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Neonatal amygdala lesions alter basal cortisol levels in infant rhesus monkeys

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Summary The amygdala is mostly thought to exert an excitatory influence on the hypothalamic—pituitary—adrenal (HPA) axis, although its role regulating HPA basal tone is less clear, particularly during primate development. The current study examined the effects of neonatal amygdala lesions on basal HPA function and the postnatal testosterone (T) surge of rhesus monkeys reared with their mothers in large outdoor social groups. An early morning basal blood sample was collected at 2.5 months of age, whereas at 5 months samples were collected not only at sunrise, but also at mid-day and sunset to examine the diurnal rhythm of cortisol. At 2.5 months of age sham-operated males exhibited higher cortisol than females, but this sex difference was abolished by neonatal amygdalectomy, with lesioned males also showing lower basal cortisol than controls. Although neonatal amygdalectomy did not alter the postnatal T surge, there was a positive relationship between T and basal cortisol levels. At 5 months of age, neither the sex difference in cortisol, nor its correlation with T levels were apparent any longer. Instead, the diurnal cortisol rhythm of both males and females with amygdalectomy showed a blunted decline from mid-day to sunset compared to controls. These results indicate that neonatal amygdala damage alters basal HPA function in infant rhesus monkeys, affecting males only at early ages (at 2.5 months), while leaving the postnatal Tsurge intact, and resulting in a flattened diurnal rhythm in both genders at the later ages. Thus, the primate amygdala has a critical influence on the HPA axis in the first few months of life.

1. Introduction

The amygdala is anatomically positioned to play a critical role in the evaluation of salient and threatening cues from the environment and in the modulation of behavioral, autonomic, and neuroendocrine responses to potential threats (e.g., Freese and Amaral, 2009). The amygdala influences

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neuroendocrine stress responses through indirect inputs to the hypothalamic paraventricular nucleus (PVN), via direct projections to the bed nucleus of the stria terminalis (Herman et al., 2003; Freese and Amaral, 2009). Thus, in response to a perceived threat, stressor-specific pathways from the amygdala activate the PVN, yielding a cascade of events beginning with the secretion of corticotrophin releasing hormone (CRH) into the hypophyseal portal blood followed by the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland into the systemic circulation. ACTH then binds to receptors in adrenocortical cells, which in turn increases the synthesis and release of glucocorticoids, such as cortisol in primates (Herman et al., 2003). A stimulatory role of the amygdala on these neuroendocrine responses has mostly been demonstrated in adult animals. Thus, electrical stimulation of the primate amygdala increases cortisol secretion (Mason, 1959), whereas either complete bilateral lesions of the amygdala nuclei or selective lesions of the central nucleus (CeA) of the amygdala reduces glucocorticoid secretion in response to a stressor in both rodents (Herman et al., 2003) and primates (Kalin et al., 2004; Machado and Bachevalier, 2008). Most of these studies, however, have focused on the role of the amygdala regulating HPA axis stress reactivity (for review see Herman et al., 2003) with little consideration of its role on basal cortisol secretion and its circadian secretory rhythm. Allen and Allen (1975) reported that the rodent amygdala was necessary to maintain ACTH secretion after adrenalectomy, suggesting a potential stimulatory role of the amygdala for tonic (basal) control of the HPA axis in the absence of glucocorticoid regulation. However, a more recent study showed that CRH knockdown in the CeA of adult mice actually increases basal corticosterone (Regev et al., 2012). In primates, no effects on baseline (pre-stressor) cortisol levels have been reported after adult amygdala lesions in monkeys (Sapolsky et al., 1991; Kalin et al., 2004; Machado and Bachevalier, 2008). Even less studied is the role of the amygdala in the regulation of basal HPA axis function during prepubertal development.

Human studies suggest that the basal HPA axis secretory rhythm emerges between 8 and 12 weeks of age (see review Tarullo and Gunnar, 2006). The few studies that have examined the ontogeny of basal HPA function in monkeys indicated either stable or slight decreases in basal cortisol secretion between 2 and 24 weeks of age (Champoux et al., 1989; Higley et al., 1992; Clarke, 1993) with an adult-like diurnal pattern of cortisol secretion already present by 1 year of age (Sanchez et al., 2005; Barrett et al., 2009). Thus, the available developmental data point to a progressive maturation of HPA axis function throughout infancy and raise the question of whether the amygdala plays a critical role in this maturation. Few studies have examined the effects of amygdala lesions on HPA axis function in developing rhesus monkeys, either during the juvenile period (Norman and Spies, 1981) or in infancy (Goursaud et al., 2006; Raper et al., 2012). Two have reported no effects on basal activity (Norman and Spies, 1981; Goursaud et al., 2006). However, these negative results may have resulted either from studying the juvenile rather than the infant developmental period (Norman and Spies, 1981) or from the lack of true baseline samples in the experimental design (Goursaud et al., 2006). In the most recent study (Raper et al., 2012), lower basal cortisol was found in adult animals with neonatal amygdala lesions, although cortisol was not measured in infancy. Thus, the amygdala's influence on basal HPA axis functioning during early primate development remains to be directly investigated.

The current study had two main aims: (1) to examine the effects of neonatal neurotoxic amygdala lesions on basal HPA function of rhesus monkeys during infancy, and (2) to determine whether these effects are sexually dimorphic. In adulthood, gonadal hormones modulate the HPA axis activity. Thus, estrogens in females have mostly a stimulatory effect on the basal HPA axis (Burgess and Handa, 1992; Stavisky et al., 2003), whereas testosterone appears to inhibit corticosteroid secretion, at least in rodents (Seale et al., 2004). Although the relationship between gonadal hormones and the HPA axis in adults is complex and not clearly understood, a few studies have also reported sex differences in basal cortisol levels during childhood, prior to the pubertal increases in gonadal hormones. Thus, boys have higher basal cortisol levels than girls in some studies (Davis and Emory, 1995; Elmlinger et al., 2002; Ouellet-Morin et al., 2010); but opposite findings have also been reported (Essex et al., 2002; Koupil et al., 2005; Sondeijker et al., 2007). The differing results may reflect differences in the age at which boys and girls were sampled. Importantly, Davis and Emory (1995) reported higher cortisol levels in boys than girls during a developmental phase when the hypothalamic—pituitary—gonadal (HPG) axis is temporarily activated in boys, resulting in a transient postnatal testosterone (T) surge (Forest, 1979). A similar HPG activation occurs neonatally in male rhesus monkeys, with elevated T levels from birth through 4 months of age followed by HPG inactivation until puberty (Robinson and Bridson, 1978; Mann et al., 1989). Furthermore, amygdala androgen receptors (AR; Choate et al., 1998) are present in higher concentrations in males than females (Pomerantz and Sholl, 1987), suggesting that the amygdala may be an important site for the regulation of the HPG axis and for interactions between the HPG and HPA axes. To investigate this potential regulatory role of the amygdala on HPA and HPG activity during infancy, we measured both basal cortisol and T at 2.5 months (during the postnatal T surge) and at 5 months of age (after the surge, when T was expected to be low) in male and female infant monkeys with and without neonatal amygdala lesions.

2. Methods

2.1. Subjects

Twenty-eight infant rhesus monkeys (*Macaca mulatta*) were selected from middle-ranking multiparous mothers living in large social groups at the Yerkes National Primate Research Center (YNPRC) Field Station (Lawrenceville, GA), Emory University. The social groups were housed in 38 m × 38 m outdoor compounds with indoor housing and capture area. Social groups consisted of 20—30 adult females with their immature offspring and two unrelated adult males. Infants were divided into two treatment groups: neonatal amygdala lesion (Neo-A; males = 9, females = 7) and sham-operated controls (Neo-C; male = 6, females = 6). Infants in Group Neo-A received MRI-guided bilateral neurotoxic lesion of the amygdala at an average of 25.6 ± 0.8 days of age (range: