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Stress decreases, while central nucleus amygdala lesions increase, IL-8 and MIP-1α gene expression during tissue healing in non-human primates

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Abstract

Stress impairs healing and in part this effect is thought to be mediated by glucocorticoids. However, the brain systems that underlie the effects of stress on healing remain to be determined. Since the central nucleus of the amygdala (CeA) plays a role in mediating an individual's behavioral and physiological reactivity to stress, we investigated, in rhesus monkeys, whether selective lesions of the CeA altered the gene expression of chemokines (IL-8 and MIP-1α) that are associated with early dermal healing. We used rhesus monkeys because they provide an excellent animal model to investigate brain mechanisms relevant to human stress, anxiety, and psychopathology. Hypothalamic–pituitary–adrenal (HPA) activity was assessed in the monkeys prior to the wound healing experiment demonstrating that the CeA lesions reduce HPA activity. In the healing experiment, stress decreased IL-8 and MIP-1α gene expression in both CeA lesioned and non-lesioned animals. Conversely, the CeA lesions increased the tissue expression of IL-8 and MIP-1α mRNA prior to and after stress exposure. These results demonstrate that in primates the CeA is a key brain region involved in the regulation of processes associated with wound healing. Because of brain and behavioral similarities between rhesus monkeys and humans, these results are particularly relevant to understanding brain mechanisms that influence healing in humans.
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1. Introduction

While adaptive, the stress response can also have deleterious effects (McEwen and Seeman, 1999). For example, studies in rodents and humans demonstrate that psychological stress significantly delays wound healing (Glaser et al., 1999; Marucha et al., 1998; Sheridan et al., 2004). In part, this effect is thought to be mediated by activation of the hypothalamic–pituitary–adrenal (HPA) axis. Studies in rodents and humans implicate corticosterone or cortisol in this process, as it has been shown that activation of the HPA axis in response to psychological stress can significantly delay wound healing (Kiecolt-Glaser et al., 1995; Marucha et al., 1998; Padgett et al., 1998) and suppress the function of important parameters of the immune system (Padgett et al., 1998). To understand the brain mechanisms that mediate the effects of stress on wound healing, we studied rhesus monkeys with bilateral lesions of the central nucleus of the amygdala (CeA). We used rhesus monkeys because they are similar to humans in brain structure and

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social behavior and therefore are an excellent model for exploring basic mechanisms underlying human fear, anxiety, and stress (Kalin and Shelton, 2003).

We hypothesized involvement of the amygdala in mediating the effects of stress on wound healing since numerous studies in rats, monkeys, and humans demonstrate the importance of the amygdala in mediating the stress response as well as associated fear and anxiety (Kalin et al., 2004; Phelps and LeDoux, 2005). The amygdala is a complex structure that consists of numerous nuclei, including the lateral and central nucleus. In processing responses to fear-related stimuli, the lateral nucleus of the amygdala receives information from other brain regions which via intraamygdaloid connections is conveyed to the CeA (Amaral et al., 1992; LeDoux, 1998). Through direct and indirect pathways, the CeA sends efferents to brain regions that mediate fear-related emotional, autonomic, and hormonal responses to psychological and physical stressors (Amaral et al., 1992). In prior work using site-specific neurotoxic lesions of the CeA in non-human primates we established the importance of the CeA in mediating trait-like anxiety and in the expression of fear-related behavioral and physiological responses, including HPA activation (Kalin et al., 2004). Therefore, in the present study, we used a subset of these animals to examine the role of CeA in mediating effects of stress on molecular changes associated with early wound healing. The effects of CeA lesions on HPA activity prior to this healing study were also assessed.

We focused our efforts on assessing the impact of the CeA lesions on the mRNA expression of two chemokines, interleukin [IL]-8 and macrophage inflammatory protein MIP-1α. Following tissue injury, these chemokines are expressed early in the inflammatory process (Holzheimer and Steinmetz, 2000; Werner and Grose, 2003), and are critical for the proper recruitment and activation of neutrophils and monocytes, respectively (DiPietro et al., 1998; Gillitzer and Goebeler, 2001; Godaly et al., 2001). MIP-1α highly correlates with macrophage numbers at the wound site (Werner and Grose, 2003), and IL-8 has been strongly associated with stress-mediated changes in wound tissue in humans (Glaser et al., 1999). Although pro-inflammatory cytokines (e.g., IL-1β, IL-6, and TNF-α) have been shown to be important in wound inflammation (for review see Werner and Grose, 2003), these two pro-inflammatory chemokines were focused upon as they are chemotactic to the main infiltrating immune cells in the early response following wounding and correlate highly with other inflammatory markers (e.g., IL-1β) (Glaser et al., 1999; Sato et al., 1999; unpublished observations in humans).

Since stress impairs healing processes, we predicted that stress would decrease the gene expression of the chemokines in wounded tissue and that this effect would be reduced in the CeA-lesioned animals. Based on earlier work, we also expected that the CeA-lesioned animals would exhibit decreased HPA activity (Kalin et al., 2004).

2. Materials and methods

2.1. Experimental subjects and lesioning procedure

The subjects were 24 male rhesus monkeys (*Macaca mulatta*; 2.9–5.6 years of age). Sixteen animals served as non-lesioned controls and eight animals received bilateral ibotenic acid lesions of the CeA. These animals are a subset of CeA-lesioned animals from which other behavioral and physiological data have been reported (Kalin et al., 2004). Animal housing and all experimental procedures were in accordance with institutional guidelines. Lesion procedures were performed aseptically under anesthesia by delivering from 2 to 10 1 μl injections of ibotenic acid (1 mg ibotenic acid hydrate/100 μl of phosphate buffered saline) bilaterally into the CeA. The stereotaxic coordinates for the injections were defined for each monkey from their individual MRI (Kalin et al., 2004). To assess the extent of CeA damage, as well as damage to adjacent regions, the lesioned animals were euthanized using methods consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. The brains were fixed, removed, and coronally sectioned for Nissl staining with thionine and glial staining with an antibody to glial fibrillary acidic protein (Kalin et al., 2004). In the eight animals, the amount of bilateral CeA damage ranged from 52 to 98% (mean = 71%) (see Table 1). The lesions were highly specific with some damage occurring in surrounding regions including the medial nucleus and dorsally in the basal forebrain areas (for more detail see Kalin et al., 2004). The animals were lesioned on average 18 months prior to this study. To understand the effects of the lesions on the HPA axis, cortisol and ACTH were assessed 16.9 months prior to this study on two occasions separated by one week. Blood was sampled without anesthesia between 08:15 and 09:15 h. Animals were then exposed to 30 min of confinement stress after which blood was immediately resampled.

2.2. Wound, biopsy, and stress procedures

All tissue samples were obtained while the animals were anesthetized with ketamine HCl (15 mg/kg IM.) On day 1, between 08:15 and 09:30 h, a full thickness dermal wound (3.5 mm in diameter) was placed on the left or right scapular area (counterbalanced among subjects) of each animal's back using a sterile tissue punch. This collected tissue represented unwounded skin. To evaluate the molecular changes occurring with early healing, 6 h post-wounding the animals were anesthetized with ketamine and the initial wound was biopsied. Since healing occurs at the wound margin, a 6.0-mm dermal biopsy was taken from the tissue surrounding the previously wounded skin that encompassed the site of the first 3.5 mm wound. Animals were allowed to recover from anesthesia for 2 h, and then were removed from their home cage and confined for 1 h in a transport cage. This procedure is stressful and results in marked activation of the HPA axis (Kalin and Shelton, 1984; Kalin et al., 2004). The same wounding and biopsy procedures were repeated on days 2 and 3, with the exception that on day 2 the new wound was placed in the midline of each animal's back, and on day 3 the new wound was placed in the scapular area contralateral to the day 1 wound site. Animals were again exposed to

Table 1
Percent of CeA destruction

% Destruction			
Subject	Left CeA	Right CeA	Total CeA
1	99	97	98
2	90	78	84
3	55	89	72
4	59	77	68
5	64	71	68
6	83	52	67
7	67	47	57
8	51	52	52
Mean ± SE	71.1 ± 6	70.4 ± 7	70.7 ± 5

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