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Comparison of Cortisol Stress Response in Patients with Panic Disorder, Cannabis-Induced Panic Disorder, and Healthy Controls

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Keywords

Panic disorder · Cannabis · Stress reactivity · Cortisol · Hypothalamic-pituitary-adrenal axis

Abstract

Background/Aims: Little research effort has so far been dedicated to the analysis of the hypothalamic-pituitary-adrenal axis of aetiologically differing subgroups of patients with panic disorder (PD). The current study aimed at a deeper understanding of the cortisol stress response in cannabis-induced PD (CIPD) patients. **Methods:** Matched groups of 7 PD patients (mean age $\pm$ SD: 32.95 ± 9.04 years), 7 CIPD patients (31.94 ± 8.40 years), and 7 healthy controls (HC) (31.13 ± 8.57 years) were included in the study. The Trier Social Stress Test (TSST) was used for stress induction. Salivary cortisol samples were collected and panic- and depression-related questionnaires were applied. **Results:** A stress response to the TSST was found in 28.6% of PD patients, in 51.1% of CIPD patients, and in 100% of HC subjects. Statistical analyses revealed a cortisol hyporesponsiveness in PD and CIPD patients. While cortisol values of PD patients and HC partici-

pants differed significantly, CIPD patients' cortisol courses balanced between those of PD patients and HC subjects.

Conclusions: Current findings show a distinctive pattern of the stress-induced cortisol reaction in CIPD patients, which is markedly different from the hormonal response in PD patients as well as HC subjects. Previous findings of cortisol hyporesponsiveness in PD patients compared to HC subjects were confirmed.

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Introduction

Panic disorder (PD) is characterized by recurrent and sudden episodes of panic attacks which result in behavioural changes up to avoidance behaviour as well as constant concern of future attacks (DSM-IV) [1]. PD with or without agoraphobia is a relatively common disease as the 12-month prevalence rates range up to 2.0% of the German adult population [2]. PD correlates with secondary comorbid diseases such as depression and substance abuse [3]. The connection between substance abuse and

anxiety including PDs is bidirectional. Therefore, PD and substance use frequently co-occur, and usage of drugs and alcohol poses a risk factor for the development of PD. Cannabis use was proven to be significantly linked to the development of anxiety disorders including PD [4].

On a psychoneuroendocrine level, disease-specific physiological alterations of the hypothalamic-pituitary-adrenal (HPA) axis activity in patients with PD have been confirmed to be co-responsible for the pathogenesis of PD [5–7]. Clear evidence for hypocortisolism expressed in a blunted cortisol responsiveness to stressors has been replicated for PD several times [8–10]. A comorbid depressive disorder causes a slight, non-significant increase in cortisol levels of patients with PD following stress induction. However, cortisol reactivity of PD patients with comorbid depression still runs clearly below that of healthy people [8].

Substance consumption also influences the HPA axis activity [11]. The way in which substance consumption influences HPA axis activity depends on many factors such as type and amount of substances, duration of consumption or degree of dependency. Considerable research effort has focused on examining the consequences of cannabis consumption, as it poses a widespread and serious public health problem [12]. With regard to psychoneuroendocrine effects, evidence concerning the influence of cannabis use on HPA axis activity remains inconclusive. Results from cannabis usage showed significantly elevated baseline cortisol levels [13, 14]. However, frequent cannabis consumers also displayed a blunted cortisol response to delta-9-tetrahydrocannabinol (Δ^9 -THC) compared to healthy control (HC) persons, indicating the development of tolerance to the neuroendocrine effects of cannabis [14]. After a psychosocial stress test, cannabis users showed significantly lower cortisol responses than abstainers [15]. Apparently, dosage, frequency of consumed cannabis, and study design seem to explain the differences in the results and the impact on neuroendocrine processes.

To our knowledge, no research has yet been published on PD patients, whose first panic attack was cannabis-induced regarding their HPA axis reactivity compared to “regular” PD patients. On the one hand, in previous investigations, PD patients showed hypocortisolism as a reaction to psychosocial stress induction [16]. Cannabis users also showed significantly lower cortisol responses than abstainers in a psychosocial stress test [15]. On the other hand, in preclinical studies, the acute administration of Δ^9 -THC is associated with an increase in cortisol levels [17]. Therefore, it can be proposed that the HPA

axis reactivity in patients with cannabis-induced panic disorder (CIPD) shows hypocortisolism under standardized psychosocial stressor induction compared to healthy individuals. However, compared to “regular” PD patients, the cortisol reactivity in patients with CIPD might be higher under standardized psychosocial stressor induction.

Methods

Study Participants

Patients with PD were tested at the Carl Gustav Carus University Hospital of the Technische Universität Dresden, Germany. Diagnoses of patients were confirmed using the Structured Clinical Interview (SCID) [18] for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) axis I and II disorders [1]. Patients with a primary DSM-IV diagnosis of PD or a diagnosis of PD with or without agoraphobia, whose first panic attack occurred under acute cannabis intake, were included in the study. The induction of PD by cannabis was determined by the SCID and the anamnestic interview. Patients with a secondary diagnosis of dysthymia or mild depression were not precluded from participation. Exclusion criteria included any other mental illness diagnosed by way of the SCID and severe chronic illness as determined by physical examinations and routine laboratory tests as well as familiarity using the Trier Social Stress Test (TSST) [19]. Habitual cigarette smoking (≤ 10 cigarettes per day) and pharmaceutical treatment of PD, dysthymia, and mild depression were allowed to avoid significant selection bias in the recruitment of study participants. Patients were matched individually for age and gender with HCs and a sample with PD patients without drug use.

The sample was collected from 2009 to 2013. The final patient sample consisted of 7 patients with a primary diagnosis of PD and 7 patients with CIPD. The latter reported cannabis consumption on a rare to occasional basis (between 2 and 4 months no more than two times weekly) at the occurrence of the first panic attack. Patients with CIPD did not consume cannabis during the entire testing period. All patients were male in order to exclude the confounding effect of the menstrual cycle. The mean age at the onset of the PD was 29.17 years ($SD = 7.36$) in PD patients and 24.33 years ($SD = 7.45$) in CIPD patients and the duration of the PD was 4.78 ($SD = 2.80$) and 4.08 ($SD = 4.30$) years, respectively. According to the Panic and Agoraphobia Scale [20], most of the panic symptoms in both groups were rated as moderate to severe (PD: mean = 2.50 [$SD = 0.84$], CIPD: mean = 2.20 [$SD = 0.84$]). Three PD and 4 CIPD patients were diagnosed with a secondary diagnosis of mild depression. At the time of testing, 4 PD and 3 CIPD patients were on antidepressant medication (selective serotonin reuptake inhibitors [$n = 3$], serotonin norepinephrine reuptake inhibitors [$n = 1$], tricyclic antidepressants [$n = 1$], benzodiazepines [$n = 2$], monoamine oxidase inhibitors [$n = 1$], phytosedatives [$n = 2$], promethazine [$n = 1$], buspirone [$n = 2$], and quetiapine [$n = 1$]). All other participants were free of antidepressants or psychotropic drugs. Furthermore, at the time of testing, the abstinence from cannabis consumption for the past 4 weeks was confirmed by a blood test. All participants were asked to refrain from cigarettes, alcohol, and coffee on the day prior to testing and the

Table 1. Characteristics of the total sample

	Panic disorder patients	Cannabis-induced panic disorder patients	Healthy control subjects	F/χ^2	p
<i>Sociodemographics</i>					
Total, n	7	7	7		
Age, years ^a	32.95 (9.04)	31.94 (8.40)	31.13 (8.57)	0.156	0.926
Smoking, % ^a	4 (57.14)	5 (71.43)	4 (57.14)	0.385	0.840
Depressive disorder ^a	3 (42.86)	4 (57.14)	0 (0)	5.306	0.062
Antidepressant medication, % ^a	4 (57.14)	3 (42.86)	0 (0)	5.306	0.062
<i>Clinical measures</i>					
PAS total score [0–52] ^{a, c}	27 (10.24)	25 (8.75)	2.29 (4.86)	12.523	0.000***
ACQ loss of control [0–4] ^a	0.57 (0.30)	1.06 (0.48)	0.57 (0.34)	4.324	0.095
ACQ physical concerns [0–4] ^{a, d}	1.52 (0.39)	1.48 (1.28)	0.33 (0.08)	8.753	0.007**
ACQ total score [0–4] ^{b, e}	0.89 (0.21)	1.10 (0.52)	0.32 (0.18)	8.336	0.005**
BSQ total score [0–4] ^b	1.40 (0.66)	1.96 (1.08)	0.79 (0.59)	2.968	0.087
MI alone [0–4] ^b	1.71 (1.41)	1.44 (1.30)	0.11 (0.12)	3.569	0.058
MI accompanied ^b [0–4]	1.28 (1.15)	0.86 (0.79)	0.08 (0.11)	3.389	0.065
SCL-90 global severity index [0–>2.53] ^{a, f}	1.08 (0.65)	1.61 (0.05)	0.33 (0.22)	5.436	0.036*
<i>Subjective level of distress</i>					
PASA stress index [–3.75 to 3.75] ^a	–1.13 (1.98)	–1.06 (0.09)	–1.56 (2.03)	0.214	0.950
VAS mean [0–100] ^a	54.79 (7.30)	56.44 (6.81)	37.75 (0.18)	3.750	0.064
TSST-Responder, % ^{a, g}	2 (28.57)	4 (51.14)	7 (100)	7.308	0.026*

Mean (SD) are listed except where noted. PAS, Panic and Agoraphobia Scale; ACQ, Agoraphobic Cognitions Questionnaire; BSQ, Body Sensations Questionnaire; MI, Mobility Inventory; SCL, Symptom Checklist; PASA, Primary Appraisal Secondary Appraisal scale; VAS, Visual Analogue Scale. ^a Kruskal-Wallis test. ^b Univariate analysis of variance. ^c Post hoc analyses: PD > CIPD ($p = 1.000$), PD > HC ($p \leq 0.001$), CIPD > HC ($p = 0.001$). ^d Post hoc analyses: PD > CIPD ($p = 1.000$), PD > HC ($p = 0.017$), CIPD > HC ($p = 0.020$). ^e Post hoc analyses: CIPD > PD ($p = 0.966$), CIPD > HC ($p = 0.005$), PD > HC ($p = 0.042$). ^f Post hoc analyses: CIPD > PD ($p = 0.684$), CIPD > HC ($p = 0.049$), PD > HC ($p = 0.139$). ^g Post hoc analyses: CIPD > PD ($p = 0.651$), HC > PD ($p = 0.015$), HC > CIPD ($p = 0.213$). * $p \leq 0.05$; ** $p \leq 0.005$; *** $p \leq 0.001$.

testing day itself and these variables were controlled. Furthermore, not all participants were engaged in physical exercises.

Male HC participants ($n = 7$) had been recruited through newspaper advertisements and were matched by age to the patient samples as described above.

Sociodemographic and clinical sample characteristics are briefly illustrated in Table 1. All participants gave written informed consent prior to participation. The current study was approved by the local Ethics Committee of the Medical Faculty of the Technische Universität Dresden, Germany (No. #EK7012006).

Clinical Measures

Information concerning sociodemographic variables (gender, age, smoking status) as well as medication intake was assessed within a routine medical examination. To determine the severity of panic-related symptoms, the following questionnaires were applied: (1) the Panic and Agoraphobia Scale [20] for assessing the global severity of PD. It consists of 13 questions answered on a 5-point Likert scale. The internal consistency (Cronbach's alpha) of the scale ranges between 0.88 and 0.89. The inter-

rater reliability is $r = 0.78$ ($p < 0.05$) [20]. (2) The Symptom Checklist [21] was used for patients to assess their physical and psychological impairment. It is one of the most commonly used procedures in clinical-psychological diagnostics [22]. The Symptom Checklist is a 90-item questionnaire using a 5-point Likert scale to measure each item. (3) The Agoraphobic Cognitions Questionnaire [23] was implemented to self-evaluate the intensity of panic and agoraphobic beliefs and catastrophic cognitions about panic. It consists of 14 items using a 5-point Likert scale ranging from 1 (thought never occurs) to 5 (thought always occurs). Furthermore, it comprises two scales. Those scales relate to loss of control and physical concerns. (4) The Bodily Sensation Questionnaire [23] measures fear of bodily sensations that often occur during panic attacks. The total score of the Bodily Sensation Questionnaire is calculated as the average score of the 17 items with a 5-point Likert scale regarding specific body sensations. (5) The Mobility Inventory [24] was used to self-assess patients' agoraphobic avoidance behaviour in different situations. Ratings of situations had to be made for two conditions: when confronted with the situation alone and accompanied by another

person. It consists of 27 questions that are answered on a 5-point Likert scale ranging from 1 (never avoided) to 5 (always avoided). All questionnaires have been reported to show good psychometric characteristics regarding reliability and validity.

Trier Social Stress Test

In order to test the hypothesis, the TSST [19], a well-established, validated psychosocial stress paradigm, was applied. The TSST aims at inducing acute moderate psychosocial stress under laboratory conditions [25] and has proven to be a reliable tool to evoke stress in anxiety disorders and drug dependence [26]. All participants were confronted individually with the standardized TSST protocol, which consists of a mock job interview (5 min) and a subsequent mental arithmetic task (5 min) in front of a 2-person committee. Subjective levels of distress were determined by the Primary Appraisal Secondary Appraisal Questionnaire [27] prior to and a Visual Analogue Scale following the TSST. Testing was conducted between 3 p.m. and 6 p.m. to avoid significant circadian differences in cortisol levels. Any eating or drinking was not allowed from at least 2 h before until the end of the testing session. It was ensured that all participants were confronted with identical procedures within the same setting.

Cortisol Sampling

Over the course of the TSST session, a total of 7 saliva samples per person were collected (10 min before and 0, 10, 20, 30, 40, and 50 min after completion of the TSST) by way of Salivette swabs (Sarstedt, Nümbrecht, Germany) to ensure a fast and hygienic procedure. Samples were then kept frozen at -20°C before being assayed for cortisol. For preparing the examination and producing a clear supernatant of low viscosity, samples were centrifuged at 3,000 rpm for 5 min. For cortisol analysis, 50 μL were removed using a commercially available immunoassay with chemiluminescence detection.

Statistical Analyses

Differences between groups in sociodemographic and clinical measures were evaluated by using Kruskal-Wallis tests for non-parametric data and univariate analyses of variance (ANOVA) for normally distributed data. To check normal distribution of data, Shapiro-Wilk tests were conducted beforehand. For analysing group differences in the cortisol stress response, a 3 (group: PD patients, CIPD patients, HC participants) $\times$ 7 (time: -10, 0, 10, 20, 30, 40, and 50 min) repeated-measures ANCOVA was accomplished. Baseline cortisol values (-10 min) were added as covariates. Greenhouse-Geiser or rather Huynh-Feldt corrections were applied whenever the sphericity assumption was violated. In the event of significant results, LSD post hoc tests were applied to provide specific information on which results significantly differed from each other. Significant results of non-parametric data were reviewed by means of a Wilcoxon test.

The cortisol stress response following the TSST was defined as a baseline-to-peak increase in cortisol levels of at least 1.5 nmol/L [28]. Regarding cortisol data, all available values were included in the assay as they were located within three standard deviations above and below the mean. Statistical analyses were conducted with the software Statistical Package for the Social Sciences for Windows, version 25 (SPSS Inc., Chicago, IL, USA).

Fig. 1. Mean ($\pm$ SD) salivary cortisol concentrations of panic disorder (PD) patients, cannabis-induced panic disorder (CIPD) patients, and healthy control (HC) subjects. TSST, Trier Social Stress Test.

Results

Clinical Measures

An overview of sociodemographic and clinical data is provided in Table 1. Groups did not differ significantly regarding age, smoking status, depressive disorders, and antidepressant medication (Table 1). Significant group differences were apparent in clinical measures of anxiety, depression as well as the Symptom Checklist global severity index (Table 1). HC participants consistently showed the lowest values across all questionnaires. While PD and CIPD patients rated their panic-related symptomatology as moderate to severe (PD: mean = 2.50; SD = 0.84, CIPD: mean = 2.20; SD = 0.84), substantially lower values were observable in HC participants (mean = 0.14; SD = 0.38). See Table 1 for detailed information on post hoc analyses.

TSST Cortisol Response

Baseline cortisol levels before the TSST did not differ statistically between groups ($F_{2,18} = 0.720$, $p = 0.500$, $n = 21$).

ANCOVA results revealed a non-significant Greenhouse-Geiser corrected main effect for time ($F_{1.91, 32.49} = 0.743$, $p = 0.478$, $n = 21$, $\eta^2 = 0.042$), a significant main effect of group ($F_{2,17} = 6.947$, $p = 0.006$, $n = 21$, $\eta^2 = 0.45$) as well as a significant time by group interaction effect

($F_{3.82, 32.49} = 8.463$, $p \leq 0.001$, $n = 21$, $\eta^2 = 0.499$). The salivary cortisol course of the three study groups is illustrated in Figure 1. Post hoc analyses (LSD-corrected with $\alpha = 5\%$) revealed significant group differences between PD and HC participants ($p = 0.021$). Descriptive differences were found between all groups (HC > PD [$p = 0.021$]; HC > CIPD [$p = 0.596$]; CIPD > PD [$p = 0.743$]).

Discussion

The current study aimed at examining the HPA axis activity of patients whose first panic attack was cannabis-induced, when confronted with a threatening and uncontrollable psychosocial stressor.

Our data point out that CIPD patients display a peculiar pattern of cortisol reactivity to psychosocial stress, compared to PD patients, whose PD did not develop following cannabis use. The present study revealed that patients with CIPD present blunted cortisol reactivity under standardized psychosocial stressor induction compared to healthy individuals. This is in line with cannabis users that displayed significantly lower cortisol responses than abstainers under a different psychosocial stress test [15]. The present results also stated that the cortisol reactivity in patients with CIPD is higher under standardized psychosocial stressor induction compared to “regular” PD patients. This effect might be explicable by preclinical studies showing that the acute administration of Δ^9 -THC is associated with an increase in cortisol levels [17].

Baseline cortisol values did not differ significantly among groups. This matches findings of Petrowski et al. [8], who reported a blunted cortisol reactivity to the TSST with concurrent normal cortisol awakening responses in PD patients compared to HC participants. The similar baseline cortisol levels between PD patients and HC subjects have already been reported elsewhere [29]. Interestingly, baseline cortisol values (–10 min, 0 min) of CIPD patients were slightly higher than those of HC participants (and higher than PD patients), although this difference did not reach statistical significance (Fig. 1). This fact accounts for the idea of a higher reactivation of the HPA axis compared to PD patients and hence elevated cortisol levels in resting conditions without stress exposure in substance-consuming people as shown by Armario [30].

The ANCOVA revealed a pattern of cortisol hyporesponsiveness in both, PD and CIPD patients compared with HC subjects. In terms of the comparison between PD and HC subjects, our findings are in keeping with previous findings of a cortisol hyporesponse in patients with

PD [8–10, 29, 30, 32]. As cortisol levels of CIPD patients were located between those of PD patients and HC subjects, our assumption of HPA axis reactivity in CIPD patients balancing between hypocortisolism and cortisol reactivity of healthy people when exposed to the TSST can be confirmed.

Regarding the cortisol course of CIPD patients, our results match previous findings of a reduced HPA axis activity after the consumption of cannabis [14, 33, 34]. However, it contradicts findings of regular or increased HPA axis activation following cannabis consumption [13, 14, 35, 36]. Current results are most likely comparable to van Leeuwen et al. [15] even though not the same psychosocial stress paradigm was applied. Although current differences between CIPD patients and HC participants did not reach statistical significance, results of both studies point in the same direction of an HPA hypoactivation in CIPD patients when confronted with a psychosocial stressor compared to HCs.

Compared with PD patients, CIPD patients showcased a slightly heightened cortisol reactivity. This could be due to the fact that in study participants self-reported cannabis consumption took only place on a rare to occasional basis excluding habituation processes to cannabis as those described by Ranganathan et al. [14]. Still it remains remarkable that cortisol response patterns to psychosocial stress clearly differ between CIPD and PD, indicating that cannabis consumption as an aetiological factor for PD has a considerable influence on psychoneuroendocrine functioning and HPA axis activity. PD in CIPD is primarily chemically induced, whereas the development of PD in the PD patient group has different causes, but not substance consumption. As psychoneuroendocrine patterns differ between groups, results raise the question of whether the manifestation of PD differs, depending on its aetiological origin. This and further questions would have to be addressed in future investigations, since this study must be considered a pilot study that emphasizes the need for deeper exploration of HPA axis activity in CIPD patients.

Since the three groups did not differ significantly regarding age and smoking status, these variables can be excluded as significant confounding factors. The same applies to the comorbidity of depression and antidepressant medication, which were balanced between PD and CIPD patients and did not differ significantly from the values of HC subjects. Furthermore, a previous study comparing PD patients to patients with a mild major depressive disorder revealed a cortisol hyporesponsiveness in PD patients in response to the TSST. Additional analy-

ses showed no impact of comorbid depressiveness on the cortisol stress response. Major depressive disorder patients did not differ in the hormonal stress response neither compared to the healthy participants nor to the PD patients [37]. Additionally, patients with moderate to severe major depressive disorder are rather linked to heightened HPA axis activity and cortisol hyperresponsiveness to stressors [38, 39]. Higher cortisol levels after the TSST during the recovery period have also been confirmed in a meta-analysis on depression and cortisol response to psychological stress [40]. Therefore, the blunted cortisol response cannot be reasonably explained by comorbid depressive disease.

However, the present study is limited by the small size of the total sample. This is due to the rare condition of CIPD patients in clinical practice. Another limitation is the lack of chemical analyses quantifying blood levels of THC in the past and at the time of the first panic attack. The exact analysis of THC levels would allow for more differentiated analyses. However, abstinence from cannabis consumption in the previous month was confirmed by a blood test. Furthermore, all participants were male to exclude the confounding effect of the menstrual cycle. While women in the luteal phase of the menstrual cycle and men show similar salivary cortisol levels after psychosocial stress, respective hormone levels during the follicular phase of the menstrual cycle tend to be lower [41]. For further research, sex-related HPA axis response patterns should be examined in patients with CIPD.

Future research should additionally collect corticotropin-releasing hormone and plasma adrenal corticotropin

data as well as blood cortisol samples to more precisely determine the differences in HPA axis activity between PD and CIPD patients.

Nonetheless, current results provide evidence for an enhanced HPA axis activity upon laboratory stress induction in CIPD compared to PD patients. This study is the first to exhibit a distinctive pattern of cortisol responsiveness to psychosocial stress in CIPD patients and thus emphasizes the importance of aetiological factors of PD for psychoneuroendocrine functioning within the disease. Besides, data provide further support to previous findings of hypocortisolism in PD patients compared to HC subjects. Depressiveness had no impact on the cortisol response in neither group. Hopefully, current results encourage further examinations of CIPD patients, for gaining an enhanced understanding of the complexity of their psychoneuroendocrine functioning.

Statement of Ethics

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Disclosure Statement

All authors declare that they have no conflicts of interest.

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