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Diminished neurokinin-1 receptor availability in patients with two forms of chronic visceral pain

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ABSTRACT

Central sensitization and dysregulation of peripheral substance P and neurokinin-1 receptor (NK-1R) signaling are associated with chronic abdominal pain in inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). Although positron emission tomography (PET) has demonstrated that patients with injury-related chronic pain have diminished NK-1R availability in the brain, it is unknown whether these deficits are present in IBD and IBS patients, who have etiologically distinct forms of non-injury-related chronic pain. This study's aim was to determine if patients with IBD or IBS exhibit deficits in brain expression of NK-1Rs relative to healthy controls (HCs), the extent to which expression patterns differ across patient populations, and if these patterns differentially relate to clinical parameters. PET with [^{18}F]SPA-RQ was used to measure NK-1R availability by quantifying binding potential (BP) in the 3 groups. Exploratory correlation analyses were performed to detect associations between NK-1R BP and physical symptoms. Compared to HCs, IBD patients had NK-1R BP deficits across a widespread network of cortical and subcortical regions. IBS patients had similar, but less pronounced deficits. BP in a subset of these regions was robustly related to discrete clinical parameters in each patient population. Widespread deficits in NK-1R BP occur in IBD and, to a lesser extent, IBS; however, discrete clinical parameters relate to NK-1R BP in each patient population. This suggests that potential pharmacological interventions that target NK-1R signaling may be most effective for treating distinct symptoms in IBD and IBS.

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1. Introduction

Patients with chronic somatic pain exhibit functional and structural alterations in brain circuits that modulate cognitive and affective processes [4–6,33,38,78]. The relationship between chronic pain and neurotransmitters is less clear [4]. Substance P (SP), a neuropeptide that modulates effects of acute or chronically recurring physical and emotional distress, acts centrally and peripherally through neurokinin-1 receptors (NK-1Rs). NK-1Rs are expressed at high levels in brain regions implicated in pain and emotion regulation, including insula, cingulate cortex, dorsal prefrontal cortex (PFC), amygdala, and striatum [29]. NK-1Rs have therefore been considered a promising pharmacological target for treating chronic pain and psychopathology [30,50]. Despite encouraging outcomes in patients with irritable bowel syndrome [39,76], clinical trials with NK-1R antagonists for depression and other chronic pain syndromes have been disappointing [25,37,52]. Disease-related specificity in NK-1R expression may contribute to these inconsistent findings.

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SP modulates physical and emotional distress by differentially influencing NK-1R expression in the central nervous system. In rodents, acute nociceptive stimuli [2] and stress [59,70] produce a rapid release of SP in the spinal cord and brain [45,68]. The magnitude of SP release, and subsequent binding-related NK-1R downregulation, is proportional to the intensity and duration of the stimulus [2]. Conversely, chronic pain [1,35] and stress [9] upregulate NK-1Rs in the spinal cord, but downregulate NK-1Rs in limbic and striatal brain regions [17,74]. In humans, positron emission tomography (PET) studies show that patients with anxiety disorders [24,51] or injury-related chronic pain [42] have diminished NK-1R availability in amygdala and PFC, while SP is elevated in the cerebral spinal fluid [67] and plasma [3] of noninjured chronic pain patients. This suggests that chronic pain and emotional distress are associated with heightened SP release, indexed by elevated SP in cerebral spinal fluid and plasma, and reduced NK-1R availability in the brain, possibly related to SP-induced receptor downregulation. To develop effective treatments that target SP system dysfunction, it is critical to determine if this association exists across discrete patient populations.

In this pilot study, PET with the radioligand [^{18}F]SPA-RQ was used to quantify availability of NK-1Rs in the brains of 2 patient populations with abdominal pain symptoms but discrete pathophysiology, namely inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). IBD is characterized by abdominal pain and discomfort due to intestinal inflammation during disease flares. IBS is characterized by chronic abdominal pain and discomfort that occurs without detectable pathology, but commonly in the presence of stress and comorbid psychopathology [47,48]. Our behavioral [57] and brain-based research [11,46] suggests that clinically remitted IBD patients have less abdominal pain and are better able to engage endogenous pain inhibition systems during acute aversive visceral stimulation compared to IBS patients. This difference in symptomatology may reflect differences in NK-1R expression in the brain. Here, we tested the extent to which NK-1R downregulation in the brain generalizes across, or is specific to, discrete chronic pain disorders, and the degree to which downregulation relates to clinical parameters.

2. Methods

2.1. Participants

Participants provided informed consent prior to enrolling in the study, which was approved by the institutional review board of the University of California, Los Angeles. Twenty-seven participants completed the study: 9 healthy controls (HCs); 9 IBS patients; and 9 IBD patients (see Table 1 for demographics). All were free of psychiatric illness as determined by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV [22]), and of medication known to affect SP/NK-1R or central nervous system function, such as steroids and psychotropic medication. Self-reported medical history and physical examination supported that HCs were free of physical illness. Diagnosis of IBS or IBD (Crohn disease or ulcerative colitis) was verified via medical records. Patients had not been treated with biologics, and they discontinued steroidal or nonsteroidal anti-inflammatory medication 2 weeks prior to the study. At the time of enrollment, patients with IBS were required to meet Rome III diagnostic criteria for functional gastrointestinal disorders [43], and underwent a rectal examination to ensure that symptoms were unrelated to physical abnormalities. Patients with IBD were not in an acutely active flare state as per clinical assessment by a gastroenterologist, rectal examination, and reflected by high scores on the Inflammatory Bowel Disease Questionnaire ($M \pm SD = 180.00 \pm 25.24$; full remission $\geqslant 170$ [34]).

2.2. PET acquisition

NK-1R availability was quantified with the radioligand [^{18}F]SPA-RQ, a high-affinity NK-1R antagonist [29,58,73]. Images were acquired using a Siemens ECAT EXACT HR+ scanner (Siemens Healthcare Solutions, Deerfield, IL, USA: in-plane resolution full-width at half-maximum [FWHM] = 4.6 mm, axial FWHM = 3.5 mm, axial field of view = 15.52 cm) in 3-dimensional (3D) mode. A 7-minute transmission scan was acquired using a rotating ^{68}Ge/^{68}Ga rod source for attenuation correction. Dynamic data were acquired in list mode following a bolus injection of [^{18}F]SPA-RQ (5 mCi in 30 seconds). After 85 minutes of data acquisition, participants were given a 13-minute break, and were then returned to the scanner bed. After a second transmission scan, dynamic data were collected for another 85 minutes. Thus, the total dynamic scanning sequence consisted of 170 1-minute frames, acquired continuously across both 85-minute blocks of scanning. Short-duration frames were utilized to minimize signal noise associated with within-frame head motion. Data were reconstructed using ECAT v7.3 software using the OSEM algorithm (Ordered Subset Expectation Maximization; 6 iterations, 16 subsets), correcting for decay, attenuation, and scatter.

2.3. Structural MRI acquisition

Participants also underwent structural magnetic resonance imaging (MRI) with a 1.5-T Siemens SONATA scanner. A single, high-resolution sagittal T1-weighted 3D volumetric scan was acquired using a whole-brain MPRAGE sequence (repetition time/

Table 1
Participant characteristics.

	Healthy control		IBD		IBS		Group differences	
	Mean	SD	Mean	SD	Mean	SD	F	*P*-value
Demographics								
n (female/male)	9/0		8/1		9/0			
Age	27.44	5.32	31.56	8.44	31.78	12.25	0.64	0.534
Gastrointestinal symptom characteristics								
24-hour symptom severity	–	–	3.78	3.42	9.56	5.43	7.29	0.016
Duration of symptoms (years)	–	–	10.56	8.95	18.67	13.88	2.17	0.160
Symptoms of anxiety and depression								
Anxiety (HAD)	4.56	5.18	5.89	2.80	4.00	2.18	0.65	0.533
Depression (HAD)	2.89	4.17	1.78	1.86	2.45	0.87	0.91	0.417
State anxiety (STAI)	43.44	5.86	51.33	13.66	51.67	8.65	1.98	0.160
Temperature for pain threshold (°C)	46.69	2.86	45.33	1.49	46.35	2.28	0.87	0.432

IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; HAD, Hospital Anxiety and Depression scale; STAI, State-Trait Anxiety Inventory.

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