Brief Report

EFFECTS OF TIAGABINE ON CHOLECYSTOKININ-TETRAPEPTIDE (CCK-4)-INDUCED ANXIETY IN HEALTHY VOLUNTEERS

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There is increasing evidence that a dysregulation of the \(\gamma\)-aminobutyric acid (GABA) system plays a role in the pathophysiology of panic disorder. Selective enhancement of GABAergic neurotransmission has been shown to improve anxiety in experimental animals and in patients with panic disorder. Tiagabine is an antiepileptic drug, which increases GABA via selective blockade of GABA reuptake. Apart from its anticonvulsant activity anxiolytic properties could therefore be suggested. To investigate the putative anxiolytic properties of the GABA reuptake blocker tiagabine, we studied the impact of tiagabine treatment on cholecystokinin tetrapeptide (CCK-4)-induced panic. Fifteen healthy volunteers received 15 mg tiagabine daily for 1 week. A CCK-4 challenge was performed before and after treatment. Panic was assessed using the API- and PSS-score. There was a marked improvement of CCK-4-induced panic after 1 week of treatment. Both API- and PSS-scores showed a significant reduction. Our results suggest anxiolytic properties of tiagabine in humans, which provide sufficient rationale to assess its putative anxiolytic effects in patients with panic disorder under controlled conditions. Depression and Anxiety 18:140–143, 2003. © 2003 Wiley-Liss, Inc.

Key words: panic; cholecystokinin-tetrapeptide (CCK-4); tiagabine; cortisol; ACTH; GABA

INTRODUCTION

There is considerable evidence both from the preclinical and clinical view that among other neurotransmitters the \(\gamma\)-aminobutyric acid (GABA) system might play a role in the pathophysiology of panic disorder [for review, see Kent et al., 2002]. Single photon emission computed tomography (SPECT) studies suggest reductions in frontal lobe benzodiazepine receptor binding [Bremner et al., 2000] in panic disorder. Also one study that used positron emission tomography (PET) showed a reduced benzodiazepine receptor binding in panic disorder patients [Malizia et al. 1998]. A recent investigation that used magnetic resonance spectroscopy revealed reductions in total occipital cortex GABA in panic patients [Goddard et al., 2001]. Finally, preliminary results suggest that a family history in panic disorder might especially influence the magnitude of GABA reductions seen in panic disorder patients [Goddard et al., 2002].

Vigabatrin increases brain GABA via selective inhibition of the main GABA catabolizing enzyme GABA-transaminase. The compound has been shown to reduce anxiety-related behavior in animal studies [Sherif et al., 1994]. Moreover, vigabatrin exerts substantial anxiolytic effects both in patients with
panic disorder [Zwanzger et al., 2001a] and on CCK-4-induced panic symptoms in healthy volunteers [Zwanzger et al., 2001a,c]. There is also some evidence that valproate improves symptoms in panic disorder by its GABAergic mechanism [Keck et al., 1993; Woodman et al., 1994]. These findings suggest that selective enhancement of GABAergic neurotransmission may constitute a new therapeutic strategy for human anxiety.

The antiepileptic drug tiagabine acts as a GABA reuptake inhibitor via blockade of the GABA transporter I (GAT-I) [Meldrum, 1996]. To evaluate the putative anxiolytic properties of tiagabine we investigated the impact of tiagabine treatment on CCK-4-induced panic in healthy volunteers.

**METHODS**

Fifteen healthy volunteers (11 men and 4 women, mean age = 27.3 ± 1.4) were investigated. Any history of psychiatric illness or somatic disease was excluded prior to baseline evaluation. The study was approved by the local ethical committee in accordance with ethical standards laid down in the declaration of Helsinki. After a complete description of the study, all subjects gave their written informed consent. At day 0 and day 7, subjects were challenged with 50 μg CCK-4 (Clinalfa, Laufelfingen, Switzerland, dissolved in 10 ml 0.9% saline) intravenously at 10:00 a.m. as previously reported [Zwanzger et al., 2001c]. Tiagabine (Gabitril®; Sanofi-Synthelabo, Germany) was administered from day 0 (after CCK-4 challenge) to day 7 in a daily dosage of 15 mg. Panic symptoms were assessed by the Acute Panic Inventory (API) [Dillon et al., 1987] and a DSM-IV-derived Panic Symptom Scale (PSS) [Bradwejn et al., 1992]. Blood samples were taken during the challenge for determination of plasma cortisol and ACTH concentrations. Clinical rating scores, ACTH, and cortisol concentrations (peaks and area under the curve, AUC, determined by the trapezoidal rule) were analyzed by ANOVA with a repeated measures design with treatment as within subject factor. Alpha = .05 was set as the nominal level of significance. To control the subject’s compliance to drug intake tiagabine serum levels were determined by high-performance liquid chromatography (HPLC).

**RESULTS**

Fourteen out of 15 subjects reported a marked decrease of CCK-4-induced panic and anxiety after 1 week of tiagabine treatment. Both API and PSS sum scores decreased significantly during the second CCK-4 challenge. The maximum heart rate after CCK-4 injection showed a slight but significant reduction after tiagabine treatment (Table 1). There was a marked increase in cortisol and ACTH concentrations following both the first and the second CCK-4 challenge. However, tiagabine treatment did not affect the CCK-4-induced ACTH and cortisol release, since peak and AUC values of cortisol and ACTH remained unchanged after treatment (Table 1). All subjects reached sufficient tiagabine plasma levels (mean 126 ± 11 ng/ml).

**DISCUSSION**

Our results demonstrate that tiagabine reduces CCK-4-induced panic symptoms. These findings extend preclinical results, suggesting anxiolytic-like properties of tiagabine in experimental animals [Schmitt and Hiemke 1999]. Moreover, this is supported by first clinical experiences in panic disorder patients, which showed a reduction of panic and

| TABLE 1. API and PSS scores, maximum heart rate, peak cortisol, peak ACTH, cortisol, AUC, and ACTH AUC values at baseline and after tiagabine treatment |
|-----------------------------------|----------|----------|--------|----------|----------|--------|----------|----------|
| API - Score                       | Mean     | sd       | Mean   | sd       | F       | df     | P        |
|                                  |          |          |        |          |         |        |          |
| PSS - Score                       | 25.9     | 13.1     | 17.7   | 9.5      | 9.190   | 14     | 0.009    |
| Maximum heart rate               | 18.1     | 10.7     | 11.4   | 7.6      | 7.530   | 14     | 0.016    |
| Cortisol peak [nmol/l]           | 106.0    | 13.4     | 99.0   | 11.5     | 12.470  | 14     | 0.003    |
| ACTH peak [pmol/l]               | 466.0    | 182.0    | 464.0  | 275.0    | 0.005   | 14     | 0.942    |
| Cortisol AUC [nmol/l* min]       | 17.0     | 15.0     | 19.0   | 32.0     | 0.616   | 14     | 0.447    |
| ACTH AUC [pmol/l* min]           | 23,401.0 | 12,176.0 | 23,076.0 | 17,325.0 | 0.030   | 14     | 0.864    |

Values are expressed as mean ± sd. AUC = area under the curve.
agoraphobia following tiagabine treatment [Zwanzger et al., 2001b]. Our findings are in line with effects of common antipanic agents such as imipramine [Bradwejn and Koszycki 1994], citalopram [Shlik et al., 1997], fluvoxamine [van Megen et al., 1997], and GABAergic compounds such as vigabatrin [Zwanzger et al., 2001c] on CCK-4-induced panic, which all have been shown to reduce CCK-4-induced panic symptoms. Compared to effects obtained with vigabatrin, the results after 1 week of tiagabine treatment seem to be less pronounced. Therefore, it is still unclear whether treatment with 15 mg tiagabine would be sufficient in the treatment of panic disorder. However, since dose recommendations range from 15 to 30 mg daily, an extension of the treatment period with higher doses of tiagabine may result in more marked effects. The lack of a placebo condition is certainly a limitation of our study. However, since recent data showed no significant improvement of CCK-4-induced panic after placebo treatment [van Megen et al., 1997] and reproducible effects after rechallenge [Bradwejn et al., 1992], a mere placebo effect of tiagabine appears to be rather unlikely.

In line with prior investigations, there was a marked increase in ACTH and cortisol plasma levels after CCK-4 administration [Koszycki et al., 1998]. In contrast to vigabatrin [Zwanzger et al., 2001c], no reduction of CCK-4-induced ACTH and cortisol stimulation after tiagabine treatment was observed. Several issues have to be discussed: First, reduction of panic symptoms and HPA system activity might be independent from each other. If so, our findings would support the view that effects of CCK-B agonists on HPA axis activity are primarily pharmacological and not related to experimentally induced anxiety [Abelson et al., 1994]. Therefore, the lack of influence on HPA system response could be due to the different mechanism of action of the two drugs, since tiagabine blocks GABA reuptake, whereas vigabatrin is an inhibitor of GABA transaminase [Meldrum 1996]. However, this in turn would be in contrast to a recent study that showed an association of CCK-4-induced panic and HPA system response in panic disorder patients [Strohle et al., 2000]. In view of these findings, it could be suggested that a reduction of CCK-4-induced anxiety after tiagabine treatment with a 15 mg dose is not sufficient to affect the response of the hypothalamic pituitary adrenal (HPA) system.

In conclusion, tiagabine treatment leads to a significant reduction of CCK-4-induced panic symptoms in healthy volunteers. Although results from experimentally induced panic in healthy volunteers are not necessarily transferable to panic disorder patients, in light of preclinical data and first clinical experiences in panic disorder anxiolytic properties of tiagabine may be assumed. Given the fact that there are no abuse liability and withdrawal symptoms for compounds targeting the GABA binding site of the GABA receptor in contrast to benzodiazepines, such compounds appear to be suitable for the treatment of human anxiety. Since vigabatrin is supposed to cause visual field constrictions in long-term treatment in contrast to tiagabine, future studies should address the putative anxiolytic effects of tiagabine in patients with panic disorder under placebo-controlled conditions.

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REFERENCES

