

Idiopathic environmental intolerance: Increased prevalence of panic disorder–associated cholecystokinin B receptor allele 7

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Background: A growing body of evidence suggests that idiopathic environmental intolerance (IEI) is a psychophysiologic disorder with prominent features of anxiety/panic and somatization, although proponents of a toxicogenic explanation claim, despite a lack of convincing evidence, that symptoms arise from exposure to otherwise nonnoxious environmental agents. Patient behaviour is characterized by strenuous avoidance of perceived triggers to the point of severe impairment of normal social and vocational functioning. IEI proponents claim that previous studies showing a high prevalence of psychopathology in patients with IEI and studies showing panic responses to known panicogenic challenges merely reflect the anxiety-producing result of living with IEI.

Objective: We explored whether IEI and panic disorder, personality traits, or both shared an underlying neurogenetic basis that would predate the anxiety of IEI symptomatology. The DNA of patients with IEI was examined for the presence of known panic disorder–associated cholecystokinin B (CCK-B) receptor alleles and for personality trait–associated dopamine D4 receptor polymorphisms.

Methods: Eleven patients with typical IEI symptoms were recruited and were individually matched to normal control subjects from an existing bank for age, sex, and ethnic background. Genomic DNA was extracted from peripheral blood samples. CCK-B and dopamine D4 receptor polymorphisms were examined by using standard PCR-based techniques.

Results: There was a significantly higher prevalence of the panic disorder–associated CCK-B receptor allele 7 in subjects with IEI (9/22 [40.9%]) compared with control subjects (2/22

[9.1%], $P = .037$). There was no difference in personality trait–associated polymorphisms of the gene encoding dopamine D4 receptor between patients and control subjects. **Conclusions:** These findings provide preliminary evidence that IEI and panic disorder share a common neurogenetic basis, which would predate the anxiety-producing effects of IEI symptoms. Further studies with larger samples are warranted, but these results support previous studies that suggest that panic disorder may account for much of the symptomatology in at least some cases of IEI and provide a basis for rational treatment strategies. (*J Allergy Clin Immunol* 2001;107:887-90.)

Key words: Idiopathic environmental intolerance, panic disorder, cholecystokinin, cholecystokinin B receptor, dopamine D4, dopamine D4 receptor gene, genetic association study

Proponents of the toxicogenic theory of idiopathic environmental intolerance (IEI; formerly known as multiple chemical sensitivity) claim that symptoms in afflicted individuals, including shortness of breath, lightheadedness, difficulty concentrating, gastrointestinal upset, and paresthesias, are due to exposure to chemicals present in the environment. Scientific evidence to support these claims is lacking.¹ Instead, there is a growing body of work that suggests that IEI is a psychophysiologic disorder with prominent features of panic/anxiety and somatization.²⁻⁷ In addition to sharing many of the same symptoms as episodic panic attacks, patients with IEI often exhibit the anticipatory anxiety and phobic avoidance of triggers that are characteristic of panic disorder. Various studies have found a high incidence of psychopathology in patients with IEI.⁸⁻¹⁰ Moreover, when suitably blinded, affected individuals are no more likely to react to their purported trigger than to placebo.¹¹ On open challenge to their purported trigger, subjects who experienced their usual symptoms were shown to hyperventilate, without other objective evidence of respiratory changes.³ Panicogenic challenges (those capable of inducing panic attacks in patients with panic disorder but not in normal control subjects), including intravenous sodium lactate and 35% carbon dioxide inhalation, have been shown to induce panic attacks in patients with IEI,^{4,5} suggesting that IEI shares an underlying neurobiologic diathesis with panic disorder.

To further investigate the similarity of IEI and panic disorder, we chose to see whether the 2 conditions shared

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Abbreviations used

CCK: Cholecystokinin

IEI: Idiopathic environmental intolerance

neurogenetic features and focused on the cholecystokinin (CCK) system.

CCK, a brain-gut neuropeptide, is another well-recognized panicogenic agent. Two CCK (CCK-A and CCK-B) receptors have been identified. In various models of anxiety, CCK-B agonists produce anxiogenic effects, whereas CCK-B antagonists produce anxiolytic effects (see Bradwejn et al¹²). Patients with panic disorder show an enhanced sensitivity to CCK-4, a CCK agonist, and exhibit lower cerebrospinal fluid and lymphocyte CCK concentrations compared with healthy control subjects.¹³ Recently, an association between alleles 6 and 7 of the gene encoding CCK-B receptor and panic disorder has been reported.¹⁴ We postulated that patients with IEI might exhibit a similar preponderance of these CCK-B receptor alleles.

To explore the relation of IEI to behaviour-associated personality traits, we focused on the dopaminergic system. The reliably measured human personality trait of Novelty Seeking has been associated with particular longer variants of the dopamine D4 receptor exon III polymorphism.^{15,16} Because patients with IEI exhibit pronounced avoidance behaviour, we postulated that they might exhibit a tendency to have specific shorter variants at this dopamine D4 locus.

METHODS

Subjects

This study was approved by the St Michael's Hospital Research Ethics Board. Exclusion criteria included previous diagnosis or treatment for psychiatric disease. Patients were directly questioned about previous psychiatric or psychologic disorders on 2 separate visits by 2 different investigators. Patients were recruited from allergy practices, previous studies of IEI,^{5,17} and advertisements in area hospitals. Previously cited IEI criteria⁸ included duration of IEI symptoms of at least 3 months; symptoms in at least 3 organ systems, including the central nervous system; and sensitivity to at least 4 substances. Atopy and other medical conditions were excluded as a cause of symptoms. Thirteen candidate patients were recruited, and 11 patients gave informed consent and underwent final screening. All 11 met our criteria and were individually matched to normal control subjects from an existing bank for age, sex, and ethnic background.

Control subjects

The control subjects were recruited from several sources, including advertisements, general medical clinics, and hospital staff. The control subjects were screened with an abbreviated version of the structured clinical interview from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Screening questions were asked regarding all major mental disorders, including schizophrenia. If there was any evidence for a major mental disorder, then the subject was excluded.

Procedures

Genomic DNA was extracted from blood samples with the QIAamp Blood Mini Kit (Qiagen) or the high salt method.¹⁸

Genotyping of patient and control samples was performed and read simultaneously in a blinded fashion.

CCK-B receptor. The DNAs were genotyped by using a highly polymorphic dinucleotide repeat microsatellite marker located in the 5' regulatory region of the human brain gene encoding the CCK-B receptor. PCR amplification was done on 150 ng of template DNA. After an initial denaturation step at 95°C for 5 minutes, the following components were added: 1× PCR buffer (Perkin-Elmer); 1.5 mmol/L MgCl₂; 0.2 μmol/L 3' end-labeled forward primer; 0.4 μmol/L reverse primer; 200 μmol/L each of deoxyadenosine triphosphate, deoxycytidine triphosphate, deoxyguanosine triphosphate, and deoxythymidine triphosphate; and 0.5 U of AmpliTaq DNA polymerase (Perkin-Elmer) in a final reaction volume of 10 μL. The PCR parameters were at 94°C for 30 seconds, 59°C for 30 seconds, and 72°C for 30 seconds for 30 cycles. With a GeneAmp 9600 Perkin-Elmer Cetus PCR machine, PCR products were separated on a 6% denaturing polyacrylamide gel and visualized by means of autoradiography. The genotypings were read independently by 2 of the investigators.

Dopamine D4 receptor gene exon III. Primers flanking the polymorphic region in the third exon of the gene encoding the dopamine D4 receptor were used to amplify the segment. PCR was carried out as described previously.¹⁹ DNA bands were assigned a number (corresponding to the number of 48-bp repeats they contained [ie, 2, 3, 4, 5, 6, 7, 8, or 10]) on the basis of fragment size.

Statistical analysis

χ^2 analysis on the allele counts for the dopamine D4 exon III receptor locus and the CCK-B receptor polymorphisms for panic disorder (risk alleles 6 and 7) versus other CCK-B receptor alleles was performed. The Fisher exact test was used where there were too few subjects to be analyzed by means of χ^2 analysis. Odds ratios were calculated as previously described.¹⁴

RESULTS

Results for CCK-B receptor allele typing for patients with IEI and control subjects (22 alleles in each group) are shown in Table I. Nine (40.9%) of 22 alleles from patients with IEI were CCK-B receptor allele 7, which has previously been shown to be associated with panic disorder,¹⁴ compared with 2 (9.1%) of 22 alleles from matched normal control subjects; this difference was statistically significant ($P = .037$, $\chi^2 = 4.364$, $df = 1$). The excess of CCK-B receptor allele 7 in patients with IEI yielded an odds ratio of 6.9 (95% CI, 1.1-55.6). The proportion of patients with IEI having CCK-B receptor allele 6 in the current study was 5%, which was not different from that found among the control subjects. Although a previous study¹⁴ found an increased prevalence (21%) of CCK-B receptor allele 6 in patients with panic disorder, additional studies in the same laboratory have not found any differences in the prevalence of CCK-B receptor allele 6 between patients with panic disorder and control subjects (unpublished observations).

Results for dopamine D4 receptor allele typing are shown in Table II. There was no significant difference in allele prevalence between patients with IEI and matched control subjects ($P = .52$, $\chi^2 = 3.14$, $df = 3$).

DISCUSSION

We have shown that patients with IEI have a statistically significant increased prevalence of CCK-B receptor

TABLE I. CCK-B receptor allele distribution in 11 patients with IEI and 11 matched control subjects (a total of 22 alleles in each group)

Allele	1	3	4	5	6	7	8	9	10	11	12	14	15
Patients	1	1	1	3	1	9*	1	1	2	0	1	1	0
Control subjects	2	1	1	3	3	2*	1	3	1	2	1	0	2

CCK-B receptor alleles are identified in the top line. The number of patient alleles found to be of each receptor subtype are recorded below in the second line, and the number of control alleles of each receptor subtype are recorded in the third line.

*Statistically significant difference: $P = .037$.

allele 7, which has previously been shown to be associated with panic disorder.¹⁴ Although these results are statistically significant, the sample size (and therefore power) was small, and these findings will need to be replicated in larger studies.

In the previous study 23.7% of CCK-B receptor alleles in patients with panic disorder were found to be allele 7, suggesting that other genetic or nongenetic factors are operative in the remainder of patients with panic disorder. In the current study 9 (40.9%) of 22 alleles from patients with IEI were found to be allele 7, which is a higher proportion than that previously reported in patients with panic disorder.¹⁴ Although this difference may reflect sampling error, if confirmed in larger studies, we might speculate that patients with IEI share a neurobiologic diathesis with a subgroup of patients with panic disorder in which CCK-B is particularly relevant. Two (9.1%) of 22 control alleles were found to be allele 7 compared with 15.7% as previously reported.¹⁴ To date, there is no clinically distinct phenotype associated with the presence or absence of allele 7 in patients with panic disorder.

No association with dopamine D4 receptor polymorphism was found in our patients with IEI. Previous studies have suggested that longer alleles (≥ 5 repeats) at this locus are associated with the human personality trait of Novelty Seeking,^{15,16} and we had speculated that the shorter alleles (< 5 repeats) might be more prevalent in patients with IEI who avoid novelty, sometimes to the point of becoming housebound. No evidence to support this was found in the current study; however, the sample size might not have been sufficiently large to detect a small difference between the groups. A recent report also failed to find any significant differences in dopamine D4 receptor or dopamine transporter alleles in panic disorder.²⁰ Other aspects of the dopaminergic system previously associated with anxiety or phobias^{21,22} were not addressed in the current study.

The association of specific CCK-B receptor alleles in patients with both IEI and panic disorder suggests they may share an underlying neurogenetic basis. This extends previous observations that suggest IEI and panic disorder may arise from a similar, if not identical, neurobiologic diathesis that may be summarized as follows: (1) shared symptomatology (including episodes reminiscent of panic attacks, anticipatory anxiety, and phobic avoidance of perceived triggers); (2) studies that show a high prevalence of psychopathology (particularly anxiety and depression) in patients with IEI⁸⁻¹⁰; (3) hyperventilation-induced hypocarbia after open,³ but not blinded,¹¹ challenge of

TABLE II. Dopamine D4 receptor (exon III) allele distribution in 11 patients with IEI and 11 matched control subjects (22 alleles in each group)

Allele	2	3	4	7
Patients	1	0	18	3
Control subjects	2	1	13	6

Dopamine D4 receptor (exon III) alleles are identified in the top line (on the basis of the number of 48-bp repeats they contain). The number of alleles from patients with IEI of each receptor subtype identified is recorded below in the second line, and the number of control alleles of each receptor subtype is identified below in the third line. There was no significant difference between the groups.

patients with IEI with perceived triggers; (4) panic attacks after single-blinded challenge with panicogenic stimuli^{4,5} in patients with IEI; and (5) anecdotal reports of improvement when patients with IEI are treated with panic-directed psychotherapy and pharmacotherapy.^{6,23-25}

Proponents of a toxicogenic explanation for IEI have countered some of the above studies by claiming that panic symptomatology in IEI arises from the stress of dealing with the illness. However, the current study suggests that patients with IEI may have an underlying genetic predisposition to panic disorder that predates IEI symptomatology. In fact, an underlying neurogenetic predisposition that leads to the eventual development of panic disorder would account for a large part of the symptomatology attributed to IEI. Other psychologic, biologic, and social factors may then further modify the clinical presentation.^{2,26}

The current study provides a further basis for the rational treatment of IEI with panic-directed strategies, preferably by psychiatrists familiar with this treatment paradigm.²⁵ Unfortunately, patient acceptance of and compliance with psychiatric intervention is often poor,^{23,27} and recruitment into formal intervention studies has been difficult.⁵ Treatment efforts may be complicated by the inappropriate reinforcement of anticipatory anxiety and phobic avoidance of perceived environmental triggers (including antipanic pharmacotherapeutic agents) by so-called clinical ecologists,^{23,28-30} which allows the symptomatic patient to avoid panic-provoking triggers, at least temporarily.³¹ Improved understanding of the psychophysiologic basis of IEI by both physicians and patients hopefully will lead to greater acceptance of antipanic treatments and more successful outcomes.

In conclusion, we have shown an increased prevalence of CCK-B receptor allele 7 in a small sample of patients

with IEI, which has also been reported in patients with panic disorder. These preliminary results suggest that IEI and panic disorder may share a neurogenetic basis, and larger studies to confirm these findings are warranted.

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