

## THE PHYSIOLOGY AND NEUROCHEMISTRY OF SELF-INJURIOUS BEHAVIOR: A NONHUMAN PRIMATE MODEL

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### 1. ABSTRACT

Self-injurious behavior (SIB) is a serious behavioral condition that afflicts millions of individuals in the United States alone. The underlying factors contributing to the development of self-injury in people are poorly understood, and existing treatment strategies for this condition are limited. A low but persistent percentage of socially reared individually housed rhesus monkeys also spontaneously develop SIB. Data obtained from colony records suggest that the risk of developing SIB in socially reared rhesus monkeys is heightened by adverse early experience and subsequent stress exposure. The present review summarizes the physiological and neurochemical findings obtained in this nonhuman primate model of SIB, focusing on monoamine neurotransmitters, neuropeptides, and neuroendocrine systems. The results indicate that monkeys with SIB exhibit long-lasting disturbances in central and peripheral opioid and stress response systems, which lead to increased levels of anxiety. Based on these findings, we propose an integrated developmental-neurochemical hypothesis in which SIB arises from adverse life events in a subset of vulnerable monkeys, is maintained by a persisting dysregulation of several neurochemical and physiological systems, and functions to periodically reduce anxiety when the levels of anxiety become excessive. Implications of this hypothesis for understanding self-injury in patients with borderline personality disorder and members of the general population are discussed.

### 2. INTRODUCTION

Self-injurious behavior (SIB), the deliberate harm of one's own body without suicidal intent (1), presents a serious behavioral condition that afflicts millions of individuals in the United States alone. Self-injurious behavior is associated with a variety of disorders, including developmental (e.g., mental retardation, autism) (2), neurological (e.g., Tourette's syndrome, frontal lobe epilepsy) (3-5), psychiatric (e.g., personality disorders,

eating disorders, schizophrenia etc.) (6-10) and genetic (e.g., Lesch-Nyhan syndrome, Prader-Willi syndrome, Cornelia de Lange syndrome etc.) (11-14) disorders and has been described with increasing prevalence in the general population (15-17). Depending on the population examined, prevalence rates and forms of SIB can vary greatly (11; 12; 18). For example, whereas self-cutting and burning are generally found in non-clinical and clinical (i.e. borderline personality disorder) populations, head-banging and self-biting are the most common forms observed in developmental disorders (11; 18).

Several hypotheses have been formulated as to why people engage in self-destructive and self-injurious behavior. These hypotheses arise from different theoretical orientations, ranging from behavioral (e.g., negative and positive reinforcement hypothesis, self-stimulation hypothesis) (19; 20) and psychodynamic (e.g., anxiety or hostility reduction) (21-23) to organic (e.g. serotonergic, dopaminergic and opioidergic hypotheses) (24-29). Given the heterogeneity of conditions and disorders associated with SIB in humans, it is likely that self-injury has more than one etiology and does not simply represent a single entity or syndrome (30; 31). Indeed, the heterogeneity of SIB has contributed to the difficulty in finding effective treatment paradigms for this disorder (32-34).

The expression of SIB is not limited only to human populations. Spontaneously occurring SIB has also been described in many nonhuman primates, including the great apes, Old World monkeys, New World monkeys, and prosimians (35-39). However, with the exception of self-injury in macaques, existing reports in nonhuman primates are sparse and largely limited to descriptive studies of zoo populations (37-39). SIB in macaques has been more extensively investigated, but previous approaches have mostly been limited to models in which the syndrome is induced experimentally through some type of social

## **A Primate Model of Self-Injurious Behavior**

isolation after birth (40-43), brain lesions (28; 44; 45), and/or pharmacological stimulation (41; 43; 44; 46). There is a clear need for the exploration and development of novel animal models for SIB to provide a better understanding of the underlying etiologies and associated pathophysiologies of this multifaceted syndrome, as well as for the testing of potentially useful pharmacotherapies.

One such novel animal model is the spontaneous development of SIB in socially reared, individually housed macaque monkeys (35; 47). Because it does not rely on early social isolation or on surgical or pharmacologic manipulations for its expression, this model of SIB is more likely than previous models to share some of the same etiologic and pathophysiological factors that contribute to the development of self-injury in people. As an added benefit, there is a wealth of knowledge about the genetic and physiological characteristics of macaques, and the similarity of these characteristics to those of humans. For example, macaques and humans share between 90 and 94 percent of their genetic makeup (48) and also have nearly identical endocrine and neurophysiological systems. For these reasons, macaques have long been among the most frequently used species in the field of biomedical research (49). In addition, macaques exhibit complex social hierarchies and are responsive to adverse social and environmental experiences (50-58), making them highly suitable for studying environmental and physiological factors contributing to the etiology of psychiatric disorders in humans.

### **3. THE PRIMATE MODEL**

#### **3.1. Self-Injurious Behavior in Macaques**

A low but persistent percentage of individually housed macaques spontaneously develop SIB at some point in their lives. In rhesus monkeys, this pathology usually takes the form of self-directed biting that on occasion can result in severe tissue damage and mutilation (35; 47). Lifetime prevalence rates for SIB in individually housed macaques have been estimated between 5 and 28 percent (35; 59). For example, at the New England Primate Research Center (NEPRC) approximately 11 percent of the individually housed rhesus monkeys carry a veterinary record of one or more episodes of self-inflicted wounding (59). An additional 16 percent of the individually housed monkeys engage in extensive self-directed biting in the absence of any self-inflicted wounding requiring veterinary attention (59). Presently it is still unclear whether biters that carry a veterinary record of self-inflicted wounding and those without such a record represent two separate populations, or whether self-biting serves as a precursor for the subsequent development of wounding (47). Long-term longitudinal studies are needed to answer this question. Although SIB in captive rhesus monkeys can take several forms, including excessive hair-pulling and head-banging, self-directed biting is the most prevalent form by which wounding occurs (47; 60). Monkeys with a veterinary record of self-inflicted wounding differ significantly in their behavioral profile from monkeys without a wounding history (47). As expected, wounders show significantly higher levels of self-directed biting, appear to be more

reactive to ongoing everyday events, as represented by higher baseline levels of vocalization and outward directed aggression (i.e. threat), and show less affiliative behavior (i.e. submissive behavior) (47; 61).

Analyses of colony and veterinary records at three major primate research centers identified several risk factors for the development of SIB in macaques (36; 47; 59; 62). For self-inflicted wounding, several of these risk factors are related to individual cage housing. Thus, age of first individual caging (47; 59; 62), the proportion of the first 48 months of life spent in individual cage housing (36), and the total duration of individual cage housing (59; 62) have been found to significantly predict the development of a veterinary record of self-inflicted wounding later in life. In general, wounders are individually housed significantly earlier than non-wounders (47; 59; 62), have spent a greater proportion of their first 48 months in an individual cage (36), and overall have spent more years in individual cage housing (59; 62). The number of minor veterinary procedures experienced was also found to predict the presence of a veterinary record of self-inflicted wounding. In this case, wounders tend to have experienced a significantly greater number of minor veterinary procedures such as blood draws compared to non-wounders (59). Interestingly, males appear to be more likely to develop SIB than females (35; 59). With a few exceptions, the same factors also significantly predict the development of self-directed biting in the absence of self-inflicted wounding (59). Thus, current data suggest that early rearing history (i.e. age and duration of social separation) and adverse lifetime experiences (i.e. number of veterinary procedures) play a significant role in the development of SIB in individually housed macaques.

As in the case of humans, SIB in macaques has proven difficult to manage. Simple behavioral manipulations such as introduction of enrichment devices have mainly been ineffective in altering the incidence of SIB (63-65). In contrast, several studies have reported reductions in self-biting and/or self-wounding following various pharmacologic interventions (66-68). Another approach has been to attempt socialization of individually housed male monkeys with females (69). Although these latter studies have achieved varying degrees of short-term success in reducing SIB, none was carried out long enough to determine whether the behavioral pathology was permanently eliminated.

#### **3.2. Neurochemical and Physiological Correlates of SIB**

Several biological systems have been implicated in the expression and maintenance of SIB in people, including the central monoamine and endocrine systems (70; 71). More specifically, dysregulations in central serotonergic (5-HT) (26; 27) and/or dopaminergic (DA) (24; 28; 72; 73) neurotransmission, as well as in central and peripheral opioid systems (27; 74; 75) have been proposed to play a role in the expression of SIB. The following section will review existing neurochemical and physiological findings in socially reared nonhuman primates with SIB and discuss them in the context of organic hypotheses that have been proposed for self-injury

in people. In addition, where appropriate, alternative hypotheses will be proposed that warrant further investigation in both pre-clinical and clinical populations.

### 3.2.1. Role of Serotonin and Dopamine

Several studies have suggested that reduced brain 5-HT system function may be linked to the expression of SIB (8; 70; 71; 76). The evidence supporting this hypothesis is limited and based primarily on clinical findings in patients with personality disorder demonstrating attenuated prolactin and/or cortisol responses to pharmacological challenge with d-fenfluramine (a 5-HT releaser and reuptake inhibitor) (26; 77) or meta-chlorophenylpiperazine (m-CPP) (a 5-HT<sub>2</sub> receptor agonist) (78). Additional support can also be derived from the success of serotonin reuptake inhibitors (SSRIs) in reducing SIB in a subset of individuals with borderline personality disorder (79-81).

Altered 5-HT system function has recently also been implicated in the expression of SIB in rhesus monkeys (68). Treatment with the 5-HT precursor l-tryptophan resulted in significant reductions in rates of self-directed biting in seven rhesus monkeys with a history of self-inflicted wounding (68). These findings raise the possibility that high levels of self-biting in monkeys could be due to a deficiency in serotonergic transmission. To examine whether altered 5-HT system function plays a role in the expression of SIB in our primate model of spontaneously developing SIB in socially reared monkeys, basal CSF levels of 5-HIAA were assessed on two separate occasions in 1995 and 1997 (82). Monkeys with a wounding record did not differ in their basal CSF 5-HIAA levels from animals without such a record, nor were these levels correlated with rates of self-directed biting (82). A subsequent study in which these animals were challenged with the 5-HT releasing agent d,l-fenfluramine likewise failed to reveal a relationship between 5-HT system activity and either wounding or self-directed biting, although an inverse relationship between prolactin responses to FEN and aggression was found (83). Taken together, these findings provide no evidence for altered 5-HT system function in our primate model of SIB. However, we cannot rule out the possibility of a subtle abnormality in serotonergic function in our animals that is not revealed by measurement of basal CSF 5-HIAA levels or by endocrine responses to fenfluramine challenge. Alternatively, findings of low serotonergic activity in individuals with personality disorder and SIB may be more closely related to behavioral traits of aggressive and impulsive behavior. Such traits have been linked to reduced 5-HT system function (84-88) and are commonly found in personality disorder (89). Future studies examining 5-HT system activity in individuals with SIB independent of aggression and impulsive behavior are needed to shed some light on this question.

Altered DA system function has also been associated with SIB in certain subgroups of people with this disorder. In particular, reductions in basal ganglia DA have been proposed to play a role in the expression of SIB and stereotypy in individuals with developmental disorders

and Lesch-Nyhan disease (90). Such reductions could, in turn, lead to supersensitivity of postsynaptic DA receptors. There are several rodent and primate models that implicate sensitization of postsynaptic D<sub>1</sub>, and possibly also D<sub>2</sub>, receptors in the development of SIB (24; 28; 44; 46; 72; 73; 91-95). Interestingly, however, the efficacy of DA antagonists (i.e. neuroleptics) to reduce SIB in individuals with developmental disorders has been inconsistent and marginal at best (96-98). We examined basal activity of the DA system in our primate model by measuring morning CSF levels of homovanillic acid (HVA), the major metabolite of DA. No differences were found between monkeys with and without a veterinary history of self-wounding (82). Furthermore, the levels of HVA were unrelated to rates of self-directed biting (82). However, the lack of differences in basal HVA levels between groups does not preclude the possibility of group differences in DA levels in localized areas of the brain that are not evident using CSF measurements, or functional changes in DA activity (e.g., changes in postsynaptic receptor fields such as D<sub>1</sub> receptor sensitization). Behavioral and physiological responses to an acute DA agonist challenge (e.g. apomorphine or amphetamine) should be examined. Thus, presently we cannot rule out a role for DA receptor sensitization in self-biting or self-wounding in our animals.

To summarize, studies performed to date have demonstrated that the incidence of self-directed biting and SIB in monkeys may be influenced by manipulations of serotonergic or dopaminergic activity. Nevertheless, there is presently no evidence for a role of these systems in spontaneously developing SIB. Additional pharmacologic challenge studies, imaging of central 5-HT and DA receptors, and other approaches are needed in order to resolve this apparent discrepancy.

### 3.2.2. Role of Peripheral and Central Opioids

Endogenous opioids have been implicated in the expression of SIB in several developmental and psychiatric disorders, including mental retardation, autism, and borderline personality disorder (27; 75; 89; 99; 100). Evidence for such a role is based on (1) the partial success of opioid antagonist treatment to ameliorate SIB (101; 102), (2) reports of altered pain sensitivity during episodes of SIB (103-105), and (3) findings of altered endogenous opioid levels in individuals with SIB (106-109). There are two principal opioid hypotheses, both of which have been extensively reviewed elsewhere (27; 70; 71; 99; 110). In the opioid self-administration hypothesis (sometimes also referred to as the addiction hypothesis), individuals with SIB are thought to be addicted to their own endogenous opioids and to engage in SIB in order to release or self-administer opioids (29; 110). In this hypothesis, reductions in SIB following opioid antagonist treatment are thought to be mediated by blocking the opioid mediated euphoria that is commonly described by individuals following SIB (111; 112). In the second hypothesis, the pain hypothesis (25; 113; 114), increased basal opioid activity is proposed to underlie the expression of SIB. More specifically, elevated endogenous opioid activity is suggested to increase the pain threshold (i.e. hypoalgesia) (25), consequently, individuals are thought to feel no pain during SIB and possibly engage

in the behavior as a form of self-stimulation (110). This hypothesis is supported by reports of elevated levels of central and/or peripheral opioids (74; 108; 115; 116), as well as demonstrations of elevated pain thresholds in individuals with SIB (103-105; 117). Here, opioid antagonist treatment is proposed to be effective by reinstating the pain associated with SIB and therefore making the behavior more aversive (118; 119).

We have likewise found evidence consistent with a role for endogenous opioids in the expression of SIB in monkeys (120). We demonstrated that rhesus monkeys with SIB preferentially direct their self-biting activity toward body areas that can be associated with acupuncture/acupressure analgesia (120). A similar relationship has previously been demonstrated for people with SIB (121). Acupuncture/acupressure-induced analgesia in humans is thought to be at least partly mediated by the release of endogenous opioids (122), particularly met-enkephalin (123; 124). Monkeys also show acupuncture-induced analgesia (125-127) that can be reversed with opioid antagonist treatment (128). Together, these findings raise the possibility that in some monkeys, self-directed biting might serve to release and self-administer endogenous opioids. When we examined basal opioid activity in the periphery and CNS in our primate model, monkeys with a veterinary record of self-inflicted wounding showed significantly reduced levels of beta-endorphin-like immunoreactivity (IR) in blood plasma (129), and met-enkephalin-like IR in CSF (130). More importantly, the amount of CSF met-enkephalin-like IR was positively related to the percentage of bites directed toward body-sites that can be associated with acupuncture analgesia (determined as the number of bites directed towards acu-sites / total number of bites) (130). Neither plasma beta-endorphin, nor CSF met-enkephalin levels were related to the current rates of self-directed biting around the time of sampling (129; 130). Interestingly, we also found a positive association between plasma beta-endorphin and age at which the monkeys were first individually housed (129), suggesting that the reduced opioid activity observed in monkeys with SIB may be a result of this early rearing experience and thus precede the development of SIB. These findings of reduced opioid activity are consistent with published reports of reduced plasma levels of beta-endorphin in individuals with autism (109; 131) and borderline personality disorder (132). In accordance with the opioid self-administration hypothesis (29; 110), some monkeys with SIB may engage in self-directed biting to release endogenous opioids such as met-enkephalin or beta-endorphin. However, this idea must remain speculative until self-biting can be shown to enhance opioid release and until the effects of opioid antagonist treatment on this behavior have been evaluated.

### 3.2.3. Role of Peripheral and Central Stress Response Systems

Adverse early experience and lifetime trauma have been linked to long-lasting changes in peripheral (i.e. hypothalamic-pituitary adrenal axis) and central (i.e. brain CRF) stress response systems in both monkeys (52; 133; 134) and humans (135; 136). Such experiences also seem

to be important risk factors in the development and expression of SIB in both groups (36; 59; 137-140). However, existing studies assessing alterations in peripheral and central stress response systems in people with SIB have been limited and often negative (106; 141; 142). One exception is a recent case report of a patient with borderline personality disorder by Sachsse *et al.* (2002). These investigators examined the relationship between episodes of SIB and fluctuations in levels of nocturnal urinary cortisol excretion and found significant increases in urinary cortisol directly preceding an episode of SIB, followed by an immediate return to baseline (143). These findings were interpreted to suggest a possible role for SIB in stress regulation. When we examined HPA axis function in our primate model, monkeys with a history of SIB showed a complex, yet persistent HPA dysregulation, that is characterized by a blunted plasma cortisol response to mild stress (82) and attenuations in both adrenocortical sensitivity and glucocorticoid negative feedback sensitivity (144). These changes in HPA axis function were related both to outcome measures (i.e. wounding) and to the expression of the pathology (i.e. frequency of self-directed biting). Presently, we do not know whether these alterations in HPA axis function are a result of adverse early rearing and therefore precede the development and expression of SIB, or are a consequence thereof. This question is particularly interesting in light of a recent hypothesis proposing a role for adrenocortical insufficiency in the genesis and expression of anorexia nervosa, a disorder in which some individuals also display SIB (145). Longitudinal studies examining HPA axis function in colony animals during development are needed to address this question.

In addition to stress, anxiety has been implicated in the expression of SIB in people (15; 23; 146). Several investigators have proposed a tension/anxiety reduction model in which SIB is thought to relieve the individual from escalating feelings of anxiety and tension. The resulting relief consequently functions as a reinforcer for the self-injurious act (21; 23). This hypothesis is supported by (1) findings of higher anxiety scores in non-clinical and clinical populations with SIB when compared to non-SIB controls (15; 23; 146), (2) studies describing anxiety and tension relief in individuals following an episode of SIB (147-149), and (3) psychophysiological findings in people directly implicating a role for SIB in tension reduction (148).

Behavioral and physiological findings in our primate model of SIB similarly support such a role for anxiety in the expression of SIB. Monkeys with a history of SIB show increased behavioral reactivity to normal everyday events (47), and during self-biting episodes, demonstrate distinct heartrate patterns that are consistent with a role for SIB in tension reduction (150). When we subsequently examined basal CSF levels of corticotropin releasing factor (CRF), a key anxiety-related neuropeptide (151), the levels in monkeys with SIB were found to significantly predict their current rates of self-directed biting (152). To our knowledge, this is the first direct evidence for a possible involvement of one of the major

anxiety-related neuropeptides in the expression of SIB. Additional support for a role of anxiety in the expression of SIB in socially reared monkeys comes from the initial results of drug treatment trials in colony animals at NEPRC that have been referred to the veterinarian because of severe self-inflicted wounding. Treatment with the benzodiazepine diazepam resulted in significant reductions in self-directed biting and the incidence of wounding (measured as the number of wounds per week) in half of the monkeys. To our surprise, however, the treatment actually increased the wounding incidence in the remainder of the animals (153). Examination of colony records indicated that the positive responders (animals that showed reduced SIB following treatment) had spent significantly more time housed individually and had experienced a greater number of minor veterinary procedures than the negative responders. Both of these variables have previously been shown to be risk factors for the development of SIB (59). These findings suggest the existence of at least two subpopulations of monkeys with SIB, one population in which SIB emerges as a consequence of certain lifetime experiences and is responsive to anxiolytic drug treatment, and another population in which SIB is related more strongly to other factors (e.g., genetics) and is nonresponsive to anxiolytic treatment. We hypothesize that SIB plays an important role in tension or stress reduction, particularly in the positive responders.

#### **4. AN INTEGRATED HYPOTHESIS OF SIB IN MACAQUES: IMPLICATIONS FOR UNDERSTANDING SELF-INJURY IN HUMANS**

There is a long history of using animal models to study human psychopathological disorders. Such models have been particularly valuable in the development of new pharmacotherapies for depression, anxiety disorders, and schizophrenia. Unfortunately, previous animal models of SIB have thus far been less successful in identifying new areas for potential drug development.

We have argued that self-injurious behavior in socially reared, individually housed rhesus monkeys is a promising model for studying the underlying etiology and pathophysiology of self-injury in humans. The syndrome in monkeys shows a number of similarities with SIB found in the general population and in individuals with borderline personality disorder. Such similarities include a history of adverse early and lifetime experience (36; 59; 137-140), an involvement of anxiety in the expression of SIB (15; 23; 47; 146; 152), and a role for SIB in reducing tension and anxiety (21; 23; 47; 130; 150). To our knowledge this is the first animal model of self-injury that does not rely on specific experimental (i.e. pharmacological and/or surgical) manipulations to induce the syndrome. Rather, SIB in these monkeys develops spontaneously as a result of a complex mixture and interaction of extrinsic (e.g. onset and duration of individual cage housing) and intrinsic (e.g. anxious endophenotype) factors, making this model especially relevant for the understanding of the physiological and neurochemical processes underlying the development and expression of self-injury in humans.

Our results suggest that dysregulations in both central and peripheral opioid and stress response systems are involved in the expression of SIB in our subjects. These physiological findings are consistent with several of the hypotheses that have been proposed for self-injury in humans, including the neurochemical self-administration hypothesis (29), the opioid addiction hypothesis (110), and the anxiety and tension reduction hypothesis (21; 23). However, none of these hypotheses alone is sufficient to explain the overall pattern of results we have obtained. Consequently, we propose an integrated developmental-neurochemical hypothesis to account for the onset and maintenance of SIB in socially reared monkeys. Specifically we propose that adverse early experience (e.g., early social separation) followed by later repeated stressful events (e.g., veterinary procedures) can result in lasting alterations in neuropeptide and neuroendocrine systems associated with the regulation of stress and anxiety. Dysregulation of these systems contributes to periodic episodes of heightened anxiety which lead to self-directed biting and occasional wounding. Self-directed biting, in turn, would serve to counteract these feelings of anxiety by eliciting euphoria associated with the release of endogenous opioids. This hypothesis is not only consistent with the results obtained in our primate model, it is also supported by existing opioid findings in humans demonstrating (1) a role for endogenous opioid activity in the perception of anxiety and tension (154), (2) reduced levels of endogenous opioids in individuals with borderline personality (132) and developmental (109; 131) disorders who exhibit SIB, and (3) increases in peripheral opioid but not HPA activity during episodes of SIB, which are predictive of a positive response to opioid antagonist treatment (106; 155). The proposed hypothesis provides testable predictions for both primate and human populations, and indeed studies are presently underway to examine more closely the role of opioid and stress response systems in the expression of SIB in monkeys.

The present primate model would be strengthened by additional behavioral evidence demonstrating increased behavioral reactivity and/or anxious behavior in monkeys with SIB. Unfortunately, existing tests for anxiety in individually housed nonhuman primates are limited, and the behavioral correlates of anxiety in monkeys are presently not well understood (156). Likewise, our current understanding of central monoamine system function in the expression of SIB in this primate model is incomplete. The elucidation of polymorphic variants in monoamine-related genes and their potential contribution to SIB may prove useful in this regard. This is particularly important as it pertains to the 5-HT system given its important role in the regulation of anxiety and aggression in humans (157). Further research is needed to answer these questions. Moreover, parallel studies on other sample populations, including ones that also contain individually housed female monkeys, would be valuable in determining the generality of the findings obtained on the monkeys that we have studied at NEPRC.

Despite these limitations, SIB in socially reared monkeys shows great promise for understanding the

underlying pathophysiology of self-injury in the general population and in individuals with borderline personality disorder. It is hoped that such information will lead to the identification of new drug targets and eventually to the development of more effective pharmacotherapies for this destructive syndrome.

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