Psychoneuroendocrinology 87 (2018) 35–42

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Blunted basal corticosterone pulsatility predicts post-exposure susceptibility to PTSD phenotype in rats

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ARTICLE INFO

Keywords:
Animal model
Post-traumatic stress disorder (PTSD)
HPA axis
Corticosterone
Circadian rhythm
Pulsatility/ultradian
Resilience
Vulnerability

ABSTRACT

The basal activity of the hypothalamic–pituitary–adrenal axis is highly dynamic and is characterized by both circadian and ultradian (pulsatile) patterns of hormone secretion. Pulsatility of glucocorticoids has been determined to be critical for optimal transcriptional, neuroendocrine, and behavioral responses. We used an animal model of post-traumatic stress disorder (PTSD) to assess whether stress-induced impairment of behavioral responses is correlated with aberrant secretion of corticosterone. Serial blood samples were collected manually via the jugular vein cannula during the light-(inactive)-phase in conscious male rats at 20-min intervals for a period of 5 h before and 6.5 h after exposure to predator scent stress. The outcome measures included behavior in an elevated plus-maze and acoustic startle response 7 days after exposure. Individual animals were retrospectively classified as having “extreme”, “partial”, or “minimal” behavioral responses according to pre-set cut-off criteria for behavioral response patterns. Corticosterone secretion patterns were analyzed retrospectively. Under basal conditions, the amplitude of ultradian oscillations of corticosterone levels, rather than the mean corticosterone level or the frequency of corticosterone pulsatility, was significantly reduced in individuals who displayed PTSD-phenotype 8 days later. In addition, extreme disruption of behavior on day 8 post-exposure was also characterized by a blunting of corticosterone response to the stressor. Animals with behavior that was only partially affected or unaffected displayed none of the above changes.

Blunted basal corticosterone pulse amplitude is a pre-existing susceptibility or risk factor for PTSD, which originates from prior (life) experiences and may therefore predict post-exposure PTSD-phenotype in rats.

1. Introduction

Glucocorticoid (GC) hormones play a major role in orchestrating the complex physiological and behavioral reactions essential for homeostasis (McEwen, 2002). As such, these hormones enable the organism to prepare for, respond to, and cope with the acute demands of physical and emotional stressors. The release of GCs, commensurate with stressor severity, enables the body to properly contain stress responses and promote recovery by rapidly restoring homeostasis (Yehuda et al., 1998). Inadequate GC release following stress not only delays recovery by acutely disrupting biological homeostasis but can also interfere with the processing or interpretation of stressful information, resulting in long-term disruptions of memory integration processes (McEwen, 2002). A salient example of such an impaired post-traumatic process in the clinic is post-traumatic stress disorder (PTSD) (American Psychiatric Association, 1994).

The secretion of GC hormones is a highly dynamic process which displays a characteristic circadian pattern of corticosterone release, with higher levels at the onset of the active phase and lower levels at the onset of the inactive phase. In addition to this circadian release, corticosterone secretion also displays rapid ultradian rhythmicity in the blood (Windle et al., 1998), in target tissues, such as the brain (Droste et al., 2009), saliva (Trifonova et al., 2013), and in subcutaneous tissue (Bhake et al., 2013; Qian et al., 2012; Spiga et al., 2015). In the rat, corticosterone pulses have a near-hourly frequency (Sarabdjitsingh et al., 2010a), and changes in the amplitude of these pulses throughout the 24 h cycle determine the circadian variation in hormone secretion (Spiga et al., 2015).

The mechanism underlying the origin of GC pulsatility is not completely understood, but recent evidence suggests that corticosterone pulsatility is generated independently of both the suprachiasmatic nucleus and the “hypothalamic pulse generator” (Spiga and Lightman, 2015). Using both mathematical modeling and in vivo experimental work, evidence shows that corticosterone pulsatility is inherent within the pituitary-adrenal system (Walker et al., 2010), which arises due to an intrinsic positive feed-forward (activation) and negative feedback

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http://dx.doi.org/10.1016/j.psyneuen.2017.09.023
Received 14 June 2017; Received in revised form 24 September 2017; Accepted 28 September 2017

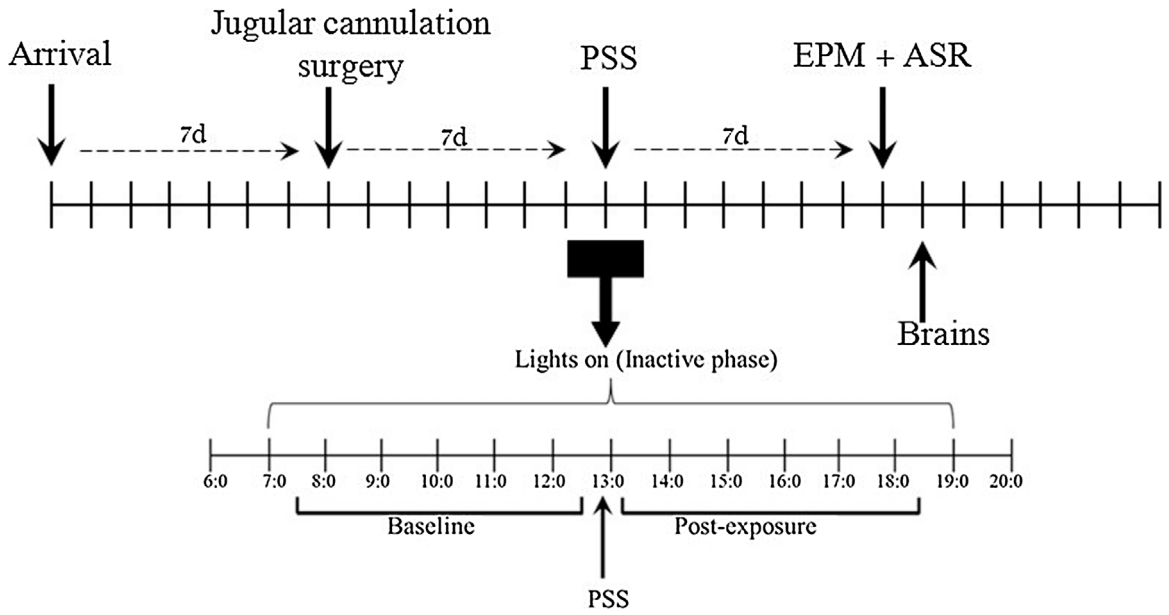

Fig. 1. Timelines for experiments.

loop (inhibition) in the hypothalamic–pituitary–adrenal (HPA) axis (George et al., 2016; Walker et al., 2010). Increasing evidence supports the importance of this pulsatile release in determining the behavioral, neuroendocrine, and genomic response to stressors (Spiga et al., 2015). Furthermore, corticosterone pulsatility is crucial for optimal transcription of glucocorticoid-regulated genes (Stavreva et al., 2009)

A growing body of evidence suggests that amplitude of pulsatility is dynamic not only during the day, but that the ultradian rhythm varies at various points and transitions throughout the life span (puberty, lactation, and aging) (Joels et al., 2012; Lightman et al., 2008) and is affected by sexual diergism (Seale et al., 2004a, 2004b), chronic stress (Windle et al., 2001), and a number of other physiological and pathological conditions (Young et al., 2004).

Our group has initiated a series of studies that examine the role of GCs in the susceptibility to extreme behavioral responses to stress ("PTSD-like phenotype") in a well-validated animal model for PTSD (Cohen et al., 2013; Cohen et al., 2003; Cohen et al., 2005). Our findings highlight the pivotal role of the initial response of the HPA axis in producing normative stress responses and in determining the long-term neuro-hormonal imbalance underlying the behavioral symptoms of PTSD (Cohen et al., 2008; Cohen et al., 2006; Zohar et al., 2011). Indeed, it is unclear whether the poor cortisol stress response or dysregulation observed in the acute aftermath of trauma, represents a pre-trauma vulnerability factor or results from exposure to trauma (Yehuda et al., 2010). Because corticosterone secretion is strongly influenced by circadian and ultradian rhythms (Reul et al., 1990; Sarabdjitsingh et al., 2010b; Sarabdjitsingh et al., 2012; Stavreva et al., 2009; Tapp et al., 1984), and because alterations in basal pulse frequency and amplitude are known to influence activity and reactivity to acute stressors (Reul et al., 1990; Sarabdjitsingh et al., 2010b; Sarabdjitsingh et al., 2012; Stavreva et al., 2009; Tapp et al., 1984), corticosterone pulsatile patterns were evaluated under both baseline conditions and following predator scent stress (PSS) exposure.

The aim of this study was to examine whether PSS-induced impairment of behavioral responses is mediated in part by aberrant secretion of corticosterone. We thus investigated whether the disruption in behavioral stress response stems from an aberrant secretion of corticosterone before and after PSS exposure. We examined if plasma corticosterone pulsatility (frequency and amplitude) under basal conditions (before exposure) and post-PSS exposure was correlated to behavioral stress response patterns. We collected blood samples 5 h before exposure (baseline) and 6.5 h after PSS exposure. The pulsatility characteristics were analyzed according to the retrospective classification of individual rats into behavioral response groups.

2. Methods

All procedures were performed under strict compliance with ethical principles and guidelines of the NIH Guide for the Care and Use of Laboratory Animals. All treatment and testing procedures were approved by the Animal Care Committee of Ben-Gurion University of the Negev, Israel (IL-09-06-2014).

2.1. Animals

A sample of 26 adult male Sprague-Dawley rats, weighing 190–220 g on the day of surgery, was used. The rats were housed, three per cage, in a vivarium with a stable temperature, a 12:12 light-dark cycle (lights off at 07:00 p.m.; luminous emittance during the light phase: 200G50 lx), with unlimited access to food and water. All rats were maintained under this regime for a 1-week habituation period before the experiments began. All procedures were performed during the resting phase of the rats, between 07:30 and 18:30. Rats were handled daily commencing the week prior to experimental procedures. During the experiments, rats were single-housed in opaque plastic bins (50.8 × 25.4 × 25.4 cm), which were lined with bedding material.

2.2. Experimental design

After 7 days of a post-surgical recovery period, blood was collected at 20 min intervals from 26 rats, for a period of approximately 5 h for the collection of baseline rhythms. Immediately afterwards rats were exposed to 10 min of PSS following blood collection at 20 min intervals for a period of another 6.5 h for the collection of corticosterone profiles of stress response and recovery. The behavioral assessments were conducted 7 days post-exposure, first in the elevated plus maze (EPM) paradigm and 1 h later in the acoustic startle reaction (ASR) paradigm. These data subsequently served for classification into behavioral response groups (Cohen et al., 2013, 2003, 2005). The experimental design used here is schematically depicted in Fig. 1.