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Birth weight is associated with salivary cortisol responses to psychosocial stress in adult life

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Summary Fetal programming of the hypothalamus-pituitary-adrenal (HPA) axis was proposed as one mechanism underlying the link between prenatal stress, adverse birth outcomes (particularly low birth weight) and an enhanced vulnerability for several diseases later in life. In recent studies, birth weight was significantly related to basal cortisol levels as well as to cortisol responses to pharmacological stimulation.

In order to investigate the association between cortisol responses to psychological challenge, birth weight and length of gestation, 106 young healthy males were exposed to the 'Trier Social Stress Test'. Salivary cortisol responses to the stress exposure were significantly and inversely related to the subjects' birth weight, while the analysis of the impact of gestational age yielded inconsistent results.

This finding is consistent with the concept of fetal programming of the HPA axis and provides the first preliminary evidence for an association between birth weight and adrenocortical responses to psychosocial stress. As the investigated subjects were twins, possible implications of this sample characteristic for the present findings are discussed.

1. Introduction

There is now substantial evidence that low birth weight and a low ponderal index (birth weight/length^3) are related to an increased prevalence of common cardiovascular and metabolic disorders later in life, including hypertension, coronary heart disease, type 2 diabetes, insulin resistance and hyperlipidaemia (Welberg and Seckl, 2001; Barker, 2002). Furthermore, low birth weight or thinness at birth were reported to be associated with psychopathologies such as depression, schizophrenia and autism (Weinstock, 2001; Welberg and Seckl, 2001). This link between intrauterine growth and clinical states has led to the 'fetal origins hypothesis' of adult disease, which suggests that an adverse influence acting on the fetus causes both

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low birth weight as well as an enhanced vulnerability for diseases later in life (Barker, 1992; 1999; Barker et al., 1995).

Increasing evidence supports the view that maternal stress during pregnancy can have adverse effects on fetal development and gestational age in addition to other identified factors including malnutrition, smoking, drug intake, cervical and uterine anomalies, concomitant illnesses like infection in the maternal genital tract or preeclampsia (e.g. Kramer, 2003). Maternal stress was shown to relate to low birth weight (Paarlberg et al., 1995; 1999) as well as to preterm delivery (Hedegaard et al., 1993; Paarlberg et al., 1995; Glynn et al., 2001; Wadhwa et al., 2001). Recent studies suggested that one of the processes linking intrauterine growth retardation or prenatal stress to adverse outcomes later in life might be fetal programming of the HPA axis. Prenatally stressed adult animals had lower birth weight, enhanced basal HPA axis activity, prolonged responses to stress, impaired HPA axis feedback regulation and fewer glucocorticoid and mineralocorticoid receptors in the hippocampus (Weinstock, 1997; Matthews, 2002; Huizink et al., 2004). These studies are paralleled by findings that document an impact of prenatal exposure to exogenous glucocorticoids (GCs) on HPA axis functioning later in life (for a recent review see Welberg and Seckl, 2001). In human studies low birth weight was shown to be related to alterations in HPA axis function. In adult life subjects with low birth weight had elevated basal morning cortisol levels (Phillips et al., 1998; 2000; Levitt et al., 2000), enhanced cortisol responses to an $ACTH_{1\text{-}24}$ challenge and increased total urinary cortisol metabolite excretion (Levitt et al., 2000; Reynolds et al., 2001). Recently, reduced ACTH and cortisol responses to a combined administration of dexamethasone and CRH in low birth weight subjects were reported (Ward et al., 2004). However, studies that did not detect a clear inverse association do also exist (Kajantie et al., 2003; 2004). The few studies on the relation between gestational age and HPA axis activity later in life yielded inconsistent results (Kajantie et al., 2002; 2003; 2004; Walker et al., 2002).

Although these human studies suggest an association between low birth weight and basal cortisol levels as well as HPA axis responses to some pharmacological stimuli they do not allow to assume a similar relation to responses to psychological stress and to the best of our knowledge, this has not yet been investigated. For instance, no significant correlation was found between salivary cortisol levels in the first hour after awakening and cortisol responses to psychosocial stress (Schmidt-Reinwald et al., 1999). This partial dissociation of basal and stimulated HPA axis activity may, probably in concert with other factors, be mediated by the differential effects of mineralocorticoid and glucocorticoid receptors in the brain (De Kloet et al., 1998). HPA responses to psychological stress and pharmacological challenges are also not necessarily closely related. While, for example, exogenous CRH acts directly on the anterior pituitary, HPA axis activation after stress is more complex. Stress-induced activity of CRH neurons in the hypothalamic paraventricular nucleus (PVN) is modulated by numerous signals, including direct input from the nucleus of the solitary tract, the raphe nuclei, a number of hypothalamic nuclei and the bed nucleus of the stria terminalis as well as indirect input from several limbic structures. In the PVN excitatory and inhibitory inputs are integrated and cause a net secretory signal to the pituitary gland (Herman et al., 2003). No association was observed between salivary cortisol or ACTH responses to psychosocial stress and responses to CRH administration (Kirschbaum et al., 1992; 1994). Recently, ACTH responses to psychosocial stress and Naloxone administration were found to be significantly correlated, while no significant association across the challenges was found for cortisol responses (Oswald et al., 2004).

The objective of this study was to contribute, from the perspective of psychobiological stress research, to the understanding of the relation between birth weight, gestational age and cortisol responses to psychosocial stress.

2. Methods

2.1. Subjects

The present study sample consisted of 106 male twins (mean age: 18.57, SEM: $\pm$0.23 yrs), with a mean body mass index of 21.84 $\pm$ 0.27. Participants were recruited by mail and postal addresses of potential twin pairs (pairs of individuals with identical dates of birth, birthplaces and family names) were supplied by the residents' registration office (DIZ) of Rheinland-Pfalz, Germany. Females were not included into the study because cortisol responses to this stressor in women are known to be modulated by the menstrual cycle (Kirschbaum et al., 1999). Prior to the first experimental session the absence of acute or chronic diseases was confirmed in a medical exam and a photocopy of the pregnancy records of the subjects' mothers was collected from each twin pair. All subjects reported