Psychoneuroendocrinology (2009) **34**, 402—412

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Altered tonic and phasic cortisol secretion following unilateral stroke

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Received 14 March 2008; received in revised form 25 September 2008; accepted 1 October 2008

KEYWORDS
HPA axis;
Cortisol;
Stress response;
Stroke;
Asymmetry

Summary Evidence is accumulating that cerebral laterality appears to be an important feature in the regulation of the stress response with the right hemisphere being closely linked to stress-regulatory systems, including the hypothalamic—pituitary—adrenal (HPA) axis. Although some animal and human data support this hypothesis, studies on brain damaged patients yet failed to substantiate laterality effects on cortisol secretion. The aim of this study was to examine whether unilateral stroke differentially affects tonic and phasic response characteristics of the HPA axis, and to evaluate the impact of intrahemispheric lesion location. Basal morning cortisol levels and phasic responses towards a mentally challenging task were examined in 32 stroke patients with left-sided (LH; $n = 18$) or right-sided (RH; $n = 14$) infarctions and 30 healthy controls matched for age and gender. Only LH, but not RH patients displayed increased morning cortisol levels when compared to controls. In contrast, phasic reactions were blunted in the combined patient group with RH patients showing the most distinct decline. More anterior located lesions were associated with reduced phasic, but not tonic cortisol measures. This relationship appeared to be particularly pronounced in RH patients. Results support the conclusion that the central regulation of cortisol secretion is under excitatory control of the right hemisphere and can be interpreted within a framework of asymmetrical regulation of the stress response. Left- and right-sided strokes may differentially

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0306-4530/$ — see front matter
doi:10.1016/j.psyneuen.2008.10.002

affect response patterns of the HPA axis, a stress-regulatory system that is associated with effective protection against disease and external challenges.

1. Introduction

A growing body of research indicates that cerebral laterality is an important feature in the regulation of the somatic stress response (Wittling, 1995, 2001; Sullivan and Gratton, 2002; Craig, 2005). The hypothalamic–pituitary–adrenal (HPA) axis, a neurohormonal feedback-system linking central components of the neuroendocrine stress response via a multistage cascade involving corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) with its primary peripheral effector cortisol, has been associated with laterality effects on several regulatory stages.

Evidence is accumulating from both animal and human research employing different methodological approaches that emphasizes the predominant role of the right hemisphere in activating the HPA axis (Wittling and Pflueger, 1990; Kalogeras et al., 1996; Kalin et al., 1998; Sullivan and Gratton, 1999, 2002; Buss et al., 2003; Wang et al., 2005). Studying the effects of infralimbic cortex lesions on neuroendocrine reactions towards brief stress in rats, Sullivan and Gratton (1999) reported a disruption of corticosterone responses after right-sided lesions being as efficient as bilateral lesions. In contrast, left-sided lesioned rats did not differ from shams. Extreme right frontal brain EEG activity has been shown to be associated with increased HPA axis activity and fearful behavioural components in rhesus monkeys (Kalin et al., 1998, 2000), and 6 months old toddlers (Buss et al., 2003). Moreover, right lateralized cortical activation is related to the magnitude of the cortisol awakening reaction (CAR) during an exam stress period in students (Hewig et al., 2008). Using lateralized presentation of affective visual stimuli, Wittling and Pflueger (1990) demonstrated a positive cortisol response only under right hemisphere stimulation, thus confirming the importance of the right hemisphere in mounting a phasic cortisol response in healthy human subjects. Functional neuroimaging approaches as well provide support for elevated cerebral blood flow in the right ventral prefrontal and orbitofrontal cortices being associated with the magnitude of cortisol secretion during brief mental stress (Wang et al., 2005). Laterality effects are not restricted to peripheral effectors of the HPA axis. Kalogeras et al. (1996) demonstrated differences in the amount of ACTH secretion between the left and right inferior petrosal sinus under baseline conditions and after transient stimulation by CRH. In the majority of subjects, higher values of ACTH were present in the right sinus.

Contrary to these findings from experimental animal and human research, studies so far failed to prove laterality effects on HPA axis control after unilateral brain damage in humans. While Tchiteya et al. (2003) did not observe differences in basal cortisol levels between left and right brain damaged patients, frontally extending cortical lesions were followed by elevated morning cortisol levels. Similarly, Murros et al. (1993) reported elevated evening cortisol levels in frontally extending infarcts in a sample of stroke patients. Differences between right- and left-sided strokes, however, were not tested in this study.

Alterations in basal cortisol activity, including morning cortisol levels and inhibitory feedback control, have been repeatedly demonstrated during the acute phase of stroke, often being associated with poor cognitive or functional outcomes, including higher mortality rates (Feibel et al., 1977; Olsson et al., 1989; Olsson, 1990; Olsson et al., 1992; Fassbender et al., 1994; Schwarz et al., 2003; Marklund et al., 2004; Makikallio et al., 2007). Nevertheless, studies so far provide only limited explanatory power for the evaluation of laterality effects on HPA axis control in the population of stroke patients. First, studies are lacking that explicitly tested the effects of lesion side in unilateral stroke patients. Second, the vast majority of studies were conducted immediately after the stroke incident. Elevated cortisol and catecholamine levels after acute stroke are interpreted within a general physiological stress response in reaction to the life threatening event of stroke. In the early course of the disease, however, this transient stress response may override discrete functional alterations more closely related to lesion location. Finally, detection of laterality effects may critically depend upon the paradigm employed. Contrary to the phasic stress reactivity paradigms used in experimental research, studies on stroke patients predominantly investigated basal cortisol levels, inhibitory feedback mechanisms, or diurnal patterns, reflecting changes in tonic cortisol activity.

In the present study we aimed to evaluate laterality effects on HPA axis control in patients with unilateral stroke not immediately after stroke, but during their rehabilitation phase. Based on previous findings we hypothesized that right hemisphere damage would result in a blunted cortisol response. Moreover, we sought to analyze the relationship between the proximity of the lesion to the frontal pole (see Robinson et al., 1984) and the magnitude of cortisol values. Finally, we aspired to evaluate laterality effects on both tonic (e.g., basal cortisol levels) as well as phasic changes in response to a brief mental stressor.

2. Methods

2.1. Subjects

A consecutive series of 32 (18 LH, 14 RH) stroke patients that were admitted to a neurological rehabilitation unit following inpatient treatment and 30 healthy controls matched for age, gender, and education were incorporated in the analysis (see Tables 1 and 2 for details). Patients were included if they exhibited a first-ever, ischaemic, supratentorial unilateral stroke and were able to participate in the study protocol. Bilateral, brainstem or cerebellar lesions, a previous history of transient ischaemic attacks (i.e., transitory ischaemic attacks or (prolonged) reversible ischaemic neurological deficits), other neurological disorders, and previous or current psychiatric disorders were followed by exclusion. Sufficient language abilities were preserved in all patients as indicated by the Token Test (stanine values >8, indicating minimal or no aphasic impairment; see Huber et al., 1983). Patients