

Roles of noradrenergic transmission within the ventral part of the bed nucleus of the stria terminalis in bidirectional brain-intestine interactions

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Abstract

Aims: The bed nucleus of the stria terminalis (BNST) is a limbic structure mediating autonomic and neuroendocrine responses and negative affective states such as anxiety and fear. We previously demonstrated that noradrenergic transmission via β -adrenoceptors within the ventral part of BNST (vBNST) is involved in bidirectional interactions between the brain and the upper gastrointestinal (GI) tract. The present study aimed to examine the roles of intra-vBNST noradrenergic transmission via β -adrenoceptors in bidirectional interactions between the brain and lower GI tract.

Methods: In vivo microdialysis experiments were performed to examine colorectal distention (CRD)-induced noradrenaline release within the vBNST of freely moving male Sprague-Dawley rats. Colonic transit and abdominal pain perception were examined following intra-vBNST injections of isoproterenol, a β -adrenoceptor agonist, with and without co-administration of timolol, a β -adrenoceptor antagonist.

Results: CRD increased extracellular noradrenaline levels within the vBNST and evoked abdominal contractions in a pressure-dependent manner (30–60 mm Hg). Bilateral intra-vBNST injections of isoproterenol (30 nmol/side) significantly increased CRD (30 mm Hg)-induced abdominal contractions. Intra-vBNST injections of isoproterenol (30 nmol/side) significantly increased colonic transit, which was reversed by co-administration of timolol (30 nmol/side).

Conclusion: The results of this study suggest (a) the existence of a positive feedback loop between intra-vBNST noradrenaline release and abdominal pain perception, and (b) the modulation of colonic motility by intra-vBNST noradrenergic transmission via β -adrenoceptors. Dysfunction of the lower GI tract may increase noradrenaline release within the vBNST, which, in turn, may exacerbate impairment of its motility and pain perception.

KEYWORDS

bed nucleus of the stria terminalis, brain-intestine interaction, colorectal distention, extended amygdala, noradrenaline

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1 | INTRODUCTION

It has long been recognized that bidirectional brain-gut interactions play important roles in stress and emotional responses. Gastrointestinal (GI) problems can affect mental health conditions, such as anxiety and depression, and, conversely, anxiety is closely correlated with the intensity of functional GI disorder symptoms. Patients with irritable bowel syndrome (IBS) have higher levels of anxiety and depression than do healthy controls.^{1,2} In turn, anxiety and depression provide a twofold risk for IBS onset.³ Although the investigation of the brain sites involved in the close relationship between IBS and anxiety/depression has remained limited to date, accumulating evidence points to the central nucleus of the amygdala (CeA) as a brain site responsive to higher levels of anxiety and visceral hypersensitivity in IBS animal models.^{4,5} The bed nucleus of the stria terminalis (BNST) and the CeA together form the extended amygdala,⁶ which plays important roles in controlling autonomic and neuroendocrine responses⁷ and regulating negative affective states such as anxiety and fear.⁸ We previously demonstrated that pain stimulation increased extracellular noradrenaline levels in the rat BNST, particularly its ventral part (vBNST).^{9,10} We also reported that intra-vBNST injection of a β -adrenoceptor antagonist suppressed pain-induced aversive responses^{9,10} and that intra-vBNST injection of a β -adrenoceptor agonist induced anxiety-like behaviors and food intake reduction.¹¹ These findings suggest that intra-vBNST noradrenergic transmission via β -adrenoceptors plays important roles in the response to noxious stimulation and the regulation of negative affective states. Recently, we demonstrated that gastric distention (GD) increased extracellular noradrenaline levels in the rat vBNST and that the activation of β -adrenoceptors within the vBNST reduced gastric emptying.¹² These findings suggest that noradrenergic transmission via β -adrenoceptors within the vBNST plays an important role in bidirectional interactions between the brain and upper GI tract. However, the role of intra-vBNST noradrenergic transmission in bidirectional interactions between the brain and lower GI tract remains to be elucidated. Thus, the present study examined the effect of colorectal distention (CRD) on extracellular noradrenaline levels within the vBNST and investigated the effects of intra-vBNST β -adrenoceptor activation on nociceptive responses to CRD and colonic transit.

2 | MATERIALS AND METHODS

2.1 | Animals

Male Sprague-Dawley rats weighing 180–290 g (Japan SLC; Hamamatsu, Japan) were used in all animal experiments. The rats were housed 3–4 per cage in a room maintained at a constant ambient temperature ($23 \pm 1^\circ\text{C}$) under a 12/12-hours light/dark cycle with food and water available ad libitum. All experiments were performed with the approval of the Institutional Animal Care and Use Committee at Hokkaido University.

2.2 | Drugs and microinjections

Isoproterenol (β -adrenoceptor agonist) and timolol (β -adrenoceptor antagonist) were purchased from Sigma (St Louis, MO, USA) and dissolved in phosphate-buffered saline (PBS). Bilateral microinjections were carried out as previously described.¹² At least 5 days after implantation of guide cannulae, the animals received intra-vBNST injection of isoproterenol (30 nmol/side) with and without co-administration of timolol (30 nmol/side).

2.3 | Measurement of CRD-induced noradrenaline release within the vBNST

In vivo microdialysis experiments to measure the extracellular noradrenaline levels within the vBNST were carried out as previously described.¹² In the present study, after fasting for 16 hours with water available ad libitum, rats were anesthetized with 2% isoflurane, and a lubricated polyethylene balloon (diameter: 2.5 cm) was inserted 6 cm into the colorectum of each animal through the anus and anchored by taping the catheter to the base of the tail. After awakening from anesthesia, a microdialysis probe was inserted through the guide cannula and continuously perfused with Ringer's solution at a constant flow rate of $1 \mu\text{L}/\text{min}$. After a stabilization period, the catheter of the distending balloon was connected to a pressure controller-timing device (Barostat Model Distender IIR, Star Medical; Tokyo, Japan), and three 15-minute dialysate fractions were collected as baseline samples in the absence of distention. The CRD stimulus (30, 45 or 60 mm Hg) was then applied to each rat for 30 minutes (4.5 minutes with 0.5-minute interstimulus intervals \times six times). Six 15-minute dialysate fractions were collected during and after the CRD stimulus. The noradrenaline contents in the dialysate samples were measured using an electrochemical detector (HTEC-500; Eicom; Kyoto, Japan).

2.4 | Counting the CRD-induced behavioral responses

To evaluate the nociceptive responses to the CRD, abdominal contractions and writhing behaviors were counted before and during CRD stimulus by well-trained investigators who were blind to the pressure conditions.

2.5 | Measurement of colonic transit

Under sodium pentobarbital anesthesia, PE50 polyethylene tubing was inserted into the cecum of each rat, with the tip positioned in the proximal colon 1.5 cm distal to the cecum. The other side was tunneled subcutaneously to the posterior neck. Following surgery, the animals were individually housed in cages and allowed to recover for at least 7 days. After 24 hours of fasting with water available ad libitum, either the drug or a vehicle was bilaterally administered into the vBNST. At 5 minutes following intra-vBNST injection, 0.5% Evans blue/3.5% carboxymethylcellulose/saline was injected into the



large intestine via PE50 polyethylene tubing. Each rat was decapitated 15 minutes later, and the large intestine was immediately removed. Colonic transit was calculated by the following formula: colonic transit = distance of Evans blue migration/total length of the large intestine.

2.6 | Histology

Histological analyses were performed to examine the placement of the microdialysis probes and injection cannulae. Briefly, each rat was decapitated, and the brain was rapidly removed and frozen in powdered dry ice. Coronal sections (50 μ m) were prepared on a cryostat, stained with thionin, and examined by light microscopy (40 \times). Data from rats with correct placement of the microdialysis probes (Figure 1A) and bilateral microinjection cannulae (Figure 1B-E) were used for statistical analyses.

2.7 | Statistical analyses

Data were analyzed by Student's *t* test or analysis of variance (ANOVA) followed by Holm-Sidak's post hoc tests for multiple comparisons. Differences were considered statistically significant when $P < 0.05$.

3 | RESULTS

3.1 | CRD-induced noradrenaline release in the vBNST

Nociceptive responses were evaluated before and during the CRD stimulus was administered (Figure 2A). Compared with scores before CRD stimulus administration (2.9 ± 1.0), the number of abdominal contractions significantly increased in a tension-dependent manner

during administration of CRD stimuli of 30, 45, and 60 mm Hg (26.1 ± 3.4 , 36.6 ± 3.3 , and 46.5 ± 4.2 , respectively) (one-way ANOVA, $F_{3,26} = 31.15$, $P < 0.0001$). Although no writhing behavior was observed before distension or during the 30-mm Hg CRD stimulus administration, a one-way ANOVA ($F_{3,26} = 7.68$, $P = 0.0008$) followed by post hoc tests revealed that the number of writhing behaviors significantly increased during administration of the 60-mm Hg CRD stimulus (6.8 ± 2.3 , $P < 0.01$) but not during administration of the 45-mm Hg CRD stimulus (0.6 ± 0.3 , $P > 0.05$) (Figure 2B).

Using an *in vivo* microdialysis technique in freely moving rats, we examined CRD-induced changes in extracellular noradrenaline levels within the vBNST (Figure 2C). Two-way repeated measures ANOVA revealed a significant effect of the CRD stimulus on extracellular noradrenaline levels within the vBNST (CRD stimulus: $F_{2,20} = 5.17$, $P = 0.016$; time: $F_{8,160} = 7.72$, $P < 0.001$; interaction: $F_{16,160} = 3.35$, $P < 0.001$). Holm-Sidak's post hoc tests revealed significant increases in noradrenaline levels between 0 and 45 minutes following initiation of the administration of a 60-mm Hg CRD stimulus compared with the last baseline sample (-15 to 0 minutes). However, no significant increase was observed in noradrenaline levels either during or after administration of the 30- and 45-mm Hg CRD stimuli, whereas we observed an increasing tendency during administration of the 45-mm Hg CRD stimulus.

3.2 | Effects of intra-vBNST β -adrenoceptor activation on CRD-induced abdominal contractions

The effects of intra-vBNST injections of isoproterenol (30 nmol/side) on 30-mm Hg CRD-induced abdominal contractions were examined (Figure 3). Intra-vBNST injections of isoproterenol significantly increased CRD-induced abdominal contractions (67.0 ± 7.9 , $P < 0.01$, Student's *t* test) compared with the vehicle-injected group (28.7 ± 3.8).

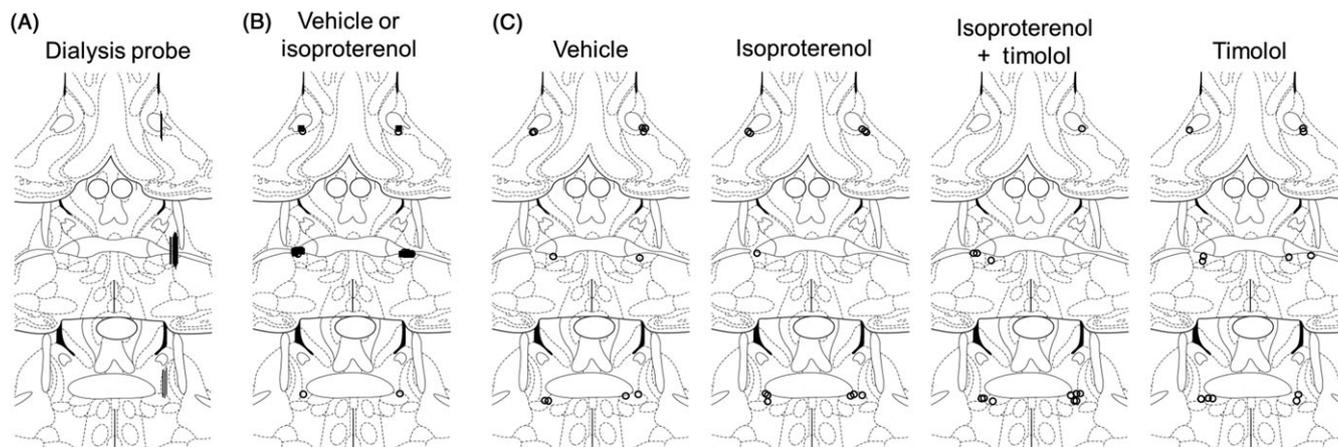


FIGURE 1 A, Placement of the microdialysis probes ($n = 23$) for the experiments shown in Figure 2. B, Placement of the microinjection cannulae for the experiments shown in Figure 3 (vehicle: closed square, $n = 6$; isoproterenol: open circle, $n = 6$). C, Placement of the microinjection cannulae (open circle) for the experiments shown in Figure 4 (vehicle: $n = 6$; isoproterenol: $n = 6$; isoproterenol + timolol: $n = 6$; timolol: $n = 6$). Illustrations of the coronal sections are reproduced from the Paxinos and Watson atlas at 0.2, -0.26 , and -0.4 mm from the bregma

3.3 | Effects of intra-vBNST β -adrenoceptor activation on colonic transit

The effects of intra-vBNST injections of isoproterenol (30 nmol/side) with and without timolol (30 nmol/side) on colonic transit were examined (Figure 4). Two-way ANOVA revealed a significant main effect of isoproterenol ($F_{1,20} = 13.7, P = 0.0014$) and a significant interaction between the effects of isoproterenol and timolol ($F_{1,20} = 9.43, P = 0.0060$). Intra-vBNST injections of isoproterenol significantly increased colonic transit ($47.5 \pm 2.4\%, P < 0.001$, Holm-Sidak's post hoc test) compared with the vehicle-injected group ($33.4 \pm 1.6\%$), and this increase was significantly reversed by

co-administration of timolol ($35.4 \pm 2.9\%, P < 0.01$, Holm-Sidak's post hoc test). There was no significant effect of timolol alone ($34.1 \pm 0.8\%$) compared with the vehicle-injected group.

4 | DISCUSSION

The present study demonstrated that CRD stimulation increased extracellular noradrenaline levels within the vBNST in a pressure-dependent manner. Additionally, intra-vBNST injections of isoproterenol, a β -adrenoceptor agonist, induced hypersensitivity to the CRD stimulation. These findings suggest the existence of a positive

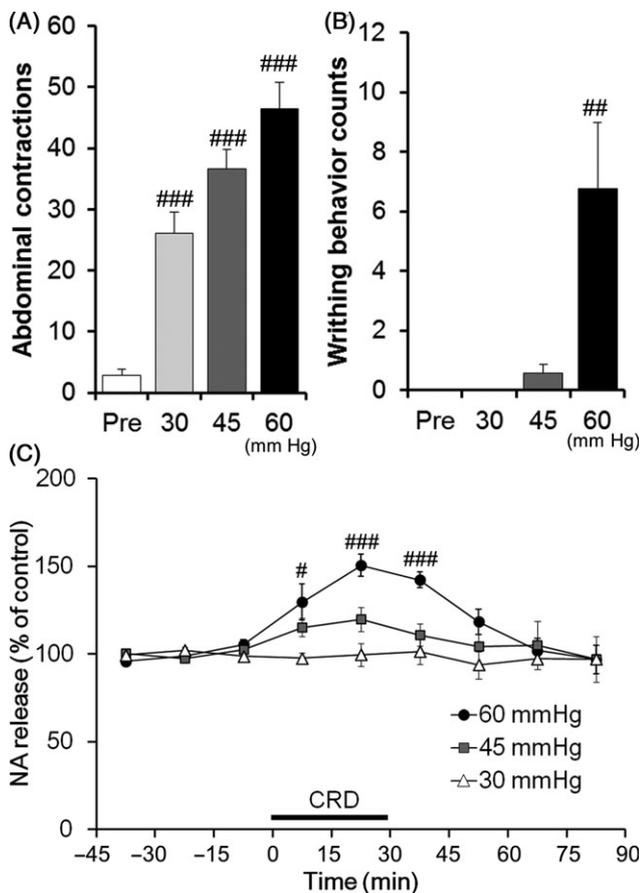


FIGURE 2 A and B, Colorectal distention (CRD)-induced nociceptive behaviors in freely moving rats. Scores for CRD-induced abdominal contractions (A) and writhing behaviors (B) before and during 30-min CRD stimulation (pre: $n = 7$, 30 mm Hg: $n = 8$, 45 mm Hg: $n = 7$, and 60 mm Hg: $n = 8$). Data are expressed as means \pm SEM. ### $P < 0.001$ and ## $P < 0.01$ compared with the value before CRD stimulation (Holm-Sidak's post hoc test). C, CRD increased extracellular noradrenaline levels within the vBNST in freely moving rats. Bold line indicates the period during which CRD stimulation was applied. Data are expressed as means \pm SEM of the percent baseline control value, which was calculated as an average of three consecutive dialysates before CRD stimulation (30 mm Hg: open triangle, $n = 8$; 45 mm Hg: gray square, $n = 7$; 60 mm Hg: closed circle, $n = 8$). # $P < 0.05$ and ### $P < 0.001$ compared with the value immediately before CRD stimulation (Holm-Sidak's post hoc test)

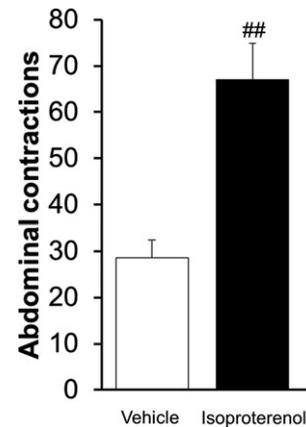


FIGURE 3 The effect of intra-vBNST injection of isoproterenol on CRD-induced abdominal contractions. Columns show counts of 30-mm Hg CRD-induced abdominal contractions in vehicle-treated (white, $n = 6$) and isoproterenol-treated (black, $n = 6$) rats. Data are expressed as means \pm SEM. ## $P < 0.01$ compared with vehicle-treated rats (Student's t test)

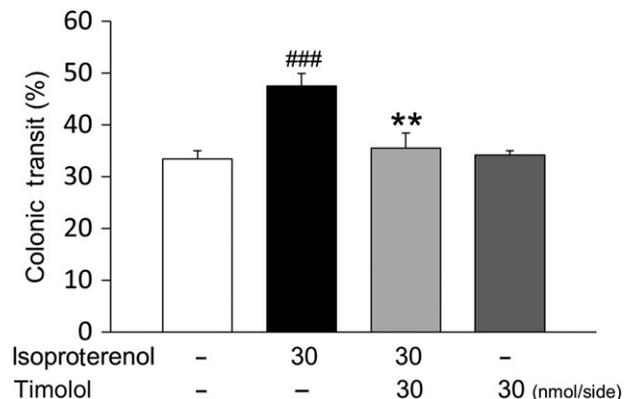


FIGURE 4 The effect of intra-vBNST injection of isoproterenol on colonic transit. Columns show percentages of colonic transit in vehicle-treated (white, $n = 6$), isoproterenol-treated (black, $n = 6$), isoproterenol + timolol-treated (light gray, $n = 6$), and timolol-treated (dark gray, $n = 6$) rats. Data are expressed as means \pm SEM. ### $P < 0.001$ and ** $P < 0.01$ compared with vehicle-treated and isoproterenol-treated rats, respectively (Holm-Sidak's post hoc test)



feedback loop between intra-vBNST noradrenaline release and abdominal pain perception (Figure 5). Furthermore, intra-vBNST injection of isoproterenol enhanced colonic transit, and this effect was reversed by co-administration of timolol, a β -adrenoceptor antagonist, suggesting that the activation of intra-vBNST noradrenergic transmission via β -adrenoceptors affects colonic function.

Abdominal contractions were induced even by low tension (30 mm Hg) of CRD, which did not increase the extracellular noradrenaline levels in the *in vivo* microdialysis experiments. Similar results were observed in our previous study, where a significant increase in abnormal behaviors, including abdominal contractions, was induced by the low tension (25 mm Hg) of GD, which did not increase the extracellular noradrenaline levels in the *in vivo* microdialysis experiment.¹² At least, a part of such an ineffectiveness of lower-tension CRD/GD on the extracellular noradrenaline levels may be due to the limitation of an *in vivo* microdialysis technique. As this method measures the concentration of the neurotransmitter reaching to the microdialysis probe from the release site by diffusion, its spatiotemporal resolution is limited. As another possible reason, the ineffectiveness of lower-tension CRD/GD may be due to the neuronal pathway mediating CRD/GD-evoked abdominal contractions. Direct pathways for vago-vagal reflexes, which connect vagal afferent input, nucleus tractus solitarius neurons, and vagal efferent projections to the GI tract,¹³ may mediate the CRD/GD-evoked abdominal contractions, regardless of whether vagal afferent information is conveyed to the BNST or not.

In this study, we demonstrated that the exogenously applied β -adrenoceptor agonist induced hypersensitivity to the CRD stimulation. The effect of intra-vBNST injection of a β -adrenoceptor antagonist on the higher-tension CRD (60 mm Hg)-evoked abdominal contractions and writhing behaviors should be examined in the future study to elucidate the role of CRD-evoked endogenous noradrenaline release in the regulation of sensitivity to the CRD stimulation.

We previously demonstrated that intra-vBNST injection of a β -adrenoceptor agonist induced anxiety-like behaviors.¹¹ Cecchi et al¹⁴ showed that noradrenaline release was increased in the BNST

of male Sprague-Dawley rats during immobilization stress and that blocking of β -adrenoceptors in the vBNST attenuated the anxiety-like behaviors induced by acute restraint stress. Fendt et al¹⁵ reported that noradrenaline release in the BNST increased during exposure to trimethylthiazoline (TMT), a component of fox odor, and that intra-vBNST administration of the α_2 -adrenoceptor agonist clonidine suppressed both the enhanced release of noradrenaline and the TMT-induced potentiation of freezing behavior. These findings suggest the critical role of noradrenergic transmission within the BNST in mediating negative emotions, such as anxiety and fear. The present study revealed that CRD stimulation increased extracellular noradrenaline levels within the vBNST. Enhanced activation of noradrenergic transmission within the vBNST may be involved in the higher levels of anxiety observed in IBS-suffering subjects.

Acute stress induces differential motor effects in the upper and lower GI tract. Gastric emptying is delayed by various stressors, while various stressors stimulate colonic motility and transit.¹⁶ As described above, various stressors increased extracellular noradrenaline levels in the BNST.^{9,10,12,14,15} Furthermore, we demonstrated that activation of β -adrenoceptors within the vBNST induces delayed gastric emptying¹² and enhanced colonic transit. Noradrenergic transmission via β -adrenoceptors within the vBNST may be involved in the stress-induced delayed gastric emptying and enhanced colonic transit. However, it remains unclear how the noradrenergic transmission within the vBNST regulates GI functions. The dorsal motor nucleus (DMN), located in the medulla, is the main motor nucleus of the vagus nerve, and the parasympathetic vagal efferent fibers make synapse with enteric nervous system neurons within gut wall and modulate the gastrointestinal motility.¹⁷ The DMN receives projections from various brain regions, including the hypothalamus and the amygdala, which are the brain regions receiving the innervation from the BNST.^{18–20} Activation of β -adrenoceptors within the vBNST may enhance the colonic motility via the activation of these neuronal pathways. Further studies are needed to elucidate the neuronal pathway regulating GI functions.

Several animal studies have shown that corticotropin-releasing factor (CRF) acts on the central nervous system to modulate visceral pain perception. Specifically, Johnson et al⁴ reported that intra-CeA infusion of a CRF type-1 receptor antagonist attenuated CRD hypersensitivity in Wistar Kyoto rats, a high-anxiety strain that models IBS abdominal pain. Fukudo and colleague demonstrated that administration of CRF into the CeA induced visceral hypersensitivity to CRD, which was reversed by co-administration of a CRF type-1 receptor antagonist.⁵ Recently, Tran et al²¹ demonstrated that the infusion of a CRF type-1 receptor antagonist into the anterolateral BNST attenuated CRD-induced abdominal contractions and stress-induced anxiety. Additionally, intra-BNST injection of CRF induced anxiety-like behaviors²² as has intra-BNST injection of a β -adrenoceptor agonist.¹¹ These findings suggest that there may be a common neuronal mechanism regulating anxiety-like behaviors and abdominal pain perception via the activation of CRF type-1 receptors and β -adrenoceptors. From this perspective, both

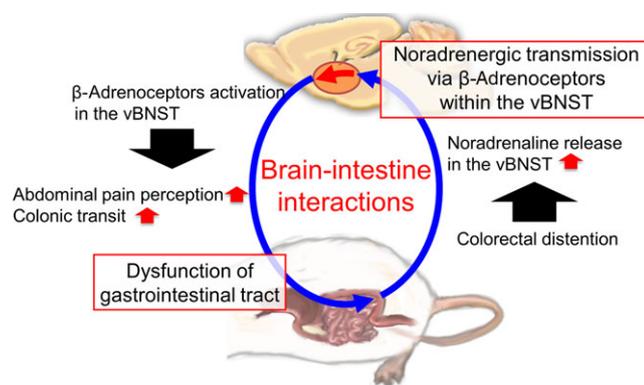


FIGURE 5 Roles of noradrenergic transmission via β -adrenoceptors within the vBNST in bidirectional brain-intestine interactions



CRF and noradrenaline increase the neuronal excitability of I_h -positive BNST neurons,^{23,24} which may mediate, at least in part, the ability of these neuromodulators to induce negative emotion. Additionally, crosstalk between β -adrenergic and CRFergic signaling within the BNST has been demonstrated. Specifically, isoproterenol increases the frequency of spontaneous excitatory postsynaptic currents in the dorsolateral BNST, which can be blocked by a β_1 -antagonist or by a CRF type-1 receptor antagonist.²⁵ In the CeA, CRD-induced elevation of extracellular noradrenaline levels is enhanced by CRF.⁵ Further studies are necessary to elucidate the effects of interactions between β -adrenergic and CRFergic signaling within the extended amygdala (BNST and CeA) on the regulation of abdominal pain perception and colonic motility.

In conclusion, the present study demonstrated that CRD increased extracellular noradrenaline levels within the vBNST and that the activation of β -adrenoceptors within the vBNST enhanced colonic transit. We previously demonstrated increased extracellular noradrenaline levels within the vBNST by GD and the reduction of gastric emptying by intra-vBNST β -adrenoceptor activation.¹² Taken together, these findings suggest an important role for the vBNST in bidirectional interactions between the brain and GI tract. Dysfunction of the GI tract may increase noradrenaline release within the vBNST, which, in turn, may exacerbate impairment of its motility and pain perception in functional GI disorders, such as functional dyspepsia and IBS.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA REPOSITORY

We have made our data publicly available through directly submitting as the Supporting Information.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

N/A.

INFORMED CONSENT

N/A.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

N/A.

ANIMAL STUDIES

All experiments were performed with the approval of the Institutional Animal Care and Use Committee at Hokkaido University.

AUTHOR CONTRIBUTION

SI, HT, and MM are involved in the conception and design of the experiments. SI, RY, and HS performed the experiments and statistical analyses and wrote the manuscript. HT and MM finalized the manuscript. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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