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Acute L-5-hydroxytryptophan administration inhibits carbon dioxide-induced panic in panic disorder patients

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Abstract

Previous research showed that lowering the availability of serotonin to the brain by tryptophan depletion increases the vulnerability of panic disorder patients for an experimental 35% CO_2 panic challenge. The results also suggested that increased availability of serotonin inhibits the response to such a challenge. In the present study, this latter possibility is examined. The reaction of 24 panic disorder patients and 24 healthy volunteers to a 35% CO_2 panic challenge was assessed following administration of 200-mg L-5-hydroxytryptophan (the immediate precursor of serotonin) or placebo. L-5-Hydroxytryptophan significantly reduced the reaction to the panic challenge in panic disorder patients, regarding subjective anxiety, panic symptom score and number of panic attacks, as opposed to placebo. No such effect was observed in the healthy volunteers. L-5-Hydroxytryptophan acts to inhibit panic, which supports a modulatory role of serotonin in panic disorder.

Keywords: Serotonin; Panic disorder; Carbon dioxide; 5-Hydroxytryptophan; Panic challenge

1. Introduction

Insight into the nature of the relationship between serotonin (5-HT) and panic disorder (PD) has been considerably enhanced by studies in which the availability of 5-HT is manipulated, especially in combination with a laboratory panic challenge. A method to reduce brain 5-HT is by tryptophan depletion. In healthy volunteers, most studies failed to detect increased anxiety or panic following tryptophan depletion alone (Park et al., 1994; Cleare and Bond, 1995; Oldman et al., 1995). In combination with a 35% CO_2 panic challenge, however, tryptophan depletion caused a greater increase in neurovegetative symptoms compared to placebo, although no true panic was induced (Klaassen et al., 1998).

Tryptophan depletion alone was not anxiogenic or panicogenic in a sample of unmedicated PD patients either (Goddard et al., 1994). Again, matters were different when combined with a panic challenge. Kent et al. (1996) found increased ventilation in PD patients following 5% CO_2 inha-

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lation. Furthermore, tryptophan depletion caused an increased panic response to a 5% CO_2 challenge in 20 PD patients (Miller et al., 2000). A similar result was obtained in a study in 24 PD patients by our group, using a 35% CO_2 challenge (Schruers et al., 2000). In that experiment, an increase in panic occurred in the depletion condition, whereas a possible panic-inhibiting effect was observed in the placebo condition. This was possibly due to an observed increase in plasma tryptophan, leading to increased brain 5-HT availability.

Previous studies have examined the effect of a raised availability of 5-HT to the brain in PD by administrating L-5-hydroxytryptophan (L-5-HTP), the immediate precursor of serotonin. In a study in 20 PD patients and 20 healthy volunteers, L-5-HTP was administrated intravenously in a dosage of 60 mg. The authors failed to find the worsening of symptoms they expected in PD patients, based on their initial hypothesis of a 5-HT receptor hypersensitivity in PD. On the contrary and quite unexpectedly, a decrease of anxiety was observed in the PD patients. Such an effect was not found in healthy volunteers. The results were obscured, however, by severe side effects, mainly nausea and vomiting (den Boer and Westenberg, 1990a). In a subsequent study, based on the same hypothesis, three different dosages of L 5-HTP (10, 20 and 40 mg) were administrated intravenously to seven PD patients and seven healthy controls. Side effects were limited, especially at the lower doses, but once again, contrary to the hypothesis, none of the dosages caused anxiety or panic, neither in PD patients nor in healthy volunteers (van Vliet et al., 1996). Taken together, the results from the above tryptophan depletion and L-5-HTP administration studies suggest a restraining effect of 5-HT on panic that may only be observed when acute manipulation of 5-HT availability is combined with a panic challenge. The present study was undertaken to investigate such an effect by administrating L-5-HTP or placebo to PD patients and healthy volunteers. We hypothesised that L-5-HTP would inhibit the panicogenic effect of a 35% CO_2 challenge in PD patients.

2. Methods

The study was approved by the Medical Ethics Committee of Maastricht University and the Maastricht Academic Hospital. All subjects voluntarily agreed, by written informed consent, to participate after receiving careful explanation of the risks and purposes of the study. Participants were made aware that they would be breathing a gas mixture containing carbon dioxide and oxygen without any known health risks. This inhalation could, however, make them experience several bodily symptoms and feel uncomfortable or anxious for a few moments, following the inhalation. Also, it was explained to them that the drug they would be taking, prior to the challenge, could be either an active or an inactive substance and that neither they nor the investigators would know which they received. Subjects were informed that they could withdraw from the study at any time. Patients were reassured that this would have no consequences for their treatment.

2.1. Subjects

Twenty-four PD patients (13 men and 11 women, mean age 39.96 ± 10.69 years) with or without agoraphobia (DSM-IV criteria) and 24 healthy volunteers (10 men and 14 women, mean age 29.75 ± 11.65 years) participated in the study. Patients were recruited from the Academic Anxiety Centre Maastricht and healthy volunteers through advertisement in a local newspaper. The diagnosis was made by means of a structured interview (Mini International Neuropsychiatric Interview; Sheehan et al., 1997) and confirmed by two experienced psychiatrists (KS and EG). There was no concurrent axis I or II disorder. Also, none of the participants had a prior history of affective disorder. Healthy volunteers were also excluded if first degree relatives were affected by a major psychiatric disorder.

Additional inclusion criteria were: age between 18 and 65; good physical health; and written informed consent. No concurrent psychotropic medication (benzodiazepines, antidepressants, or beta blockers) was allowed in the 3 weeks before the experiment. None of the patients had been on

diazepam or fluoxetine, which require a long washout period.

2.2. Design and procedures

The study consisted of two parts, one carried out in PD patients and the other in normal volunteers. Both parts were conducted according to a randomised, double-blind, placebo-controlled design. Twelve PD patients (six men and six women) were allocated to the 5-HTP condition and 12 (seven men and five women) were assigned to the placebo condition. Similarly, 12 healthy volunteers (five men and seven women) were assigned to the 5-HTP condition and 12 (five men and seven women) to placebo. The subjects ingested a capsule with 200-mg L-5 HTP or placebo at 14.00 h. At 15.30 h, they underwent a 35% CO_2 challenge.

Vital capacity was measured before inhalation of the gas mixture. The test was considered valid only if the subject had inhaled at least 80% of the previously measured vital capacity.

Immediately before and after the inhalation, anxiety was measured on a visual analogue scale of anxiety (VAAS), describing the degree of subjective anxiety from 0 mm (no anxiety) to 100 mm (the worst anxiety imaginable) and by a panic symptom list (PSL), containing the 13 panic symptoms described by DSM-IV on a scale from 0 to 4 (Klaassen et al., 1998; Schruers et al., 2000). Salivary cortisol levels were monitored as a non-invasive probe of central 5-HT function. These results were presented in a previous article (Schruers et al., 2002).

2.3. Data analysis

Due to the non-normal distribution of the data, non-parametric tests were used for all analyses. Significance levels were set at $P<0.05$ (two-tailed). Data are presented as mean values ± the standard deviation. Outcome measures were pre- and post-CO_2 as well as delta (post minus pre) VAAS and PSL scores. In the patient group, the 5-HTP and placebo conditions were compared, using a Mann–Whitney *U*-test. The pre- and post-CO_2 scores on the VAAS and PSL within each condition were compared using a Wilcoxon signed rank test. The same procedure was followed for the healthy volunteers group. Both 5-HTP conditions and both placebo conditions were compared, using a Mann–Whitney *U*-test.

The number of panic attacks following the CO_2 challenge was calculated for each group and condition, and compared with a χ^2 test. Criteria for a panic attack were an increase of at least 25 mm on the VAAS plus an increase in at least four panic symptoms on the PSL (Klaassen et al., 1998; Schruers et al., 2000).

3. Results

3.1. Patients

In the placebo condition, there was a significant rise in VAAS ($n=12$, $Z=-3.059$, $P=0.002$) and PSL ($n=12$, $Z=-3.061$, $P=0.002$). This was not the case in the 5-HTP condition, although a trend was observable (VAAS: $n=12$, $Z=-1.730$, $P=0.06$; PSL: $n=12$, $Z=-1.883$, $P=0.084$). When the 5-HTP and placebo conditions were compared, significant differences were found in the post-CO_2 VAAS ($n=24$, $U=28.5$, $P=0.012$) and PSL ($n=24$, $U=19.0$, $P=0.002$) scores, as well as delta VAAS ($n=24$, $U=36.0$, $P=0.038$) and delta PSL ($n=24$, $U=19.5$, $P=0.002$) scores. Baseline values (before the CO_2 challenge) were not significantly different for VAAS ($n=24$, $U=63.0$, NS) or PSL ($n=24$, $U=67.0$, NS) (Fig. 1). The number of panic attacks was nine in the placebo condition and three in the 5-HTP condition ($\chi^2=4.16$, $P<0.05$, with continuity correction).

3.2. Normal volunteers

In the placebo condition, a significant rise in VAAS ($n=12$, $Z=-1.960$, $P=0.05$) and PSL ($n=12$, $Z=-3.063$, $P=0.002$) was observed. In the 5-HTP condition, there was a significant rise in PSL ($n=12$, $Z=-2.987$, $P=0.003$) but not in VAAS ($n=12$, $Z=-1.690$, $P=0.091$). Comparing the two conditions, no significant differences were found in pre- and post-CO_2 VAAS (pre: $n=24$, $U=56.5$, NS; post: $n=24$, $U=53.0$, NS) or PSL (pre: $n=24$, $U=60.0$, NS; post: $n=24$, $U=$

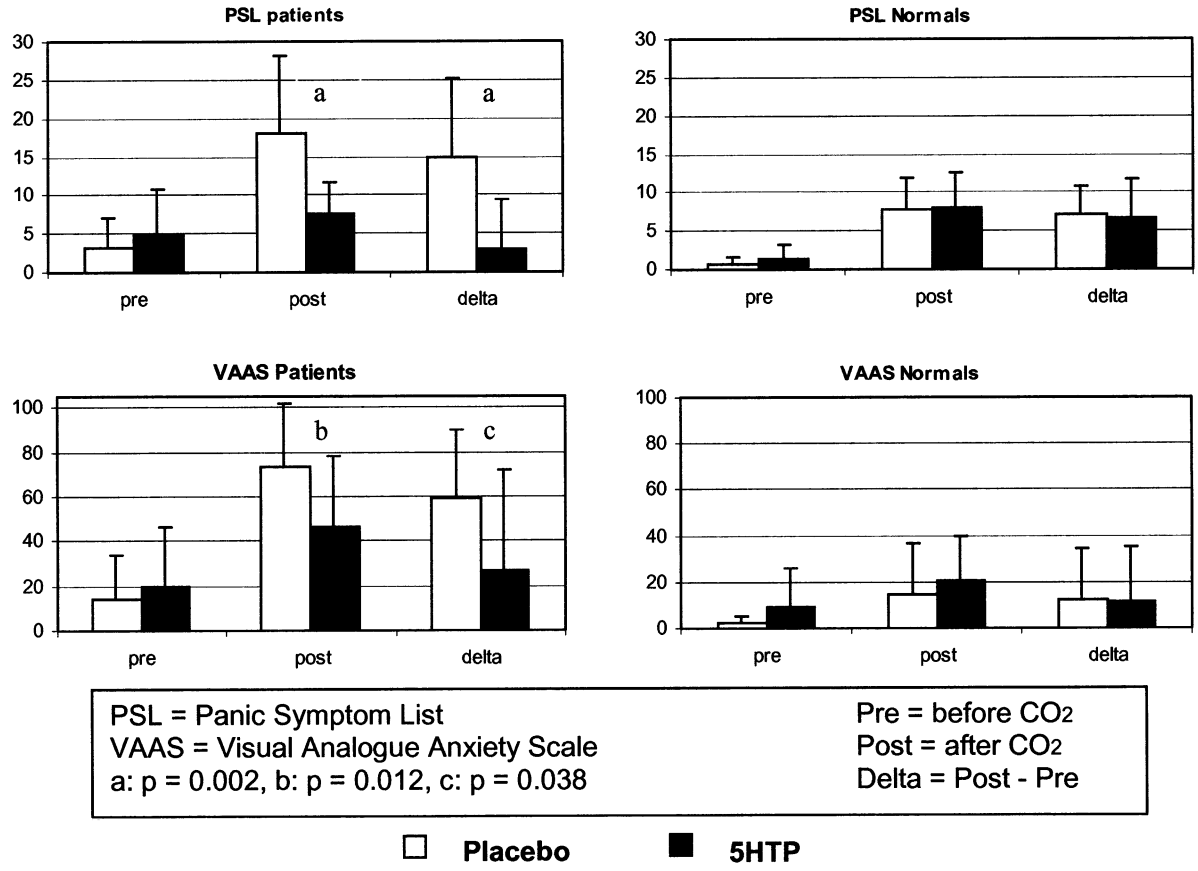

Fig. 1. The effect of 5HTP vs. placebo on the 35% CO_2 challenge.

68.5, NS) nor in delta VAAS ($n=24$, $U=62.5$, NS) or PSL ($n=24$, $U=68.5$, NS) (Fig. 1). The number of panic attacks was two in each condition.

3.3. Patients compared to normal volunteers

When the placebo conditions of each group were compared, patients had significantly higher scores on pre-CO_2 VAAS ($n=24$, $U=31.5$, $P=0.016$); post-CO_2 VAAS ($n=24$, $U=8.5$, $P=0.001$); delta VAAS ($n=24$, $U=13.0$, $P=0.001$); pre-CO_2 PSL ($n=24$, $U=33.5$, $P=0.02$); post-CO_2 PSL ($n=24$, $U=20.5$, $P=0.003$); and delta PSL ($n=24$, $U=34.0$, $P=0.028$). Comparing the 5-HTP conditions, no significant differences were found on the same scales (pre-CO_2 VAAS: $n=24$, $U=63.0$, NS; post-CO_2 VAAS: $n=24$, $U=40.0$, NS; delta VAAS:, $n=24$, $U=52.5$, NS; delta PSL: $n=24$, $U=48.5$, NS). Comparing the placebo-corrected scores, significant differences where also found for delta VAAS ($n=24$, $U=18.0$, $P=0.002$) and delta PSL ($n=24$, $U=23.0$, $P=0.005$).

The placebo-corrected number of panic attacks was six in the patient group and zero in the normal group ($\chi^2=5.55$, $P<0.05$, with continuity correction).

4. Discussion

Panic anxiety and symptoms, as well as the number of panic attacks following CO_2 inhalation, were significantly reduced by L 5-HTP in PD patients. No such effect was observed in healthy volunteers. Patients reacted with more panic anxi-

ety and symptoms to the challenge than controls in the placebo condition. This difference was not present in the 5-HTP condition.

4.1. The role of 5-HT in panic

Previous studies have suggested that 5-HT acts to inhibit panic (den Boer and Westenberg, 1990a; Ben Zion et al., 1999; Miller et al., 2000; Schruers et al., 2000). The results from the present study confirm these findings. However, the anti-panic effect of L-5-HTP in the present study already occurs 2 h after a single administration. This is at odds with findings from clinical studies with 5-HT transmission-enhancing drugs like selective serotonin reuptake inhibitors (SSRIs), showing an anti-panic effect only after several weeks of treatment. In the initial phase of treatment, even a transient worsening of the clinical condition has been reported (Bell and Nutt, 1998). Furthermore, acute administration of the 5-HT agonists *m*-chlorophenylpiperazine (mCPP) or fenfluramine has also been claimed to cause panic or anxiety (Kahn et al., 1988; Targum and Marshall, 1989). In a study comparing the clinical efficacy of fluvoxamine, ritanserin and placebo, the SSRI fluvoxamine caused an increase in anxiety in the first week of treatment. Frequency of panic attacks was not different from placebo, however (den Boer and Westenberg, 1990b). Another study, comparing the MAO inhibitor brofaromine with placebo in PD also found an increase of anxiety during the first treatment week. The number of panic attacks, however, decreased in both conditions (van Vliet et al., 1996). The initial deterioration noted with these drugs therefore seems due to an increase in general level of anxiety, part of the condition PD, but not the phenomenon of panic per se.

As for mCPP, the behavioural response caused by administration of this compound is characterised by a gradual increase of anxiety that lasts for several hours (Kahn et al., 1990). Such a response does not resemble a natural panic attack, which is characterised by sudden crescendo anxiety and neurovegetative symptoms, as described in DSM-IV. In the only study in which 'a combination of anxiety and somatic symptoms meeting DSM-III criteria for a panic attack' was found, according to well defined experimental criteria, a high dose of intravenous mCPP was used (Charney et al., 1987). However, while mCPP may be a selective serotonin receptor agonist at low doses, the effect on α_2 adrenoreceptors may become more important at higher doses and be responsible for the panic-like effect.

The 5-HT releasing agent *d*,*l* fenfluramine also precipitated an anxiogenic response, which was less acute and crescendo-like than the reaction following lactate infusion. The response lasted for several hours and was noted to 'differ markedly from the typical short-lived panic attack described by DSM-III-R' (Targum, 1992). This response could partly have been due to the catecholaminergic properties of the *l*-isomer (Judd et al., 1994). The *d*-isomer, however, does act as a specific 5-HT releasing agent and has recently been shown to reduce, rather than increase, 5% CO_2-induced panic (Anderson and Mortimore, 1999).

These findings, together with those from the present study, may suggest that 5-HT has a dual role, inhibiting panic on the one hand but possibly increasing anxiety on the other. These findings are accounted for in a hypothesis formulated by Deakin and Graeff (1991).

The theory proposes that 5-HT, via the dorsal raphe nucleus, restrains panic responses by an inhibiting effect at the level of the periaqueductal gray (PAG). The PAG has been shown to command panic, fight, flight and freezing in response to acute unconditioned aversive stimuli (Graeff et al., 1996). Carbon dioxide has been suggested to have its effect through this mechanism, acting as an internal unconditioned aversive stimulus (Schruers et al., 2000). Noradrenergic innervation of the PAG is mediated by the locus coeruleus via the dorsal tegmental bundle and the PAG also has GABA-ergic receptors that may be responsive to the inhibitory effects of high-potency benzodiazepines (Grove et al., 1997). Therefore, 5-HT/noradrenalin or 5-HT/GABA interactions could be in play as well. According to the Deakin–Graeff theory, 5-HT, via the median raphe nucleus, facilitates active escape or avoidance behaviour, as well as generalised anxiety, at the level of the

amygdala. Furthermore, the ventral amygdalofugal pathway projects to the PAG, possibly implicating 5-HT-induced amygdaloid hyperactivity also in the induction of a priming process of the PAG, lowering its threshold for the occurrence of panic (Grove et al., 1997).

4.2. Therapeutic possibilities

The present study concerns the acute effects of 5-HTP on experimentally induced panic. The results suggest that it might also be worthwhile to investigate its therapeutic possibilities in PD. In an open, uncontrolled study in 10 outpatients suffering from different anxiety states, the therapeutic effects of L-5-HTP have been studied over 12 weeks. In general, 5-HTP had beneficial effects, and it was noted in particular that panic attacks, if present, disappeared completely (Kahn and Westenberg, 1985). A similar result was obtained in an 8-week double-blind placebo-controlled study in 45 patients, again suffering from different anxiety disorders, comparing 5-HTP, clomipramine and placebo. General levels of anxiety decreased slightly in the 5-HTP group and, again, panic attacks disappeared almost completely if present. Unfortunately, a specific instrument to assess the severity of PD was not used (Kahn et al., 1987). The results from those studies, together with the ones from the present study, suggest that 5-HTP can have a clinical therapeutic effect in PD and certainly warrant further study.

A second conclusion that can be drawn from these studies is that the inhibition of the panicogenic effect of a 35% CO_2 challenge, a few hours after administration, might be predictive for the anti-panic properties of a compound. It has already been shown that the reduction of reaction to a 35% CO_2 challenge after 1 week predicts a therapeutic effect later on in treatment (Perna et al., 1997). It would, therefore, be interesting to investigate whether one single dose of an anti-panic agent bears any relationship to later therapeutic efficacy.

4.3. Limitations

Some caution is necessary when interpreting the present results. Firstly, there was a significant difference in age between the patients and the healthy volunteers. Although this may have influenced results, vulnerability to a 35% CO_2 challenge is not related to age (Perna et al., 1994). It should also be noted that the behavioural effect of a serotonergic challenge may decrease with age (Kahn and Wetzler, 1991). Yet, if such an effect has been present in the present study, it would not have affected outcome, since the patient group was the older one anyway and still showed a stronger effect of 5-HTP than the healthy volunteers.

Secondly, it might be argued that the effect observed in the 5-HTP-condition may, in part, have been due to actions of other neurotransmitters than 5-HT. Indeed, it has been suggested that 5-HTP affects noradrenalin turnover as well (van Praag and Westenberg, 1983). However, administration of 5-HTP to patients has been shown not to affect plasma levels of MHPG, the main metabolite of noradrenalin (den Boer and Westenberg, 1988).

5. Conclusion

The results from the present study show that L-5-HTP administration inhibits 35% CO_2-induced panic. This strongly supports a role for 5-HT in the modulation of panic. Further research on the therapeutic properties of L-5-HTP in PD and on the predictive value of an acute inhibition of vulnerability to 35% CO_2 for the therapeutic properties of future anti-panic agents would be welcome.

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