A Rhesus Monkey Model of Self-Injury: Effects of Relocation Stress on Behavior and Neuroendocrine Function

Matthew D. Davenport, Corrine K. Lutz, Stefan Tiefenbacher, Melinda A. Novak, and Jerrold S. Meyer

Background: Self-injurious behavior (SIB), a disorder that afflicts many individuals within both clinical and nonclinical populations, has been linked to states of heightened stress and arousal. However, there are no published longitudinal data on the relationship between increases in stress and changes in the incidence of SIB. This study investigated the short- and long-term behavioral and neuroendocrine responses of SIB and control monkeys to the stress of relocation.

Methods: Twenty adult male rhesus macaques were exposed to the stress of relocation to a new housing arrangement in a newly constructed facility. Daytime behavior, sleep, and multiple measures of hypothalamic-pituitary-adrenocortical (HPA) axis function were investigated before and after the move.

Results: Relocation induced a complex pattern of short- and long-term effects in the animals. The SIB animals showed a long-lasting increase in self-biting behavior, as well as evidence of sleep disturbance. Both groups exhibited elevated cortisol levels in saliva, serum, and hair, and also an unexpected delayed increase in circulating concentrations of corticosteroid binding globulin (CBG).

Conclusions: Our results indicate that relocation is a significant stressor for rhesus macaques and that this stressor triggers an increase in self-biting behavior as well as sleep disturbance in monkeys previously identified as suffering from SIB. These findings suggest that life stresses may similarly exacerbate SIB in humans with this disorder. The HPA axis results underscore the potential role of CBG in regulating long-term neuroendocrine responses to major stressors.

Key Words: CBG, cortisol, HPA axis, monkey, relocation, self-injury, stress

Self-injurious behavior (SIB), which may be defined as any self-directed act that results in tissue damage (1), is a significant health problem within both the general population and several clinical disorders. SIB is expressed in various forms, including but not limited to cutting, burning, biting, hair pulling, skin picking, and head banging. Approximately 40% of humans with learning disabilities living in hospitals are reported to engage in SIB (2). It is also a common symptom of autism (3), posttraumatic stress disorder (PTSD; 4,5), borderline personality disorder (6), Tourette syndrome (7), and the genetic disorders Lesch-Nyhan syndrome (8) and Prader-Willi syndrome (9). However, SIB is not restricted to individuals suffering from psychiatric or genetic disorders, because approximately 4% of the general population engages in various forms of this behavioral pathology that typically involve cutting, scratching, or burning (10). The heterogeneity of SIB with respect to both the form of expression of the pathology and its incidence has made it difficult to develop effective treatment strategies (11).

Although the factors involved in the etiology and maintenance of SIB are not yet fully understood, episodes of self-injury often serve to reduce tension, anxiety, or other dysphoric states. This notion is supported by results from both self-report (12–16) and psychophysiological (17) studies. In addition, Philipsen and coworkers (18) recently found that clonidine treatment of female patients with borderline personality disorder who had previously exhibited SIB resulted in parallel decreases in "aversive inner tension" and in the urge to injure themselves.

Given the ability of different environmental or social stressors to provoke tension and anxiety, it seems likely that stress would increase the incidence or severity (or both) of self-injury, yet this hypothesis has thus far received scant attention in the literature apart from a few relevant findings. Thus, management of stress was reported as one of the reasons for engaging in self-injury by 77% of a clinical sample that had experienced earlier trauma (mainly in the form of sexual abuse) and that was currently undergoing treatment for PTSD or other psychiatric disorders (10). Furthermore, Symons *et al*. (19) found a significant positive correlation between salivary cortisol levels and SIB severity in a group of developmentally disabled adults, supporting a possible relationship between SIB and stress. Sachsse *et al*. (20) also reported a case study of a women suffering from borderline personality disorder whose nocturnal urinary cortisol excretion showed large increases during the period leading up to an episode of self-mutilation. Finally, several studies have demonstrated a greater incidence of sleep disturbances (suggestive of increased stress) in subjects exhibiting SIB than in control subjects (21–23).

One powerful approach to investigating the relationship between SIB and stress would be to conduct a longitudinal study of behavioral and physiological responses to a major imposed stressor in subjects suffering from SIB. There are major practical as well as ethical difficulties in carrying out such a study in human subjects; however, these limitations can be overcome using an experimental animal model. Our laboratory has an ongoing research program investigating one such model—namely, individually housed adult

From the Division of Behavioral Biology (MDD, MAN), New England Primate Research Center, Harvard Medical School, Southborough, Massachusetts; Behavioral Services (CKL), Southwest National Primate Research Center, San Antonio, Texas; Department of Psychology (MAN, JSM), University of Massachusetts, Amherst; and Esoterix Laboratory Services, Inc. (ST), Aurora, Colorado.

Address reprint requests to Jerrold S. Meyer, Ph.D., Tobin Hall, 135 Hicks Way, Dept. of Psychology, University of Massachusetts, Amherst, MA 01003. E-mail: jmeyer@psych.umass.edu.

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male rhesus macaques that spontaneously develop SIB. The behaviors seen in these animals range from hair pulling and head banging to severe self-biting, that occasionally results in self-wounding. Our model, which has been well characterized both behaviorally and physiologically (24,25), has a number of advantageous features, including a similar behavioral topology to human SIB, a prevalence rate of 5%–13% (26) that is similar to that in some clinical populations (27), and the fact that, unlike most rodent models of SIB, the pathology arises spontaneously without the need for pharmacological manipulations. As discussed in Tiefenbacher *et al.* (25), we propose that our nonhuman primate model most closely resembles the impulsive SIB category of Simeon and Favazza (28).

In this study, we took advantage of an administratively mandated relocation of our subject cohort to new cages in a newly constructed building and with unfamiliar animals present within each colony room. Previous studies have demonstrated that relocation leads to behavioral and physiological alterations in elderly human subjects (29,30) and a cortisol response in nonhuman primates (31). Therefore, we anticipated that the move would constitute a significant and possibly prolonged stressor in our animals. The aims of this study were to determine both the short- and long-term behavioral responses of SIB and control monkeys to the relocation and to assess concomitant hypothalamic-pituitary-adrenocortical (HPA) axis reactivity through cortisol measurements in multiple sample matrices (plasma, saliva, and hair) along with measurement of circulating corticosteroid-binding globulin (CBG). We predicted that both groups would exhibit behavioral and endocrine signs of stress but that the SIB animals in particular would respond with an increased incidence of self-biting behavior.

Methods and Materials

Subjects

The subjects were 20 adult male rhesus monkeys (*Macaca mulatta*) ranging in age from 8 to 22 years (SIB mean = 13.4; control mean = 15.4) and maintained at the New England Primate Research Center (NEPRC). Thirteen monkeys had wounded themselves at least once with sufficient severity to require veterinary treatment (SIB group), whereas the remaining seven animals constituted a control group that had never self-wounded. Monkeys were socially reared either with their mother (eight SIB, three controls) or in the NEPRC nursery (five SIB, four control animals). See Supplement 1 (Methods and Materials) for additional information on housing of the monkeys before and after relocation. All animal procedures were approved by the Harvard Medical Area Standing Committee on Animals and were in accordance with the National Research Council Guide for the Care and Use of Laboratory Animals.

Behavioral Testing

The effects of relocation on behavior of the SIB and control monkeys was assessed using a modified frequency sampling procedure (32) in which the presence or absence of 32 categories of behavior was recorded in 15-sec intervals for a 5-min sampling period. The behaviors deemed of greatest interest for the study included self-bite, stereotypy (which includes a variety of repetitive behaviors such as self-grasp, eye poke, digit suck, hair pull, bounce, rock, body flip, and pace), eating, yawning, cage shaking, rump present (an affiliative or submissive behavior), exploration, and foraging (see Supplement 1, Methods and Materials, for additional information on the testing schedule, and Supplement 2 for a list of all behavioral categories and their definitions). Reliability between observers was calculated over all categories by percent agreement scores and averaged over 90%.

In humans, stress is known to induce disturbances in sleep (33,34). Consequently, we monitored nighttime activity of the animals during the period from 9 PM to 3:00 AM by means of a camcorder with low-light capability (Sony Handycam DCR-DVD 200). Each animal was videotaped twice, once before relocation and a second time from 8 to 27 weeks (mean ≈ 20 weeks for the SIB group; ≈ 19 weeks for controls) following the move. Videotapes were later scored for awake versus sleep state by two observers using a 1-min point sampling procedure (32). Sleep behavior was scored using a scale of 0–2 as follows: 0 = *animal was in a posture typically associated with sleep* (i.e., sitting with a hunched over posture or laying down, eyes are closed if visible to the observer); 1 = *animal was awake but resting* (i.e., eyes open, visually exploring, scratching, yawning, or adjusting body position); 2 = *animal was awake and exhibiting whole-body movements such as locomotion.* Reliability between observers was calculated by percent agreement scores and averaged over 92%. We also calculated Cohen's kappa scores for a randomly selected subset (20%) of the videotapes, and these scores ranged from .847 to .966 (mean = .914).

Sampling Procedures

Blood. Blood samples were collected approximately 2 months before relocation (baseline), 7 days following the relocation (postmove), and again 1 year later to determine recovery from the stress of the move. Samples obtained well before the move were used for baseline purposes because preparation for this event caused some disturbance within the colony and could therefore have artificially elevated the circulating cortisol levels in our animals. See Supplement 1 (Methods and Materials) for additional information on blood, saliva, and hair sampling procedures.

Saliva. Samples were obtained from 16 monkeys (11 SIB, 5 control) that had previously been trained for saliva collection using the "pole" method (35). Four samples were obtained from each animal during the week immediately before relocation. Eight samples were subsequently collected over 2 weeks following relocation (beginning 2 days postmove).

Hair. Our laboratory has recently developed and validated a procedure for measuring hair cortisol as a unique tool for assessing long-term changes in HPA system activity. Hair cortisol data obtained during the study were included in the article describing that method (36) to demonstrate that a significant, prolonged stressor does in fact elevate cortisol content of the hair. However, we reproduce the hair results again here for the important purpose of comparing them with plasma and salivary cortisol levels obtained in the same animals. To obtain baseline levels of hair cortisol before the move, the animals were shaved twice: the first shaving was performed 3 months before relocation (those samples were discarded) to define the beginning of the sampling period, and the second shaving was performed immediately before relocation to collect the hair that had grown during that 3-month period. The hair obtained at that time constituted the premove samples. Additional hair samples were then collected at 4 months (postmove) and 1 year (recovery) following relocation.

Biochemical Analyses

Serum cortisol and CBG concentrations were determined by radioimmunoassay (RIA). Salivary and hair cortisol were analyzed by enzyme immunoassay (EIA) according to published