstressed conditions (71).

Recent reports indicate a modulator role for NPS in orexin-A (hypocretin) neurocircuitry. In fact, intercerebroventricular administration of NPS increased Fos immunoreactivity in orexin-expressing neurons of the LHA in rats (63) and prevented the delay in gastric emptying that results from acute restraint stress. This latter effect was abolished by pretreatment with the orexin-A receptor antagonist SB-334867 (16), suggesting involvement of an orexin-A pathway in the gastromodulatory actions of NPS. Indeed, orexin receptors are known to be present on gastric-projecting vagal neurons (45), activation of which exerts powerful excitatory effects (22, 23, 31, 87).

Several NPSR1 single nucleotide polymorphisms have been shown to be associated with individual motor or sensory functions in patients with functional gastrointestinal disorders (41), and a NPSR1 polymorphism is also associated with irritable bowel syndrome (18). In a well-established rodent model of irritable bowel syndrome induced by postnatal maternal separation of newborns, which leads to permanent neurobiological changes in the brain-gut axis and induces gastrointestinal motor dysfunction (21, 49), daily intercerebroventricular injection of NPS prevents the alterations in solid gastric emptying and fecal output that occur in response to chronic homotypic stress (17). Disruptions in endogenous NPS production and signaling, therefore, may contribute to the gastrointestinal motor dysfunctions observed in chronic stress.

Although the modulatory actions of NPS on autonomic signaling are still under investigation, the available evidence

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suggests that exogenous NPS alleviates stress-induced gastrointestinal dysfunctions through *1*) its antistress and anxiolytic actions in forebrain stress-related neural circuitry and *2*) its direct actions via NPSR-mediated activation of brain stem vagal structures regulating outflow to the viscera.

CONCLUSIONS

Although further studies investigating the pharmacological and electrophysiological behavior of apelin, nesfatin-1, and NPS are required, these peptidergic systems may represent novel targets for the treatment of the stress-exacerbated brain-gut axis dysfunctions observed commonly in patients with functional gastrointestinal disorders.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.B. and R.A.T. drafted manuscript; M.B. and R.A.T. edited and revised manuscript; M.B. and R.A.T. approved final version of manuscript.

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