



Stress hormones and emotion-regulation in two genetic animal models of depression

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Summary Children of depressed parents often exhibit emotion-regulation deficits, characterized by either excessive withdrawal or approach strategies toward the mother. The current study examined behavioral and physiological emotion-regulation in preweanling pups (postnatal day 17–19) belonging to two different genetic animal models of depression, Wistar-Kyoto (WKY) and Flinders Sensitive-Line (FSL) rats. The study also examined the effects of stress on the two animal models, hypothesizing an interactive effect of hereditary vulnerability and exposure to stress. Chronic-stress was simulated by providing limited bedding to the dam and litter for a week, in the early postnatal period. Acute-stress was generated by exposure to an adult male rat, an ethologically valid stressor. Emotion-regulation of the pups was examined using a Y-maze preference test and radioimmunoassay of Hypothalamic-Pituitary-Adrenal (HPA) axis hormones (corticosterone & adrenocorticotropin/ACTH). WKY and FSL pups exhibited reduced approach-behavior toward the dam, an emotion-regulation profile reminiscent of avoidant attachment evident in many children of depressed parents. In contrast, the two animal models did not show similar HPA axis activity. FSL pups exhibited markedly lower ACTH levels compared to controls, while WKY pups did not differ from controls. With regard to the stress manipulations, the limited-bedding condition had no effect, while the acute-stressor induced overall effects on all groups, with more pronounced

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reactivity evident in the WKY and FSL pups. Taken together, the experiments indicate a similar behavioral profile of the two strains at the preweaning period, while suggesting HPA dysfunction in only one of the strains.

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1. Introduction

Parental depression has been shown to adversely affect the development of the offspring's emotion-regulation, along with effects on their social and cognitive development (Downey and Coyne, 1990; Gelfand and Teti, 1990; Field, 1992; Goodman and Gotlib, 1999). Infants of depressed mothers, typically described as withdrawn, and exhibiting "depressed-like" behavior, are at increased risk for future psychopathology (Field, 1992). The current study attempts for the first time to investigate emotion-regulation in preweaning pups belonging to two genetic animal models of depression, Flinder's Sensitive Line (FSL) and Wistar-Kyoto (WKY) rats (Paré, 1989; Overstreet, 1993; Paré and Redei, 1993; Paré, 2000; Overstreet et al., 2005). Genetic animal models are a relatively new type of model, exhibiting hereditary vulnerability similar to that found in depressed humans (Nestler et al., 2002). FSL rats were found to exhibit abnormalities in central neurochemical systems connected to depression (e.g., dopaminergic, serotonergic & HPA axis) and behavioral deficits resembling those of depressed humans (Yadid et al., 2000; Overstreet et al., 2005). Similarly, the WKY strain exhibits characteristic depressive-like behavior (Paré, 1989; Lahmame et al., 1997; Lopez-Rubalcava and Lucki, 2000), while showing neurochemical and hormonal abnormalities (e.g., dopaminergic, noradrenergic and HPA axis) (Solberg et al., 2001; Jiao et al., 2003; Malkesman et al., 2006). Overall, the two animal models were found to meet all three types of validity criteria for animal models of psychiatric disorders: face, construct and predictive validity (Willner, 1986).

The first phase of the current study aimed to investigate the similarities between emotion-regulation of pups from the WKY and FSL strains and that of children of depressed parents. Children of depressed parents often exhibit emotion-regulation disturbances, manifested by either excessive withdrawal or approach strategies towards the mother (Gianino and Tronick, 1988; Field, 1994, 1995). In line with these findings, we hypothesized that WKY and FSL pups will show abnormal emotion-regulation patterns, evident in either an increased or decreased tendency to approach the dam. The

pups' behavioral emotion-regulation was explored using a Y-maze preference test, creating a mildly stressing situation and investigating the pups' preference for the anesthetized dam versus a nutritive stimulus (Kavushansky and Leshem, 2004). In the second phase of the study, we focused on the HPA axis as a physiological correlate of behavioral emotion-regulation. The HPA axis is a prominent mechanism by which the brain reacts to acute and chronic-stress and was implicated in mood-disorders (Owens and Nemeroff, 1991; Brown et al., 1999; McEwen, 2000; Muller et al., 2004). Furthermore, factors associated with parental depression, such as dysfunctional maternal care and exposure to stress, were shown to affect this axis (Meaney et al., 1989; Francis and Meaney, 1999). Previous studies in our laboratory showed that on postnatal day (PND) 35 (a pre-pubertal age) FSL rats demonstrated significantly lower levels of CORT and ACTH (compared to controls), while WKY rats demonstrated an opposite profile (Malkesman et al., 2006). The current study extends these initial findings, focusing on a younger pre-weaning age (PND 16–18), while investigating links between prominent behavioral and physiological emotion-regulation components. We hypothesized that pups from the "depressive-like" strains will exhibit disturbances in HPA hormones similar to findings in depressed human children (Nestler et al., 2002; Nemeroff and Vale, 2005).

An additional aim of the study was to explore the interactive effects of stress and hereditary vulnerability on the pups' emotion-regulation. Diathesis-stress theories postulate that stress interacts with hereditary vulnerability in the establishment of mental disorders, a postulation also supported by animal research (Monroe and Simons, 1991; Nestler et al., 2002; Newport et al., 2002). In accordance, early-life stress constitutes a major risk-factor for the development and persistence of affective disorders and establishment of insecure attachment (Goldberg, 2000; Heim and Nemeroff, 2001; Nemeroff and Vale, 2005). In the current study, the effect of chronic-stress on emotion-regulation was investigated by testing the subjects either in standard rearing conditions or after exposure to a "mild chronic-stress" (Gilles et al., 1996) paradigm: limiting the amount of available bedding

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