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Henk Pols · Eric Griez · Kees Verburg
Domy van der Werf

Yohimbine premedication and 35% CO_2 vulnerability in healthy volunteers

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Summary A group of 20 healthy volunteers underwent a 35% carbon dioxide / 65% oxygen air-placebo controlled challenge test twice, premedicated 1 h before with either 20 mg yohimbine or placebo, following a double-blind randomized crossover design. Contrary to expectation the anxiety response to carbon dioxide was not higher when premedicated with yohimbine compared to premedication with placebo. Possible implications of this finding are discussed, with reference to general chemical models of panic.

Key words Panic · Carbon dioxide · Yohimbine
Anxiety

Introduction

The theory that central hypernoradrenergic activity is related to panic anxiety is partially substantiated by empirical data. The original finding that chemical or electrical stimulation of the locus ceruleus (LC) resulted in an anxiety-like reaction in monkeys, whereas ablation of locus ceruleus function resulted in a anxiolytic profile (Redmond 1977) initiated human studies. It was found that electrical stimulation of LC in humans resulted in feelings of fear and death (Mason and Fibiger 1979). Locus ceruleus activity is regulated by multiple mechanisms, including α_2, serotonergic and benzodiazepine-GABA-ergic, and adenosine- and opiate-receptor mechanisms. The input via the α_2-receptor to the LC has been studied in several yohimbine studies, and data from these studies support the theory that LC stimulation may induce panic anxiety (Uhde and Tancer 1990). However, there are several observations that contradict this theory, e.g., drugs that increase LC activity such as buspirone and mianserin do not exacerbate panic anxiety (Gorman et al. 1987), whereas clonidine, a drug with α_2 agonistic properties, is of limited value in the clinical treatment of panic anxiety (Liebowitz et al. 1981; Hoehn-Saric et al. 1981). From these data it is suggested that panic patients (PP) may have specific abnormalities in α_2 regulating mechanisms of LC output.

Increased behavioral sensitivity to the inhalation of carbon dioxide-enriched gas mixtures in PP has been repeatedly observed, although the method, dose, and duration of carbon dioxide inhalation throughout different studies varies considerably (Gorman et al. 1984; Woods et al. 1986; Griez et al. 1987; Papp et al. 1993). Our study is limited to the procedure in which a vital capacity of a 35% carbon dioxide mixture in oxygen (35% CO_2 challenge) is used. Typically, the procedure provokes high levels of anxiety and somatic symptoms of panic in PP, but only some somatic symptoms in healthy controls. Overall, using operational criteria for panic attack the 35% CO_2 challenge induces panic in more than 50% of PP, but affects less than 10% of normal controls (Griez et al. 1987; Fyer et al. 1987; Bradwejn and Koszycki 1991). Furthermore, the 35% CO_2 challenge test appears to differentiate PP from a mixed group of psychiatric controls independent of the baseline anxiety level (Griez et al. 1990). Finally, there is some preliminary evidence that clinically effective treatment of panic may attenuate the response to the 35% CO_2 challenge test (Pols et al. 1991). In summary, the 35% CO_2 challenge test meets several criteria for a valid chemical model of panic, and it almost meets the criterion for complete specificity for panic disorder (Uhde and Tancer 1990).

Yohimbine, a putative α_2 antagonist used as a probe of central noradrenergic function, is another reasonably well documented panic provocation method. Summarizing the data on this model it is clear that at doses below 20–30 mg yohimbine normal controls do not exhibit a clinically relevant anxiety response (Charney et al. 1983), whereas PP do (Charney et al. 1984). Yohimbine, at a 20 mg dose, induced panic attacks in about 54% of PP and in 5% of normal controls, with a maximum effect 1 h after intake of the capsules (Charney et al. 1987). Available data suggest

Henk Pols (✉) · Eric Griez · Kees Verburg · Domy van der Werf
State University of Limburg, Academic Psychiatric Center,
P.O. Box 616, NL-6200 MD Maastricht, The Netherlands

that yohimbine has dose-related anxiogenic effects in normals (Mattila et al. 1988), but PP appear more sensitive to yohimbine than normals (Uhde and Tancer 1990; Albus et al. 1992). In summary, yohimbine more closely meets the criterion for threshold specificity for panic disorder.

Despite extensive literature on chemical provocation of panic attacks we are left with intriguing questions. For instance, none of the methods yields a 100% panic-attack response rate in PP. In addition, operational criterial for a panic attack are not clear and very few models, if any, exhibit complete specificity for panic disorder. Furthermore, we do not know whether the experience of a panic attack is linked to a specific psychiatric diagnosis or whether anyone pushed beyond a certain arousal point would be expected to experience a panic attack. What features make PP mor vulnerable to such challenge paradigms? According to the paradigm of experimental psychopathology one could explore which conditions are required for normal control subjects to become behaviorally vulnerable to a 35% CO_2 challenge.

Subjects and methods

A group of 20 healthy volunteers (9 males and 11 females; age range 18–44 years; mean 24.1 years), gave informed consent to participate in this study. Subjects were recruited via local advertisements and were paid for participating. All subjects were in good physical condition and had no past or present history of psychiatric problems, as determined by physical examination and clinical interview. Personal and/or family history of panic attacks were exclusion criteria, and selected subjects had no previous exposure to either yohimbine or 35% CO_2.

Subjects were told that the experiment consisted of two visits to the laboratory, on which occasion they would undergo a 35% CO_2 challenge test, once premedicated with 20 mg yohimbine and once premedicated with placebo, following a double-blind randomized procedure. The interval between premedication and subsequent 35% CO_2 challenge was 1 h, and the interval between the two visits to the laboratory was a minimum of 3 days and a maximum of 7 days. They were informed that carbon dioxide inhalation and yohimbine intake at the doses used in this experiment were anxiogenic in a subpopulation of anxiety-disorder patients, but had little or no effect on healthy controls. The aim of the study was to investigate whether yohimbine premedication would alter their response to the 35% CO_2 test compared to their response while premedicated with placebo. Half of the group started the experiment with yohimbine premedication upon their first visit, followed by placebo premedication upon their second visit, with the order being reversed for the other half of the group.

Procedure

Upon arrival subjects were introduced to the laboratory environment and the procedure was reexplained briefly. At baseline they started with filling in self-rating scales for anxiety and panic symptoms. To assess subjective anxiety a visual analog scale (VAS-A) was used, ranging from 0 (no anxiety) to 100 (maximum anxiety). To assess general anxiety the Spielberger State Anxiety Inventory (STAI-X1) was used (range 20–80) and a panic symptom list (PSL-III-R) derived from the DSM-III-R, consisting of 13 panic symptoms with an intensity score from 0 (absent) to 4 (present and severe), was used to assess presence and intensity of panic symptoms (range 0–52).

Next, blood pressure and heart rate were determined by means of an autoelectronic sphyngomanometer (Kenz BPM-OS-21, Susuken Co. Ltd.). Finally, subjects were asked to chew on cotton for 30–45 s so that we could obtain salivary samples to measure salivary cortisol levels (Salivette, Sarstedt, Ltd).

Immediately following baseline measurements subjects received one capsule containing either 20 mg yohimbine or placebo, following a double-blind randomization. Baseline measurements were repeated 60 min after capsule intake, immediately followed by the 35% CO_2 test.

The 35% CO_2 challenge test consists of two inhalations with a 30-min interval. The gas mixture is either a 35% carbon dioxide / 65% oxygen gas mixture or a pressed-air placebo mixture. The order was determined by a balanced randomization table. Before and after each inhalation subjects filled in the VAS-A and PSL-III-R scales. Subjects were asked after a deep exhalation to press the self-administration mask to their nose and mouth and take a vital capacity of the gas mixture. They were then asked to hold their breath for 4 s to enhance alveolar gas exchange. The result of the test was calculated by subtracting the difference of the post- minus preinhalation of the air placebo condition from the difference of the post- minus preinhalation of the carbon dioxide condition. In addition, before and after each inhalation blood pressure and heart rate were determined and the cotton obtained for salivary cortisol assay.

Results

The design of the study resulted in scores on the VAS-A and PSL-III-R on baseline, 60 min after intake of the capsule and 90 min after completion of the 35% CO_2 test. The STAI-X1 was taken at baseline and 60 min after intake of the capsule. Therefore, the scores at 60 min reflect the effect of either yohimbine or placebo, whereas the scores at 90 min reflect the effect of either the placebo premedication and the subsequent 35% CO_2 interaction (PLAC CO_2) or the yohimbine premedication and the subsequent 35% CO_2 interaction (YOH CO_2). The results are summarized in Table 1.

No significant differences in baseline values for any of the behavioral parameters were observed, nor were any order effects detectable. From the data in Table 1 it is evident that there were no significant differences in any of the behavioral parameters 1 h after intake of the capsule between the yohimbine and placebo condition (Wilcoxon signed rank test, $P > 0.05$). No clinically relevant anxiety response was observed after the 20 mg yohimbine intake.

Table 1 Scores on behavioral parameters at different time points of the experiment. VAS-A visual analog scale of anxiety; PSL-III-R panic symptom list derived from DSM-III-R criteria; STAI-X1 Spielberger state anxiety scale

	Preyohimbine	Yohimbine	Yohimbine CO_2
	Baseline	60 min	90 min
VAS-A	5.2 ± −6.5	4.3 ± −5.1	21.2 ± −24.8
PSL-III-R	0.6 ± −0.8	0.7 ± −0.9	6.8 ± −5.5
STAI-X1	28.4 ± −5.2	27.6 ± −5.8	—
	Preplacebo	Placebo	Placebo CO_2
VAS-A	3.6 ± −4.0	5.0 ± −5.5	16.9 ± −20.6
PSL-III-R	0.6 ± −0.9	0.6 ± −0.9	7.6 ± −6.0
STAI-X1	28.9 ± −5.1	27.9 ± −5.9	—

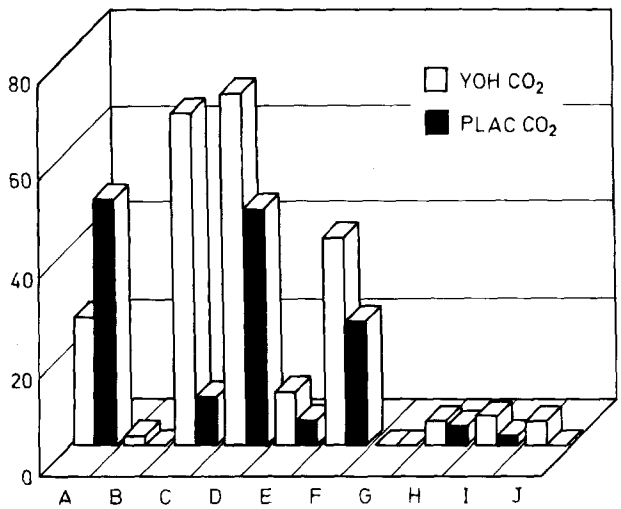

Fig. 1 Individual scores on visual analogue scale of anxiety, (VAS-A) – Yohimbine (YOH) – placebo (PLAC) order

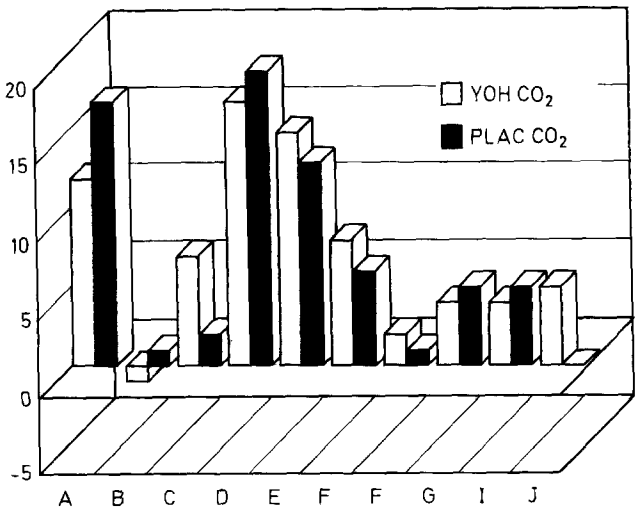

Fig. 3 Individual scores on panic symptom list (PSL) – YOH – PLAC order

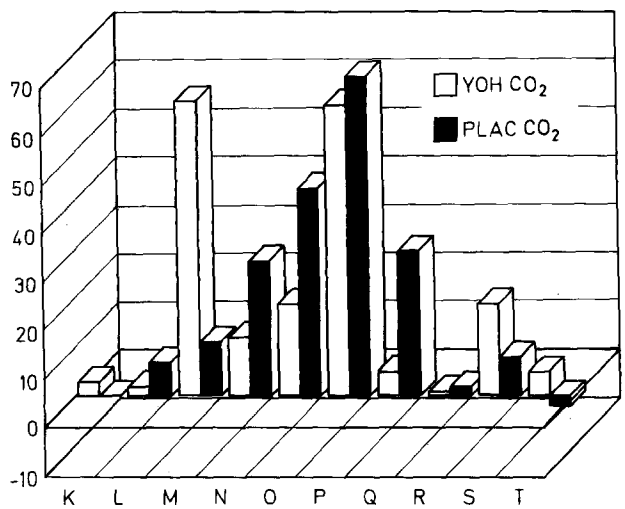

Fig. 2 Indivdual scores on VAS-A – PLAC - YOH order

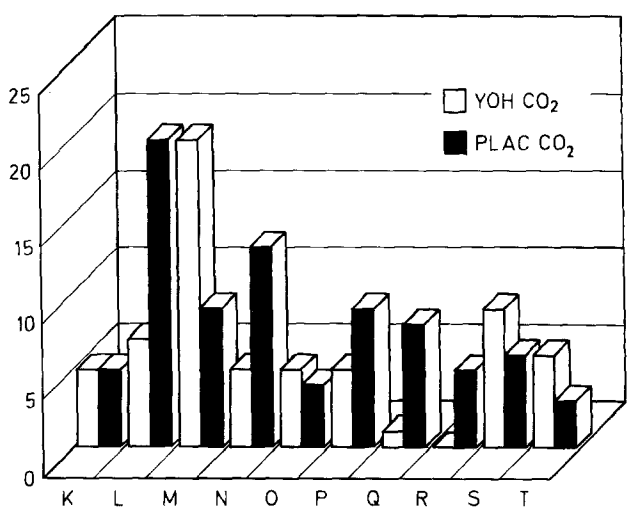

Fig. 4 Individual scores on PSL – PLAC – YOH order

At 90 min also no significant differences in any of the behavioral parameters were observed between the PLAC CO_2 and the YOH CO_2 condition (Wilcoxon signed rank test, $P > 0.05$). To test the hypothesis that premedication with yohimbine would increase the carbon dioxide vulnerability in healthy volunteers for each subject the difference in outcome on the VAS-A and PSL-III-R between the YOH CO_2 and PLAC CO_2 were calculated. Mean difference in the VAS-A (YOH CO_2 - PLAC CO_2) was 4.4 (SD ± 21.4), and mean difference in the PSL-III-R (YOH CO_2 - PLAC CO_2) was -0.8 (SD ± 5.4).

If one arbitrarily applies as a criterion for a panic attack a sudden crescendo increase in anxiety (a score on VAS-A ≥ 25) and the presence of at least four panic symptoms (a score on PSL ≥ 4) it may be deduced from Figs 1–4 that of a total of 40 CO_2 challenges these criteria are fullfilled 13 times. Subjects A, D, F, and O panicked on yohimbine premedication and on placebo premedication. Subjects M, N, and P only panicked on placebo, but not on yohimbine premedication, whereas subjects C and L panicked on yohimbine, but not on placebo premedication. (Data on salivary cortisol will be presented in a future article).

Discussion

Experimental induction of panic attacks in a laboratory setting is a promising line of research, which may provide us with a better understanding of the mechanisms involved in the pathogenesis of real-life panic attacks. Several chemical models have been explored concerning general criteria formulated for a valid panic-challenge paradigm (Guttmacher et al. 1983; Gorman et al. 1987).

One of the most important criterion is specificity, which means that the challenge stimulus should exhibit

either complete or threshold specificity for PP (Uhde and Tancer 1990). Complete specificity means that only PP will react to the challenge stimulus, and that other psychiatric or normal controls will never react with a panic attack independent of the dose that the challenge stimulus is administered. Threshold specificity implies that everyone can have a panic attack in response to the challenge stimulus, but that the dose necessary to induce panic in controls needs to be higher.

The present study was conducted to gain insight into which mechanisms may increase the vulnerability of normal healthy volunteers to the 35% CO_2 challenge test. The results are very clear: Premedication with 20 mg yohimbine did not result in a significant increase in 35% CO_2 vulnerability vs premedication with placebo, neither on a group level nor on an individual level.

Concerning the reason that carbon dioxide has panicogenic properties we are still looking for reasonable explanations. One suggestion is that carbon dioxide interacts with LC function. Animal experiments have shown that carbon dioxide increases LC function in a dose-dependent way (Elam et al. 1981). Another explanation is the specific lability of carbon dioxide-sensitive respiration-regulating centers in the brainstem (Gorman et al. 1989). A theory based on cognitive psychological factors in which processes such as conditioning to carbon dioxide and subsequent cognitive misinterpretation play a predominant role has also been proven important (Van den Hout and Griez 1984; Clarck 1986). A recent study in which the diagnostic and substance specificity of carbon dioxide-induced panic was investigated suggests that the panicogenic effect of carbon dioxide inhalation goes beyond the cognitive misinterpretation of symptoms such as breathlessness (Papp et al. 1993).

Most studies adress the question of why patients with panic attacks respond to panic-challenge paradigms, but the question of why normal controls do not respond to such test may be just as important. In a previous study we studied the effects of a 2-week 15-mg buspirone daily regimen vs placebo on carbon dioxide-induced panic-like symptoms in healthy volunteers. As buspirone increases LC firing rate, based on the hypernoradrenergic theory of panic a potentiation of carbon dioxide-induced symptoms is expected. However, the most important finding was a reduction in carbon dioxide-induced panic symptomatology and the absent effect on anxiety response (Pols et al. 1989). It might be argued, however, that interpretation of these results is flawed by the fact that buspirone has strong serotonergic and dopaminergic properties in addition to the previously mentioned noradrenergic effects.

Such studies as ours, with yohimbine that acts relatively selectively on α_2-receptors and increases central noradrenergic activity, may weaken opposing arguments. The results suggest that increasing central noradrenergic activity prior to a 35% CO_2 test does not increase the vulnerability of normal controls to this test, and therefore may cast some doubt on the relevance of LC activity in carbon dioxide-induced panic. However, we have little information on the extent that 20 mg yohimbine given orally affects LC function in healthy volunteers. It might be possible that at the 20-mg dose elevation of the threshold for the panicogenic effects to carbon dioxide was too small to have an effect in healthy volunteers. Comparable experiments in PP should be performed to gain more insight into the mechanisms involved, however, there are major ethical problems to consider. The process of conditioning and cognitive misinterpretation also seems a unlikely explanation for the present results, especially because no order effects were found. If such a process were to be active it would be expected that a carbon dioxide naive subject who exhibits a clinically relevant response at the first phase would be conditioned to carbon dioxide and at the second phase, via the mechanism of cognitive misinterpretation, the subject would exhibit a stronger response or a panic attack. We have unpublished data from a study that found that such mechanisms are not active in normal controls, and that the intraindividual test-retest reliability of the 35% CO_2 challenge test is good.

The present study is merely a small piece of the puzzle, and an ongoing comparable study in which yohimbine is replaced by a specific serotonergic agent such as fenfluramine may provide us with more clues on the relative importance of dysregulation in specific neurotransmitter systems in experimentally induced panic.

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