Table 1 (*continued*)

Reference	Subject	*N*	Source	Examination		
				Environmental factors	Biological factors	Methods
Philibert et al., 2007	Human	49	LCLs	–	Methylation	Mass spectroscopy
					HTTLPR	PCR
					Expression	RT-PCR

MZ: monozygotic; BD: bipolar disorder; C: control; AD: alcohol dependence; PTSD: posttraumatic stress disorder; DZ: dizygotic; MD: major depression; ASPD: antisocial personality disorder; PBMCs: peripheral blood mononuclear cells; LCLs: lymphoblastoid cell lines; HTTLPR: serotonin transporter-linked promoter region; PCR: polymerase chain reaction; RT-PCR: reverse transcribed-PCR; RFLP: restriction fragment length polymorphism.

Moreover, we found that DNA methylation of the CpG island shore of *SLC6A4* was significantly correlated with mRNA level in individuals with the S/S genotype (Sugawara et al., 2011a). The other group also reported that DNA methylation of the CpG island of *SLC6A4* was associated with total gene expression, whereas that in the CpG island shore was associated with gene expression of a specific splice variant (Vijayendran et al., 2012). In an *in vitro* study, the HTTLPR genotype was found to affect the transcription factor binding and chromatin modifications of *SLC6A4* in response to cocaine in JAr cells (Vasiliou et al., 2012).

These findings collectively suggest that the DNA methylation level of the CpG island and/or CpG island shore of *SLC6A4* controls its mRNA expression by interacting with HTTLPR. Further studies are needed to elucidate the molecular mechanism underlying this interaction.

EFFECTS OF ENVIRONMENTAL FACTORS ON DNA METHYLATION OF *SLC6A4*

Weaver et al. (2004) reported that hippocampal hypermethylation of the glucocorticoid receptor gene induced by low maternal care may play a role in stress vulnerability in rats. This suggested that DNA methylation might play a role as an epigenetic mark of G × E interaction. In rhesus macaques, higher methylation of *SLC6A4* was associated with higher reactivity in adults that experienced early life stress as infants (Kinnally et al., 2011), whereas DNA methylation level was not associated with rearing condition (Kinnally et al., 2010). In humans, maternal depressed mood was associated with decreased DNA methylation of promoter region of *SLC6A4* in leukocytes of both maternal peripheral blood and neonatal cord blood (Devlin et al., 2010). Furthermore, Beach et al. (2010) reported that DNA methylation level of the CpG island was increased in the subjects who had a history of childhood physical abuse. This result was replicated in an independent study in women (Beach et al., 2011). The other group reported that higher levels of *SLC6A4* promoter methylation were observed in both T cells and monocytes in the adult males with high childhood-limited aggression, who had lower *in vivo* serotonin synthesis in the orbitofrontal cortex detected by positron emission tomography (Wang et al., 2012). Therefore, environmental factors might affect the methylation status of *SLC6A4*, though the direction of the alteration is not consistent.

The number of traumatic events is reportedly associated with posttraumatic stress disorder (PTSD), and this association was suggested to be modified by the methylation level of *SLC6A4*. Subjects with more traumatic events were at increased risk for PTSD if they showed the lower methylation level of *SLC6A4*. On the other hand, those who showed the higher methylation level were considered to be protected from PTSD (Koenen et al., 2011). The other report showed that DNA methylation of *SLC6A4* promoter affected the impact of HTTLPR genotype on psychological sequelae. Higher levels of methylation predicted more unresolved loss or trauma in the subjects with L/L allele, whereas they were associated with

less traumatic experience in the subjects with S/S allele (van Ijzendoorn et al., 2010). Vijayendran et al. (2012) reported that sexual abuse influenced the methylation of *SLC6A4* by interacting with HTTLPR.

In summary, there is a complex interaction between DNA methylation status of *SLC6A4*, HTTLPR, and environmental factors, with regard to psychiatric disorders.

DNA METHYLATION OF *SLC6A4* IN PSYCHIATRIC DISORDERS

A vast amount of genetic studies of *SLC6A4* have been reported in various psychiatric disorders. A meta-analysis showed a significant association of HTTLPR and alcohol dependence (Feinn et al., 2005). On the other hand, there was no difference in the methylation status of *SLC6A4* promoter region of PBMCs between patients with alcohol dependence and control subjects (Park et al., 2011). Using LCLs, Philibert et al. (2008) reported that the DNA methylation level of *SLC6A4* promoter tended to be higher in subjects with a lifetime history of major depression than those without a history of major depression. History of alcohol dependence did not affect the DNA methylation status of *SLC6A4*.

A role of G × E interaction between *SLC6A4* and stress has been reported in depression (Caspi et al., 2003; Kendler et al., 2005). Olsson et al. (2010) examined the DNA methylation status of *SLC6A4* promoter in buccal cells. DNA methylation status of the buccal cells, which are derived from ectoderm, might be more similar to that of neuronal cells compared with peripheral blood leucocytes (PBLs), which are derived from mesoderm (Olsson et al., 2010). Whereas there was no association between depressive symptoms and methylation level or HTTLPR genotype, depressive symptoms were more common among those with elevated methylation levels in S allele carriers (Olsson et al., 2010). This result implicated that an interaction of epigenetic and genetic factors involving *SLC6A4* is related to depressive symptoms.

Because DNA methylation differences between monozygotic (MZ) twins discordant for a disease might be relevant to the discordant phenotype, we performed a comprehensive analysis of DNA methylation profiles of promoters in LCLs of MZ twins discordant for bipolar disorder (BD) (Sugawara et al., 2011a). After careful filtering, the only robust DNA methylation difference between twins was the hypermethylation at the CpG island shore of *SLC6A4* in a bipolar twin. Causal relationship between such DNA methylation difference and discordant phenotype is unknown, because the differences of methylation patterns between MZ twins reportedly increase with age (Fraga et al., 2005). However, hypermethylation of *SLC6A4* in BD was confirmed in a case-control study. DNA methylation level of *SLC6A4* was negatively correlated with gene expression in an HTTLPR genotype-specific manner. Importantly, hypermethylation of *SLC6A4* at the same CpG sites was also found in the postmortem prefrontal cortices of patients with BD. In a study of MZ twins, Wong and colleagues showed that the variation of DNA methylation in *SLC6A4* was attributable to unique environmental factors rather than heritable factors (Wong et al., 2010). Taken together, these results suggest that epigenetic modification of *SLC6A4* might be implicated in the G × E interaction involved in the pathophysiology of BD.

PERSPECTIVE

In some studies, methylation level of *SLC6A4* is reportedly higher in females than in males (Philibert et al., 2008; Beach et al., 2010; Koenen et al., 2011). The molecular basis and consequence of the gender difference remain unclear. Further studies are needed to elucidate the gender difference of *SLC6A4* methylation. Meanwhile, we should pay a careful attention to the gender in designing the case-control association study.

Many of the studies presented here have focused on methylation at the CpG island of *SLC6A4* promoter region, where DNA methylation levels are relatively low. In contrast, the region identified in our study was located about 300 bp downstream of the CpG island. Such a region, known as a CpG island shore, plays an important role in tissue specific regulation of gene expression (Irizarry et al., 2009). Therefore, DNA methylation status of the CpG island shore of *SLC6A4* might serve as a more sensitive marker for G × E interaction.

Most of the studies have examined *SLC6A4* methylation using the peripheral tissues, and only one study examined in postmortem brains (Sugawara et al., 2011a). Among the peripheral tissues, LCLs are often used for the epigenetic studies, which were established through transformation of B lymphocyte by Epstein–Bar (EB) virus. This process can alter the epigenetic status of B lymphocyte (Antequera et al., 1990). In our study, we comprehensively analyzed the genomic regions whose methylation status was affected by the transformation (Sugawara et al., 2011b). In order to avoid the artifacts caused by the EB virus transformation, these regions were excluded from the analysis.

In addition, most of patients with psychiatric disorders are taking medication, which can affect the DNA methylation status. Indeed, cocaine reportedly alters chromatin modifications and DNA-binding activity of selected transcription factors depending on the HTTLPR genotype *in vitro* in the JAr cell lines (Vasiliou et al., 2012). In the case of patients treated with drugs, culturing the LCLs in drug-free medium for several weeks after blood sampling might eliminate the effect of medication. However, it is not known to what extent preexisting drug-induced epigenetic changes are reversed by culturing in drug-free medium. The possible effect of medication, including antidepressants, mood stabilizers and antipsychotics, on the DNA methylation pattern of *SLC6A4* should be assessed in the future studies.

In conclusion, recent studies suggested the important role of DNA methylation of *SLC6A4* in G × E interaction leading to psychiatric disorders. Further studies are needed to understand the molecular basis of G × E interaction and to develop a biological marker of psychiatric disorders.

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Old drug ifenprodil, new hope for PTSD with a history of childhood abuse

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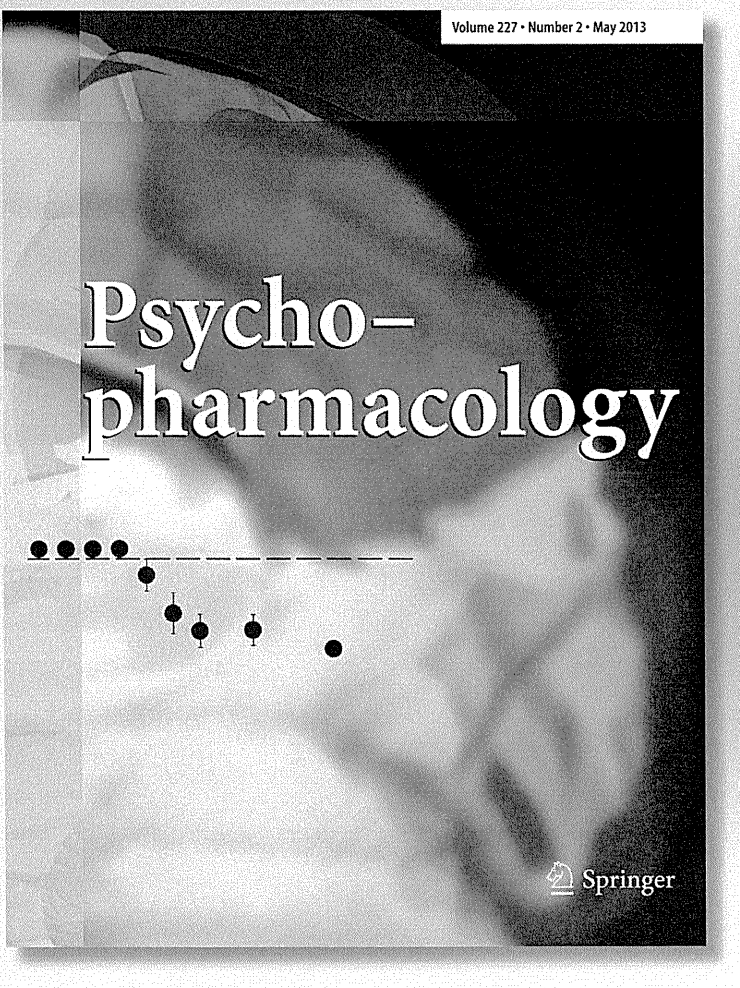

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LETTER TO EDITOR

Old drug ifenprodil, new hope for PTSD with a history of childhood abuse

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Commentary

A recent meta-analysis showed that a history of sexual abuse is associated with increased risk for a lifetime diagnosis of multiple neuropsychiatric disorders, such as post-traumatic stress disorder (PTSD), anxiety disorders, depression, eating disorders, sleep disorders, and suicide attempts (Chen et al. 2010). In particular, PTSD is highly prevalent among women who have experienced childhood sexual abuse. Reexperiencing the trauma ("flashbacks") is a hallmark symptom of PTSD, but the precise mechanisms for flashbacks are currently unknown. Several lines of evidence suggest that the glutamatergic system plays a significant role in the pathogenesis of PTSD (Chambers et al. 1999; Myers et al. 2011). However, there are currently no standard therapeutic agents for treating flashbacks associated with PTSD.

Ifenprodil (Cerocral®) has been used as a cerebral vasodilator in a limited number of countries, including Japan and France. Very recently, we reported that ifenprodil was effective in the treatment of flashbacks in three female PTSD patients with a history of childhood sexual abuse (Kishimoto et al. 2012). Subsequently, we reported that ifenprodil was also effective in the treatment of flashbacks in three female adolescent PTSD patients with a history of childhood abuse (Sasaki et al. 2013). In these case reports, these patients suffered repetitive flashbacks and depressive episodes for a long time. During this period, they were treated with several drugs (e.g., antipsychotic drugs, antidepressants, and antianxiety drugs) and with psychotherapy, but these were not effective in treating their flashback, although depressive symptoms were improved by antidepressants. They were then treated with ifenprodil (Cerocral®; 60 mg/day for adult patients and 20 mg/day for adolescent patients), and the number of flashbacks in these patients was markedly reduced after treatment with ifenprodil (Kishimoto et al. 2012; Sasaki et al. 2013). All patients were surprised with the efficacy of ifenprodil and satisfied with the improvement.

Ifenprodil was well tolerated in the adult and adolescent PTSD patients, with a history of childhood abuse. Depressive symptoms in these patients were first treated using antidepressants. While their depression improved, the incidence of flashbacks remained unchanged, and ifenprodil treatment was initiated. Ifenprodil's action against flashbacks seems to require 2 to 3 weeks of treatment. To our knowledge, these are the first reports demonstrating the beneficial effect of ifenprodil in the treatment of flashbacks in the female adult or adolescent PTSD subjects with a history of childhood abuse (Kishimoto et al. 2012; Sasaki et al. 2013). However, the precise mechanisms underling the beneficial effects of ifenprodil are currently unclear.

Ifenprodil is a prototypical antagonist of the GluN2B subunit on the *N*-methyl-D-aspartate (NMDA) receptor (Fig. 1). As well as binding to the α1 adrenergic and NMDA receptors, we reported that ifenprodil is a potent agonist at sigma-1 receptor chaperone on endoplasmic reticulum (ER) (Fig. 1) (Hashimoto and London 1993; Ishima and Hashimoto 2012). Sigma-1 receptor agonists can stimulate chaperone activity on ER, thus enabling the regulation of neuronal plasticity in the brain, suggesting a potential role of sigma-1 receptor in the pathophysiology of a number of neuropsychiatric disorders (Hayashi and Su 2007). In addition,

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ifenprodil is also an inhibitor of G protein-activated inwardly rectifying K^+ (GIRK) channels, which play an important role in reducing neuronal excitability in most brain regions (Fig. 1)(Kobayashi et al. 2006).

The NMDA receptors are crucial for synaptic plasticity underlying learning and memory, and glutamatergic neurotransmission via NMDA receptors plays a role in the pathophysiology of PTSD (Chambers et al. 1999; Myers et al. 2011). Both systemic and intra-amygdala treatments with ifenprodil before extinction training impaired the initial acquisition and subsequent retrieval of fear extinction (Myers et al. 2011). These findings suggest that the acquisition of fear extinction requires the activation of GluN2B subunit on the NMDA receptors, and that the lateral amygdala is an essential brain region underlying its mechanism. In addition, accumulating evidence has emerged about the effectiveness of the α1 adrenergic receptor antagonist prazosin in the treatment of nightmares and hyperarousal among patients with PTSD treated within the Veterans Affairs (Harpaz-Rotem and Rosenheck 2009), suggesting the role of α1 adrenergic receptor in the treatment of PTSD. It is currently unclear whether prazosin can be effective in the treatment of PTSD with a childhood abuse. Taken all together, with its high affinity for the NMDA receptor, α1 adrenergic receptor, sigma-1 receptor, and GIRK channel, it is likely that ifenprodil acts at least partially on these targets, to alleviate flashbacks in PTSD patients, although the precise therapeutic targets remain undetermined (Kishimoto and Hashimoto 2013).

In conclusion, we would like to propose that ifenprodil therapy could be an alternative treatment for flashbacks in adult and adolescent PTSD patients with a childhood abuse, since this drug is already in clinical use. Nonetheless, more detailed randomized, double-blind placebo-controlled studies of ifenprodil are needed to confirm its efficacy.

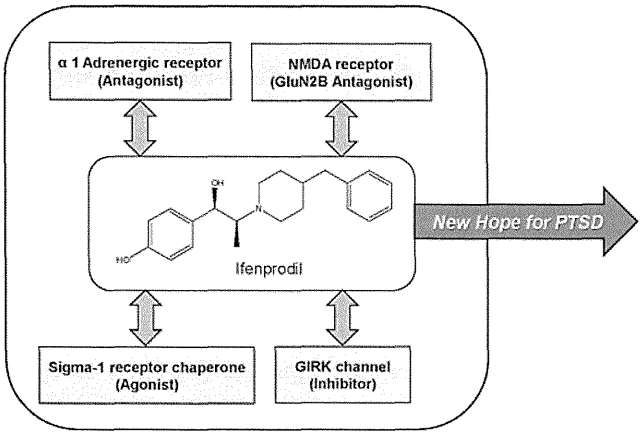

Fig. 1 Ifenprodil as a new therapeutic drug for PTSD. Major pharmacological targets of ifenprodil are α1 adrenergic receptor, GluN2B subunit of the NMDA receptor, sigma-1 receptor chaperone, and GIRK channel. Ifenprodil could act at least partially on these targets, to alleviate flashbacks in PTSD patients with a history of childhood abuse

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Ifenprodil for the Treatment of Flashbacks in Adolescent Female Posttraumatic Stress Disorder Patients with a History of Abuse

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A recent meta-analysis study showed that a history of abuse is associated with an increased risk for a lifetime diagnosis of multiple psychiatric disorders, such as posttraumatic stress disorder (PTSD), anxiety disorders, depression, eating disorders, sleep disorders, and suicide attempts [1]. In particular, PTSD is highly prevalent among women with a history of childhood abuse. Re-experiencing the event through intrusive flashbacks is one of the key diagnostic criteria for PTSD using ICD-10 [2], although the precise mechanisms for flashbacks are currently unknown [3]. Several lines of evidence suggest that glutamatergic neurotransmission via the N-methyl-D-aspartate (NMDA) receptor plays a role in certain behavioral manifestations common to PTSD, including dissociation and perceptual alterations [4, 5]. There are currently no standard therapeutic agents for treating flashbacks associated with PTSD.

Ifenprodil (brand name Cerocral), a neuroprotective agent that binds to the GluN2B subunit of the NMDA receptor [6], is used as a cerebral vasodilator in a limited number of countries including Japan and France. Here, we report on 3 cases where ifenprodil proved effective in treating the flashbacks of adolescent female PTSD patients with a history of abuse. Written informed consent was obtained from the patients and their parents for publication of this case report.

Ms. A. was a 16-year-old Japanese female diagnosed with PTSD (F43.1) and other depressive episodes (F32.8), according to ICD-10 criteria [2]. In junior high school, she was physically and sexually assaulted by a classmate for approximately 6 months. She subsequently suffered repetitive flashbacks, depressive episodes and irritation. Treatment with ifenprodil (20 mg) was initiated, and after 3 weeks, the number of flashbacks was reduced by more than 60%. The frequency of her flashbacks changed from 'frequently' (4) to 'rarely' (2), using the Likert five-point frequency scale. No side effects were reported in this patient.

Ms. B. was a 17-year-old Japanese female diagnosed with PTSD (F43.1) and other bipolar affective episodes (F31.8), according to ICD-10 criteria [2]. In junior high school, classmates physically assaulted her for approximately 2 months. She subsequently suffered repetitive flashbacks, depressive episodes and irritation. Treatment with blonanserin (8 mg) and fluvoxamine (50 mg) failed to reduce the incidence of flashbacks. New treatment with ifenprodil (20 mg) was initiated and, after 2 weeks, her flashbacks were markedly reduced by more than 80%. The frequency fell from 'very frequently' (5) to 'rarely' (2) using the Likert scale. Ms. B. also showed slight improvement in her dissociative symptoms. Her only reported side effect was a mild headache.

Ms. C. was a 19-year-old Japanese female, diagnosed with PTSD (F43.1) and other bipolar affective episodes (F31.8), according to ICD-10 criteria [2]. In elementary school, she was sexually assaulted by her uncle. She suffered flashbacks, depressive episodes and irritation for more than 10 years. She was treated with several drugs, including fluvoxamine, carbamazepine, valproate sodium, risperidone, blonanserin, quetiapine, and aripiprazole, and underwent psychotherapy, but none were effective in treating her flashbacks. Ifenprodil (20 mg) was added to the regimen and after 2 weeks, the number of flashbacks was reduced by more than 50%. Flashback frequency fell from 'very frequently' (5) to 'occasionally' (3), using the Likert scale. In this patient, the only reported side effect was nausea.

None of these cases had a history of phencyclidine, ketamine, methoxetamine or tiletamine use. Nor was there use of any other recreational drug known to block glutamatergic neurotransmission via the NMDA receptor.

Ifenprodil was well tolerated in these 3 PTSD patients with histories of abuse. The depressive symptoms and irritation in 2 patients were first treated with antidepressants or atypical antipsychotics. Although their depression and irritation improved, the occurrence of flashbacks remained unchanged. Treatment with ifenprodil dramatically reduced the incidence of flashbacks in all patients. To our knowledge, this is the first report demonstrating the beneficial effect of ifenprodil for treating flashbacks in adolescent female subjects. Recently, Kishimoto et al. [7] reported that ifenprodil showed beneficial effects in the treatment of flashbacks, in female PTSD patients with a history of childhood sexual abuse. However, the precise mechanisms underlying this effect are unclear. It is also reported that ifenprodil is a potent agonist at endoplasmic reticulum chaperone sigma-1 receptors, which play a role in neuronal plasticity in the brain [8, 9]. With its high affinity for both the NMDA and sigma-1 receptors, it is likely that ifenprodil acts, at least partially on these receptors, to alleviate flashbacks in PTSD patients, although further detailed studies are needed [7]. While selective serotonin reuptake inhibitors are effective in treating PTSD in children, adolescents and young adults [10], there is an increased risk of attempted suicide [11]. In contrast, there are no reports of an increased suicide risk in patients using ifenprodil.

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It seems likely therefore, that ifenprodil may be an effective and safe drug for the treatment of flashbacks associated with PTSD in children and adolescents.

In conclusion, ifenprodil therapy may prove to be an effective alternative treatment for flashbacks in adolescent female patients with PTSD, since this drug is already in clinical use. Nonetheless, more detailed randomized, double-blind studies are needed to confirm its efficacy.

The authors report no biomedical or financial interests, or potential conflicts of interest.

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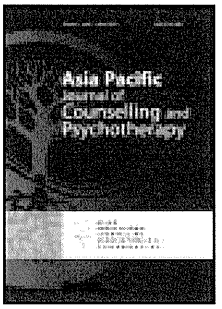

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Cognitive behavioural therapy for somatoform pain disorder in adolescents: a case study

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Cognitive behavioural therapy for somatoform pain disorder in adolescents: a case study

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This case study reveals the effectiveness of a cognitive behavioural therapy (CBT) intervention based on a functional model of interruption of pain and a hypothetical model of functional somatic syndromes in a case of adolescent somatoform pain disorder. Yu was a junior high school student in Japan who was diagnosed with somatoform pain disorder. He was initially opposed to the diagnosis of such a disorder, but the therapist and client worked together towards a realization that CBT was useful through exercise without forcing 'psychosocial' explanations on him. The CBT intervention mainly included four types of techniques: self-monitoring, behavioural experimentation, behavioural activation, and distraction. These interventions enabled Yu to reduce his avoidance of activities.

Keywords: adolescent; cognitive behavioural therapy; pain disorder; somatic symptoms

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1. Case conceptualization

Somatoform pain disorder in children and adolescents is an under-researched area. Recurrent physical complaints and somatic symptoms are common in children and adolescents, with estimates of prevalence varying between 2% and 10% (Goodman & McGrath, 1991). These symptoms are called medically unexplained symptoms (MUS) and are of various types, among which individual pains are particularly common (Dell & Campo, 2011). Illness behaviours seen in MUS, such as excessive reassurance seeking or overuse of medical services, are suggested to function like safety-seeking behaviours (Salkovskis & Warwick, 1986), as they maintain anxiety and decrease activity level (Smith, Monson, & Ray, 1986). Additionally, such behaviours can be quite costly and unnecessary (Fink, 1992). Despite the high frequency of such symptoms and potential influence, few studies have assessed MUS in children and adolescents (Eminson, 2007), especially no study has assessed specific somatoform pain disorder in children and adolescents as those cases often fail to fit within the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

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(DSM-IV's) diagnostic criteria for specific somatoform disorders. This paper presents a case report of adolescent somatoform pain disorder in which we observed improvement in the primary symptom with the use of cognitive behavioural therapy (CBT).

To the best of our knowledge, no cognitive behavioural model has been suggested to be valid specifically for adolescent somatoform pain disorder. In the present study, Eccleston and Crombez's functional model of interruption of pain (Eccleston & Crombez, 1999) and Henningsen, Zipfel, and Herzog's hypothetical model of functional somatic syndromes (Henningsen, Zipfel, & Herzog, 2007) were employed to guide the formulation and conduct of the therapy. The former model helps us to understand the way in which pain occurs and interrupts attentional systems for brief periods. It also helped us to frame our intervention in terms of the relationship between pain and attention. The latter model explains the factors maintaining pain from a psychosocial perspective: pain can be induced by psychosocial factors (e.g. interpretation of it as a symptom of a disease) and maintained by patients' medical-seeking behaviour and the behaviours of treating physicians. It made us realize the importance of behavioural activation. Hence, we thought it would be appropriate to employ these models to guide the formulation of our intervention.

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2. Treatment plan and actual progress

2.1. Profile of the patient

Yu, a 14-year-old Japanese boy, was a junior high school student. One day, Yu felt a slight pain in his chest. Interpreting it as a symptom of a physical disease, he saw a physician, but no abnormalities were observed. He suspected that he had a severe disease that was difficult to detect. He saw multiple physicians and paediatricians within a short period and underwent thorough examinations, including ECG, X-rays, a CT scan, and an MRI; nevertheless, nothing abnormal was found. Despite the absence of observable abnormalities, his symptom remained. He was prescribed multiple antidepressant medications and anti-anxiety agents, but these had little effect on his symptom and caused side effects such as finger tremors. Therefore, his doctor suggested that he should stop taking medications. He became increasingly anxious about his health and began to collect information relating to his subjective symptom on the Internet. His symptom kept deteriorating to the point that he was unable to attend school and play baseball that he liked.

He concurrently started to avoid activities as he was anxious about the exacerbation of his symptom. Seeking medical help and his avoidance of activities disturbed his social functioning. The subjective symptom deteriorated while in his preoccupation with his physical health increased. He complained of slight, continuous pain in his chest and experienced stabbing pain. He claimed that this pain made him lie down over 10 times daily. Although no physical abnormality was found, his symptom did not improve; thus, he visited our office, as suggested by his physician. At that time, he had not attended school for almost 7 months due to his pain. As a consequence of his history of illness, he was diagnosed with somatoform pain disorder in accordance with the guidelines set forth in the DSM-IV-TR. We asked him to stay in the hospital in order to undergo intensive CBT, considering that it would have been difficult to achieve appropriate treatment via outpatient services. Because he denied the diagnosis and insisted that his symptom was caused by a physical problem, we assumed that he would seek further medical help. However, he was interested in the idea of 'intensive' treatment; therefore, he consented to admission and such treatment.

2.2. Assessment

A clinical assessment using the Children's Depression Rating Scale, Revised (CDRS-R) (Poznanski, 1984) suggested that Yu was in a depressive state because of his pain (his CDRS-R score was 69 points). At the time of this treatment, no Japanese version of a reliable symptom rating scale for somatoform pain disorder exists for adolescents, and he denied psychiatric evaluation, insisting that his pain must have had a physical origin. Therefore, the therapist evaluated Yu's symptoms by asking the patient to monitor his pain by taking notes while the therapist completed the Global Assessment of Functioning (GAF scale) on a monthly basis. However, Yu persisted in his opposition to the idea that he had a somatic pain disorder, saying, 'I am not a mental patient!' He rejected psychiatric treatment and psychosocial examination for his symptom.

2.3. Formulation

The therapist and Yu developed a cognitive behavioural model showing how his symptom maintains itself (Figure 1). The formulation (i.e. psychosocial explanation) suggests that selective attention to pain made the patient detect further subjective pain; in turn, his interpretation of the pain makes him anxious and decreases his activity, which leads to still more preoccupation with pain. Several interventions were customized in order to confirm the validity of the formulation and to test his prediction that 'he should rest and stay still so as not to exacerbate his pain'.

2.4. Intervention

Structured therapy consisted of two 45-min sessions per week. During 3 months of admission, 24 sessions in total were conducted. In the first week after admission, the therapist simply observed Yu's behaviour instead of beginning the therapeutic intervention; this was done in order to disconfirm the presence of other disorders and confirm the diagnosis of a somatoform pain disorder.

2.4.1. Behavioural experimentation

Initially, the patient was unwilling to leave his ward, stating that exercise would cause pain. One week after admission, the therapist suggested playing catch as a behavioural

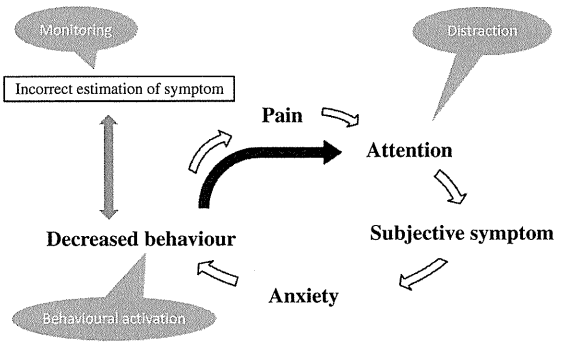

Figure 1. Therapeutic interventions aimed to reduce the cycle of pain.

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experiment (this was his favourite activity) to see if it actually causes pain. Yu was asked to rate his pain on a scale of 1–10, with 10 being the most severe. Before throwing the ball, he predicted severe pain (8) but actually reported only mild pain (1) while throwing.

2.4.2. *Self-monitoring*

From the second week of admission, the therapist asked Yu to record the frequency of his subjective symptom. Despite the explanation that such recording was important for therapeutic progress, Yu was unwilling to record this information because he was worried that the act of recording might fuel his preoccupation with his pain. Nevertheless, this type of recording ultimately had a positive effect: as treatment proceeded, he was able to realize the decrease in the frequency of his pain. This motivated him to increase his performance of behavioural tasks.

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2.4.3. *Behavioural activation and further engagement*

When the therapist and Yu first chose tasks for behavioural activation, they attached considerable importance to how enjoyable the tasks were for Yu and how easily the therapist could control task intensity and give immediate feedback to Yu. Playing catch and badminton were ultimately settled upon as the tasks for behavioural activation. This helped the therapist to develop a therapeutic alliance with Yu. In addition, Yu's belief that exercise causes pain gradually changed, and he lessened his avoidance of activities. After his avoidance decreased, the therapist and he collaboratively set a short-term goal (to leave his room and run around the hospital, even if he was experiencing pain), a middle-term goal (to go to school from the hospital every morning), and a long-term goal (to be discharged from the hospital and go to school from his house) in order to maintain his motivation to engage in the therapy.

2.4.4. *Distraction*

The therapist proposed a distraction technique when Yu began to show an interest in the relationship between his cognition and the chest pain. The therapist suggested that Yu remember the names and uniform numbers of the members of his favourite baseball team when he felt his symptom would occur. Distraction was effective, particularly when he performed behavioural tasks by himself. He told us this task helped him not to concentrate on thinking about his symptom and he felt less pain. Prior to using distraction, he could walk 1 km with great difficulty, but distraction enabled him to run up to 3 km. The distraction technique shifted focus away from his physical symptoms and facilitated a change in his belief that the pain was not related to an undetectable disease, but merely a physical sensation. More importantly, he began to accept a psychosocial explanation for his illness, engage more with the therapist, and work towards further therapeutic goals.

2.5. *Outcomes*

Before Yu was admitted to the hospital, he had not been able to go to school, and this avoidance had estranged him from his friends in school. Although he had suffered from his pain symptom and been unable to attend school for 10 months, Yu was able to attend school after 3 months of CBT without psychotropic medications. Ever since Yu left the

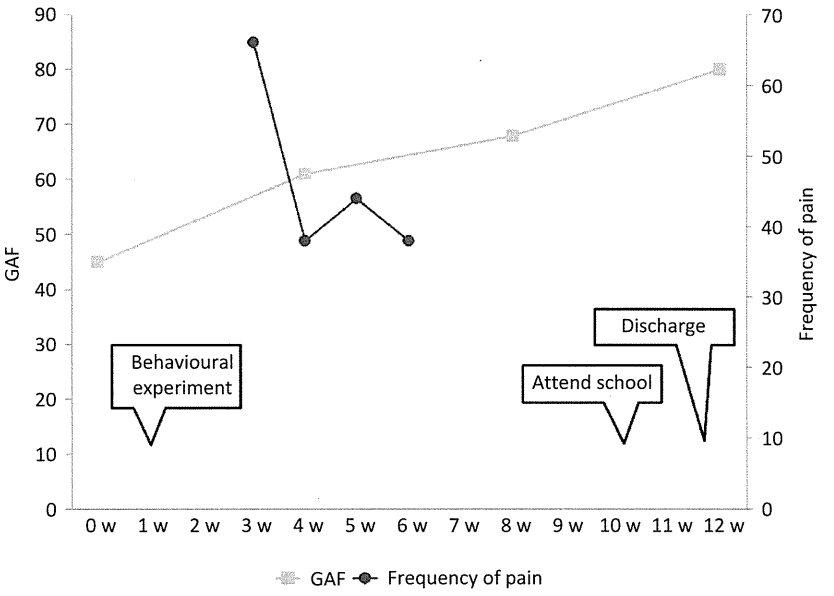

Figure 2. GAF and frequency of pain; GAF score improved throughout the intervention.

hospital, he has continued to attend school and has restarted playing baseball. He has told the therapist that he seldom feels pain.

According to Yu's self-monitoring of the frequency of his pain, he felt pain 66 times in his first week of monitoring his symptom, 38 times the second week, 44 times the third week, and 38 times the fourth week. His GAF score improved month-to-month: the first month after admission, it was 45, but increased to 61 during the second month, 68 during the third month, and 75 before discharge. Figure 2 shows Yu's GAF and weekly frequency of pain episodes from the time of his first behavioural experiment until the short-term goal was achieved. The recording of his symptom was discontinued when Yu stated that he wanted to stop monitoring because such monitoring made him conscious of his symptom.

3. Challenges and accomplishments

We have provided a case report of a CBT intervention for the treatment of somatoform pain disorder in an adolescent patient. To the best of our knowledge, this is the first case report revealing that the condition of an adolescent who fulfilled the diagnostic criteria for somatoform pain disorder improved with the use of CBT.

Yu was initially opposed to the diagnosis and did not understand the relationship between his symptom and psychosocial factors (Henningsen et al., 2007). The therapist responded empathically to his opinions without forcing 'psychosocial' explanations for his symptom on him for patients' tendencies to resist psychosocial explanations might make them more likely to reject psychosocial interventions. Thus, during the early period of treatment, the therapist focused on leading the patient to realize changes in his subjective symptom through experiential learning. The therapist and Yu worked together towards a realization that CBT was useful through exercises.

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Distraction could become a safety-seeking behaviour if it is employed just to alleviate anxiety. On the other hand, distraction enabled the patient to understand the connection between attention and pain intensity and the fact that he consequently has some control over his pain. Decreases in the frequency of pain made the patient more active, and in turn, engaging in enjoyable activities decreased his preoccupation with pain. This positive interaction seemed to facilitate the patient's acceptance of the psychosocial model of pain.

4. Lessons learnt and recommendations for other counsellors and therapists

In this study, the patient was persistently opposed to the psychosocial model, and it was difficult to develop a formulation or structure therapy from the beginning. Particularly with children and adolescents, therapists need to emphasize the importance of therapeutic alliance. Therapists need to employ the cognitive behavioural model flexibly and not adhere to precise scheduling or rigid techniques so that their patients do not think of the therapy as directive. For example, the therapist did not tell Yu to continue rating his pain when he wanted to stop, because the former thought the purpose of self-monitoring had been accomplished at that time. In addition, at first, the therapist shared only parts of his formulation, because Yu rejected a psychosocial explanation.

5. Limitations and future directions

This study has a number of limitations. First, no Japanese version of a reliable symptom rating scale for somatoform pain disorder exists for adolescents. Thus, we had to assess Yu's symptom according to its frequency by using his self-monitoring records, his activity, and his complaints. Furthermore, Yu discontinued recording his symptom during the course of his treatment. Although subjective evaluations are not sufficiently reliable, behavioural observation might be useful. If there were a symptom scale in Japanese, children and adolescents who resist psychosocial explanations might not necessarily fill out the form. Several other case reports and clinical studies of somatoform pain disorder in children and adolescents have also employed self-reports of patients' symptoms (Dhossche, Ferdinand, van der Ende, & Verhulst, 2001; Palermo & Scher, 2001; Spitzer, Barnow, Gau, Freyberger, & Grabe, 2008).

Second, the patient did not complete a Structured Clinical Interview for the DSM-IV. A psychiatrist assessed him but could not gain much information from him alone; therefore, the psychiatrist used parents' report and diagnosed Yu with somatoform pain disorder. As mentioned previously, somatic symptoms in children and adolescents often do not fit well into the DSM-IV's diagnostic criteria for somatoform pain disorder (Dell & Campo, 2011). This fact may explain why there have been very few studies of somatoform pain disorder in children and adolescents. Another challenge to be tackled is the biased views regarding psychiatric disorders among Japanese people. Some disorders, mostly depression, have drawn people's attention, and those suffering from such disorders have become less reluctant to seek psychiatric services. However, other disorders are not yet understood properly, and they can be mistaken for 'psychotic diseases'. Yu's initial denial of the diagnosis seemed to stem from such views. Psychoeducational intervention might be helpful to encourage patients in Japan to undergo appropriate therapy.

Finally, further clinical research is needed in order to validate the effect of CBT on somatoform pain disorder in children and adolescents.

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ORIGINAL RESEARCH

Tipepidine in children with attention deficit/hyperactivity disorder: a 4-week, open-label, preliminary study

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Background: Tipepidine (3-[di-2-thienylmethylene]-1-methylpiperidine) has been used solely as a nonnarcotic antitussive in Japan since 1959. The safety of tipepidine in children and adults has already been established. It is reported that tipepidine inhibits G-protein-coupled inwardly rectifying potassium (GIRK)-channel currents. The inhibition of GIRK channels by tipepidine is expected to modulate the level of monoamines in the brain. We put forward the hypothesis that tipepidine can improve attention deficit/hyperactivity disorder (ADHD) symptoms by modulating monoaminergic neurotransmission through the inhibition of GIRK channels. The purpose of this open-label trial was to confirm whether treatment with tipepidine can improve symptoms in pediatric patients with ADHD.

Subjects and methods: This was a 4-week, open-label, proof-of-efficacy pilot study for pediatric subjects with ADHD. Ten pediatric ADHD subjects (70% male; mean age, 9.9 years; combined [inattentive and hyperactive/impulsive] subtype, n=7; inattentive subtype, n=3; hyperimpulsive subtype, n=0) received tipepidine hibenzate taken orally at 30 mg/day for 4 weeks. All subjects were assessed using the ADHD Rating Scale IV (ADHD-RS), Japanese version, and the Das–Naglieri Cognitive Assessment System (DN-CAS), Japanese version.

Results: A comparison of baseline scores and 4-week end-point scores showed that all the ADHD-RS scores (total scores, hyperimpulsive subscores, and inattentive subscores) improved significantly ($P<0.001$). Furthermore, a comparison of baseline DN-CAS total scores and 4-week end-point scores showed a mild trend of improvement ($P=0.093$). Tipepidine was well tolerated, with no patients discontinuing medication because of side effects.

Conclusion: Our pilot study suggests that tipepidine therapy may prove to be an effective alternative treatment for pediatric patients with ADHD. Nonetheless, more detailed randomized, double-blind trials are needed to confirm tipepidine's efficacy.

Keywords: attention deficit/hyperactivity disorder, tipepidine, GIRK channel, pediatric, antitussive, nucleus accumbens

Introduction

Attention deficit/hyperactivity disorder (ADHD) is a common chronic psychiatric disorder, characterized by a pattern of developmentally inappropriate inattention, motor restlessness, and impulsivity, which affects between 3% and 7% of school-age children.[1] Prospective follow-up studies found that approximately 50% of children with ADHD show symptoms that continue into adulthood, and when left untreated are associated with substance abuse, depression, unemployment, and criminal offenses.[2,3]

Clinical guidelines on the pharmacological treatment of ADHD recommend psychostimulants (eg, methylphenidate, dexamphetamine, mixed amphetamine salts,

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lisdexamphetamine) and selective norepinephrine-reuptake inhibitors, such as atomoxetine.[4] Psychostimulants are known to increase synaptic dopamine concentrations through inhibition of the dopamine transporter, a mechanism that facilitates dopamine reuptake into presynaptic neurons.[5] Selective norepinephrine-reuptake inhibitors increase extracellular levels of norepinephrine and dopamine in the prefrontal cortex.[6] This accumulating evidence suggests that behavioral problems associated with ADHD may be related to cognitive dysfunction and early disturbances in dopaminergic innervation of basal ganglia and the frontal lobe.[7] Genetic and molecular studies of ADHD also demonstrate an association between this disease and dopamine-related genes.[7–12] However, psychostimulants induce a variety of side effects, including anorexia, headaches, stomach aches, insomnia, pyrexia, and tics.[13] Moreover, the frequency of suicidal ideation was greater among atomoxetine-treated patients compared with placebo groups.[14] These results highlight the need to identify new therapies for ADHD, particularly treatment with fewer side effects than currently available drugs.

Tipepidine (3-[di-2-thienylmethylene]-1-methylpiperidine) has been used as a nonnarcotic antitussive in Japan since 1959. The safety of tipepidine in children and adults has already been established. Furthermore, suicide-related side effects have not been documented for tipepidine. It is reported that tipepidine inhibits G-protein-coupled inwardly rectifying potassium (GIRK)-channel currents.[15] The activation of the GIRK channels causes membrane hyperpolarization through potassium efflux. The inhibition of GIRK channels by tipepidine is expected to modulate the level of monoamines in the brain, since GIRK channels are coupled with G-protein-coupled receptors, including 5-hydroxytryptamine $(5\text{-HT})_{1A}$, adrenaline α_2 and dopamine D_2 receptors.[15] Using in vivo microdialysis, Kawaura et al demonstrated that tipepidine increases the levels of 5-HT and catecholamines, including dopamine, in the prefrontal cortex of rats.[16] Furthermore, Fujieda et al[17] showed that tipepidine could attenuate the hyperactivity induced in methamphetamine-treated mice (an ADHD model) by modulating these monoamine systems. Given these results, we put forward the hypothesis that tipepidine can improve ADHD symptoms by modulating monoaminergic neurotransmission through the inhibition of GIRK channels coupled with monoamine receptors in the brain. The purpose of this open trial was to confirm whether treatment with tipepidine could improve symptoms in pediatric patients with ADHD.

Subjects and methods

Ethics statement

The ethics committee of Chiba University Graduate School of Medicine approved the study protocol (G24061), and all subjects provided written informed consent for participation in the study. We registered this trial on the official database of clinical research (ClinicalTrials.gov) on April 16, 2013 (NCT01835093).[18]

Study design and subjects

This was a 4-week, open-label, proof-of-efficacy pilot study for pediatric subjects with ADHD. The baseline demographic, clinical, and treatment characteristics of ADHD are shown in Table 1. All subjects received tipepidine hibenzate tablets. Tipepidine was taken orally at 30 mg/day (10 mg after breakfast, 10 mg after supper, and 10 mg before bedtime), for 4 weeks. Ten pediatric subjects with ADHD were recruited from Chiba University Hospital outpatients. All subjects were diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV criteria for ADHD,[19] and were classified into three subtypes: combined (inattentive and hyperactive/impulsive), n=7; inattentive, n=3; and hyperimpulsive, n=0. Seven boys and three girls participated in this study. Seven subjects had received some drugs before entering the trial, namely methylphenidate (18–54 mg/day, n=2), atomoxetine (75 mg/day, n=1), aripiprazole (15 mg/day, n=1),

Table 1 Baseline demographics and clinical and treatment characteristics of ADHD subjects

Age (years±SD)	9.9±2.2
Sex (male/female)	7/3
Race (% Japanese)	100
Height (cm±SD)	140.5±15.5
Weight (kg±SD)	38.6±17.3
Tipepidine hibenzate dosage (mg/kg/day ±SD)	1.288±0.349
ADHD subtypes (combined/inattentive/hyperimpulsive)	7/3/0
WISC-III/IV full IQ score±SD	87.4±13.3
Comorbidity (n)	4
Learning disorder	2
Tic disorder	1
Learning disorder and tic disorder	1
Pharmacotherapy (n)	7
Methylphenidate	2
Atomoxetine	1
Aripiprazole	1
Methylphenidate and atomoxetine	1
Atomoxetine and aripiprazole	1
Methylphenidate and risperidone	1
Naïve	3

Note: Reported values are means ± standard deviation (n=10) or percentages.
Abbreviations: ADHD, attention deficit/hyperactivity disorder; WISC-III/IV, Wechsler Intelligence Scale for Children III/IV; SD, standard deviation; IQ, intelligence quotient.