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THE ROLE OF PROOPIOMELANOCORTIN (POMC) IN SEQUENTIALLY DEPENDENT SELF-INJURIOUS BEHAVIOR^a

Curt A Sandman^{1,2}, Paul E Touchette², Sarah D Marion³, and Aleksandra Chiczy-DeMet¹

¹Department of Psychiatry and Human Behavior, University of California, Irvine

²Department of Pediatrics, University of California, Irvine

³Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles

Abstract

Self-injuring behavior (SIB) is a life-threatening behavior exhibited by many species, including humans, and has no known cause and no agreed upon treatment. The role of the stress axis in the maintenance of this mysterious behavior was examined in subjects with life-long SIB. Over a six-year period, forty hours of direct observations of behavior and the environment were recorded on palmtop computers while 36 residential subjects (28 target and 8 control subjects) conducted their daily activities. Blood samples were collected in morning and evening for all subjects and within minutes after a self-injuring act in 28 target subjects who exhibited SIB to determine levels of ACTH and B-endorphin (BE). Self-injuring events in the patient group were significantly sequentially dependent (i.e. the only predictor of a self-injuring act was an antecedent self-injuring act). Higher morning levels of BE relative to ACTH predicted [$r_{df=27}=0.57$, $p<.001$] the sequentially dependent pattern of SIB. This effect was validated in a subgroup re-tested several months later [$r_{df=22}=0.60$, $p<.001$]. A subgroup of seven subjects exhibiting sequentially dependent patterns were administered an opiate blocker (naltrexone) in a double-blind, crossover design with an additional 14 hours/week of observation for seven weeks. Naltrexone challenge interrupted the sequential pattern (improved behavior) in subjects with elevated BE immediately following SIB ($r=0.85$, $p<0.01$). The pattern of results supported the conclusion that the stress axis played a significant role in the maintenance of complex episodes of self-injury.

Keywords

Stress; ACTH; B-endorphin; Self-injuring behavior (SIB); Opiates; Naltrexone

INTRODUCTION

Intentional acts of harm to self, evident in many species, have no known cause and no agreed upon treatment. Studies of self-injury have proliferated in the past few years (over 1000 studies between 2002-2007; Medline, January, 2008), however the origin and maintenance of this behavior continue to perplex investigators. Non-suicidal self injury is associated with numerous clinical manifestations, including genetic and chronic pain syndromes, neurological, psychological and personality disorders. Self-injurious behavior (SIB) is especially prevalent among individuals with developmental disorders, including autism, with estimates of approximately thirty percent. Even higher rates are observed in

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Corresponding author: Curt Sandman, Department of Psychiatry, 2501 Harbor Blvd, Costa Mesa, California 92626, Voice 714-957-5435, FAX 714-957-5354, casandma@uci.edu.

institutionalized individuals (Green, 1967; MacKay, McDonald, & Morrissey, 1974; Sandman & Barron, 1992; Schroeder, Rojahn, & Mulick, 1978).

This dramatic behavior often is repetitious, consisting of hourly, daily, weekly, monthly or even yearly cycles (Fisher, Piazza, & Roane, 2002). Some individuals who repeatedly injure themselves appear immune to the normal experience of pain (Sandman & Hetrick, 1995). They employ an assortment of self-harmful methods that include cutting, hitting or biting themselves, hurling themselves to the ground and banging their head against solid objects resulting in broken bones, disfigurement, blindness and even loss of life (Claes & Vandereycken, 2007; Sandman, Spence, & Smith, 1999; Thompson, Hackenberg, Cerutti, Baker, & Axtell, 1994).

Expression of SIB typically develops early in life and in many cases persists over many years into later stages of adulthood, with little change in frequency or quality, despite a panoply of behavioral and medical interventions (Emerson et al., 2001). SIB is not limited to human beings. It also is evident in a range of animals from rodents (Breese, Criswell, Duncan, & Mueller, 1990; Breese et al., 2005) to non-human primates (Tiefenbacher, Novak, Jorgensen, & Meyer, 2000; Shishido, Watanabe, Kato, Horikoshi, & Niwa, 2000; Crockett, Sackett, Sandman, Chicz-DeMet, & Bentson, 2007).

Although the cause is unknown, contemporary studies suggest that a biological imbalance or defect is associated with SIB (Sandman et al., 1999; Sandman et al., 1995; Thompson et al., 1994; Chamberlain & Herman, 1990; Gillberg, 1995; Cazzullo, Musetti, Musetti, Bajo, Sacerdote, & Panerai, 1999; Lewis, Bodfish, Powell, Parker, & Golden, 1996). Evidence from several laboratories indicates that the processing and release of a stress-related molecule (proopiomelanocortin, POMC) in the hypothalamic-pituitary-adrenal (HPA) axis may be perturbed among subgroups of individuals exhibiting SIB (Sandman et al., 1999; Sandman et al., 1995; Gillberg, 1995; Bouvard et al., 1995; Ernst et al., 1993; Leboyer et al., 1994; Leboyer et al., 1999; Sandman, Barron, Chicz-DeMet, & DeMet, 1990a; Sandman, Barron, DeMet, Chicz-DeMet, & Rothenburg, 1990b; Sandman, Hetrick, Taylor, & Chicz-DeMet, 1997). Disregulation of the HPA stress axis also has been reported in Rhesus monkeys predisposed to SIB. Monkeys with high rates of SIB have elevated levels of BE fragments but not co-released ACTH (Crockett et al., 2007) and they exhibit blunted plasma HPA responses to mild stress (Novak, 2003; Tiefenbacher et al., 2000). Drugs that block aspects of POMC (i.e. opiate) activity reduce SIB and may improve other symptoms commonly observed among autistic individuals (Cazzullo et al., 1999; Sandman et al., 1997; Crews, Rhodes, Bonaventura, Rowe, & Goering, 1999; Willemsen-Swinkels, Buitelaar, van Berchelaer-Onnes, & van Engeland, 1999; White & Schultz, 2000).

Recently we reported unique sequential dependencies among behavioral and environmental events in a large sample of institutionalized individuals exhibiting SIB (Kroeker, Touchette, Engleman, & Sandman, 2004; Marion, Touchette, & Sandman, 2003). In these studies, self-injury was predicted only by its own recent history and not social or environmental contingencies in a large majority of the subjects. Similarly, recent findings in two to four year-old children who were observed over two-years with monthly functional analysis probes, indicated that for eleven of twelve subjects, SIB was not maintained by environmental or social consequences (Richman & Quigg, 2004). These findings supported the possibility that for a majority of adults, and perhaps very young children, SIB was *maintained* by internal or biological motives.

The purpose of this study was to determine if there were relations between patterns of sequentially dependent behavior and specific biological markers previously linked to SIB.

METHODS

Participants

The method of subject consent and the protocol were approved both by Institutional Review Boards of the University of California, Irvine (UCI Institutional Review Board) and by the State of California (Committee for the Protection of Human Subjects). Thirty-six subjects who resided in a facility for developmentally delayed individuals were consented for this study that involved observation of behavior and collection of plasma. Of these 36 subjects, 28 had a history of SIB and exhibited at least five incidents of self-injurious behavior during the period of observation. A group of eight subjects who did not have a history of SIB and did not exhibit SIB during the observation period comprised a control sample for whom the blood collection accompanied standard medical care. These two groups did not differ in the distribution of sex or age. All participants were over 16 years of age (mean age of 42.7 years), and none had a diagnosed medical condition that could have been responsible either for their maladaptive behavior or neuroendocrine dysregulation. The sample consisted of 17 males and 19 females. All individuals in this study who exhibited SIB, previously had been exposed to repeated behavioral and pharmacological interventions (*excluding* opiate blockers) with either limited or no success.

A subgroup of twenty-three subjects was re-tested 6-9 months later to provide a metric of stability. A secondary validation was performed by re-analysis of a second subgroup of seventeen subjects who were identified independently by clinical staff as requiring special interventions to control their severe self-injury. It is generally accepted that the development of behavioral plans to control SIB is evidence that behavior is especially severe. Thus, this subgroup provides an index of the relation between POMC and SIB in a subgroup of subjects who exhibit behavior that constitutes great danger to self. Finally, seven individuals in this last subgroup who exhibited temporally dependent SIB patterns were challenged with doses of an opioid blocker.

Procedures

Individual participants were observed in their residential environment with minimal intrusion, by research staff throughout their regular daily routines. Forty hours of data were collected in five hour epochs each day from 9:30am to 12:00pm and 1:00pm to 3:30pm for each subject in a contiguous two week period. Twenty categories of events were recorded for each subject with a palm-top, computer-assisted, observational system (Sandman, Touchette, Ly, Marion, & Bruinsma, 2000) that recorded the time each behavioral and environmental event occurred (e.g. SIB, agitation, staff behavior, etc; Sandman et al., 2000; Marion et al., 2003). Observation of a large number of self-injurious individuals with varying behavioral topographies required a coding strategy we have developed that included a broad selection of the most salient behavioral features that were observed in the field (Marion et al., 2003; Sandman, Touchette, Marion, Lenjavi, & Chic-DeMet, 2002). Self-injury was comprised of the following manifestations: hits self with open hand or fist (62% of the total number of SIB events), bites self (8%), bangs head with or against an object (16%), any other self-inflicted harmful behavior (e.g., picking lesions; 14%). As described elsewhere (Marion et al., 2003) staff interactions, peer interactions, stereotypy, staff proximity, agitation and restraint were clearly defined and recorded as discrete events. Patterns of self-injury (topography, periodicity, frequency) were determined for each subject.

Inter-rater reliability during data collection was established by comparing complete records of two independent observers simultaneously recording the behavior of 28 separate individuals during 117, 20-minute sessions. Inter-observer agreement was calculated across

4,680, 30-second intervals for each behavioral category (93,600 intervals $\times$ events/behaviors). Pearson product moment correlations between observer records were highly statistically significant for all categories of recorded events (r 's .83-.97).

Conditional probability was calculated to analyze the dependencies between two-event sequences by quantifying the extent to which one behavior (the first) was temporally related to a second behavior/event. (As presented in Figure 1, we also examined following events but our primary interest was in antecedents). Based on our previous report (Marion et al, 2003) the 30s lag interval was selected because it was the most representative of the behavior of interest (i.e. was the interval that correlated most highly with several other intervals tested). For all events recorded, co-occurrences (pairs of events) within 30 second intervals were determined. A count was made for any event (eg. staff interaction, peer proximity, stereotypy, SIB, etc) that occurred before (antecedent to) the target (e.g. SIB) within the 30s interval. Only one class of *paired events* was counted within the 30s interval minimizing the influence of rapid "bouts" of contingent events. Conditional probabilities were calculated from contingency tables for all possible pairs of events by dividing the number of two-event sequences of a target and antecedents by the total number of sequences (i.e., opportunities for occurrence). $[(E_{(c \text{ to } m)} / \text{Sum } E_{(c \text{ to all } m)}) \times 100]$, where $E_{(c \text{ to } m)}$ represented the total number of sequences between a target event (c) and an antecedent (m) event, and $\text{Sum } E_{(c \text{ to } m)}$ represented the total number of pairings between the target and all possible antecedent events.] The binomial z-score corrected chance associations between oversampled events (Bakeman & Gottman, 1997, p. 109, Formula 7.2). A positive z score indicated that the observed number of co-occurrences of two events (reflected in the conditional probability) was greater than expected. Conversely, a negative score indicated the co-occurrences of two events was less than expected.

Biological Measures

Blood (10 ml/draw) was drawn from all subjects by antecubital venipuncture in the morning (8 AM) and the same evening (4PM). Subsequently, another morning and evening sample was collected from twenty-three of the target patients nine to twelve months after the initial sample collection. For seven subjects selected to receive naltrexone, blood was collected within 10 minutes of an SIB episode (Sandman et al., 2000). Blood samples were deposited into EDTA (purple top) vacutainers and chilled on ice immediately. Samples were centrifuged at 2000 $\times$ g (15 min.) and the plasma was decanted into polypropylene tubes containing 500 KIU/ml aprotinin. The samples were stored at -70° C until assayed.

POMC-Peptide Assays—Assays were conducted for ACTH and an intact 31 amino chain endorphin fragment.

Intact β -Endorphin—Plasma levels of β E were determined by a direct solid phase two-site immunoradiometric assay (IRMA). The β E assay incorporated two antibodies with high affinity and specificity for N-terminal and C-terminal regions of the β E₁₋₃₁ molecule. Both antibodies bound β E without competition or steric interference and formed a sandwich complex between the immobilized β E antibody on the plastic bead and ¹²⁵I-labeled β E antibody. The antiserum has 16% cross-reactivity with BLPH at 500 pg/ml and has <0.01% cross-reactivity with related opiates at 5ug/ml. Samples were assayed in duplicate (200ul per assay tube). ¹²⁵I-anti- β E (rabbit) solution (100ul) was added to each tube and vortexed. The reaction was initiated by adding one anti- β E (rabbit) coated polystyrene bead to the assay tube followed by a stationary incubation at room temperature for 20 $\pm$ 4 hr. The beads were then washed twice with phosphate buffered saline and aspirated to dryness. The labeled antibody complex bound to the solid phase was measured using a Gamma Counter. The Beta-Endorphin Immunoassay system has a minimum detectable dose MDD=14 pg/ml (95%

confidence limit) with a coefficient of variance $CV=4.1\%$ (intra-assay) and $CV=9.0\%$ (inter-assay) at the highest concentrations in the present study.

ACTH—ACTH ^{125}I -antibody solution (100ul) was added to the samples, vortexed and incubated at room temperature for 20 ± 2 hours after the addition of an avidin coated bead. The solid matrix was washed with buffered surfactant in phosphate buffered saline to remove unbound components and the bound radiolabelled antibody complex quantified using a Gamma Counter. The ACTH assay has a MDD = 1.0 pg/ml (95 percent confidence) with $CV=3.0$ percent (intra-assay) at 35 pg/ml and $CV=7.8$ percent (inter-assay) at 36 pg/ml.

Pharmacological Probe

A placebo-controlled opioid blocking agent was orally administered (double-blind, cross-over design, randomly ordered) to seven subjects identified by clinical staff as exhibiting severe SIB *and* the possessing the highest index of sequential dependence (i.e. elevated transitional probability for SIB). Based on procedures employed in our previous studies (Sandman et al., 1997; Sandman, Touchette, Lenjavi, Marion, & Chicx-DeMet, 2003; Sandman et al., 1993) each subject was administered one of three doses of naltrexone (NTX; 0.5, 1.0 or 2.0 mg/kg, QOD) on separate weeks. Each positive treatment week was separated by a week of placebo treatment. Each subject was observed and their behavior and environmental events recorded for fourteen hours each week for seven consecutive additional weeks (four placebo and three treatment weeks) with the computer-assisted methods described above.

RESULTS

Sequential dependence of SIB

Compared with other events, SIB was the best, and the only positive, significant predictor of subsequent self-harm from among the variables recorded ($p<.0001$; Fig. 1). SIB was the most probable event either before (Fig. 1, black bars) or after (Fig. 1, gray bars) another SIB event (z score >9 , $p<0.0001$). Previous findings from this sample indicated that the significant sequential dependency between SIB events was pervasive, not a function of several extreme cases, and not apparent for other maladaptive behaviors (Marion, Touchette, Kroeker, & Sandman, 2005). The correlations between measures of SIB frequency and the raw ($r=0.34$) and log ($r=0.24$) measures of sequentially dependence were not significant.

SIB and POMC Peptides

There were no significant associations between either rate or frequency of SIB and morning levels either of BE_{1-31} or ACTH (r 's ranged from $-.08$ to $.15$). The primary purpose of this study, however, was to examine the relation between sequential patterns of SIB and POMC expression. Specifically, we expected that one POMC fragment (BE_{1-31}) would be elevated in relation to a co-released POMC fragment (ACTH) among subjects with sequentially dependent patterns of SIB. Subjects with high levels of POMC dysregulation (elevated BE_{1-31} [$M= 47.4 \pm 18.5$ pg/ml] relative to ACTH [$M= 34.8 \pm 17.3$ pg/ml]) in the morning (when the system normally was activated) were significantly more likely to exhibit sequentially dependent patterns of SIB ($r_{df=27}=0.57$, $p<.001$; Fig. 2a). The morning dysregulation index was normally distributed (kurtosis= .01, Skew= $-.06$) but shifted to the right (higher BE_{1-31} than ACTH for 23 of 28 subjects). The evening dysregulation index was similar to the morning pattern, but was not significantly related to SIB. As expected, levels of both BE_{1-31} [35.0 ± 16.2 pg/ml] and ACTH (25.6 ± 12.8 pg/ml) were significantly lower in the evening compared with morning concentrations.

Higher probabilities of sequential SIB were associated with lower levels of ACTH. The levels of ACTH both in the morning ($r=-0.48$, $p < .01$) and evening (-0.58 , $p<.001$) were significantly associated with measures of sequential dependence. This suggests that the fluctuating (specifically decreasing) levels of ACTH contributed significantly to the relation between SIB and the dysregulation index.

Nearly identical findings were evident when a subgroup of twenty-three subjects was retested nine to twelve months later (Fig. 2b, [$r_{df=22}=0.60$, $p<.001$]). Moreover, the relation between POMC and temporally dependent sequential patterns were strongest among a smaller second subgroup of seventeen subjects independently identified by *clinical* staff as exhibiting the most severe SIB (Fig 2c, [$r_{df=16}=0.73$, $p<0.001$]). There were no other significant relations between SIB patterns and measures of POMC activity.

One possible explanation for the significant association between sequentially dependent SIB events and POMC fragments is that clusters of SIB constituted episodes or bouts of behavior. Previously we (Kroeker et al, 2004) applied survival curve analysis to similar behavioral data and, based on several assumptions related to frequency and time between events, defined “bouts” of SIB. A subgroup of subjects ($N=12$) in the current sample were identified using the criteria described in Kroeker et al (2004). There was no significant relation between POMC and number (93 ± 87) of bouts ($r = 0.10$, $p>.10$) or the average length (3.1 ± 1.9) of bouts ($r = -.17$, $p>.10$).

POMC and agitation

The relation between POMC and another behavior exhibited by the full sample, agitation, was assessed to determine if activity or exertion could account for our findings. There was no systematic relation between POMC fragments or POMC regulation and agitation ($r=.24$, $p=.19$).

POMC and control subjects

For the eight control subjects, four had dysregulation indexes that were positive (BE higher than ACTH) and four ($p < ns$) had indexes that were negative (ACTH higher than BE). This distribution was not significantly different from chance for the control subjects but it was strikingly different from the target group in which 23 of 28 subjects had positive indexes ($p<.001$; binomial test). The dysregulation index (mean $.07 \pm .32$) of the control subjects was significantly ($F_{1,14} = 5.93$, $p=.03$) lower [virtually zero] than subjects with the sequentially dependent SIB.

SIB, POMC and an Opiate Blocker

The relation between SIB and POMC was examined further by challenging a subgroup of seven subjects with an opiate blocker. A decrease in the conditional probability of SIB compared with the observations of SIB collected during placebo was observed in five of the seven subjects only at the 1mg/kg dose. Change in the (transitional) probability of self-injury after administration of 1 mg Naltrexone, (QOD) was related significantly ($r=0.85$, $p<0.01$) to the concentration of BE_{1-31} immediately following a self-injuring episode (Fig. 3). Elevated plasma levels of the endogenous opiate BE_{1-31} immediately following self-injuring acts, predicted that a centrally-acting opioid blocker would interrupt the sequential links in SIB. Morning POMC dysregulation was not correlated with opioid levels following SIB ($r=.00$, $p=.98$), however entering these independent markers into multiple regression significantly ($F_{2,6}=14.15$, $p=.01$) improved the prediction of response to opiate blockers. Greater morning dysregulation in conjunction with elevated levels of BE after SIB predicted decreased SIB after treatment with NTX.

DISCUSSION

Sequentially dependent patterns of SIB were most evident among individuals whose morning resting plasma POMC fragments were uncoupled. Specifically, highly sequentially dependent patterns of SIB were associated with elevated levels of basal plasma BE₁₋₃₁ relative to ACTH. An uncoupled pattern is unusual because cleavage of POMC is tightly controlled, occurs in a specific order (Mains & Eipper, 1999) and usually results in highly coupled expression of ACTH and BE (Strand, 1999).

An extensive literature (reviewed in Sandman & Kastin, 1981, 1990; Strand, 1999) supports the conclusion that although ACTH and BE arise from a common precursor, they have reciprocal influences on the brain and behavior. Within physiological limits, in both developing and adult organisms, ACTH exerts enhancing influences on neural and behavioral efficiency in contrast to the largely depressing influences of BE (Sandman & Kastin, 1990). For instance, in animal models ACTH fragments administered concomitantly with opiates attenuated tolerance and dependence (Hendrie, 1989; Krivoy, Kroeger, & Zimmerman, 1977; Szekely et al., 1979). Similar examples of reciprocity were reported for generation of characteristic waveforms ('eliptogenic' spiking) in the electroencephalogram of the nucleus gigantocellularis following periaqueductal gray stimulation [Sandman & Kastin, 1981], social behavior (Beckwith, Sandman, Hothersall, & Kastin, 1976; Panskepp, Herman, Conner, Bishop, & Scott, 1978) learning and memory in the rodent (Sandman, Alexander, & Kastin, 1973; Sandman, Miller, Kastin, & Schally, 1972; Beckwith et al., 1976; McGivern, Berka, Berntson, Walker, & Sandman, 1979) and human fetal learning (Sandman et al., 2003). Opiates and opioid peptides inhibit ACTH release and opiate receptor antagonists cause ACTH release by blocking the tonic inhibition of the endogenous opioid peptides (al'Absi et al., 2004). The balanced or coupled release of these peptides may have a greater significance for brain and behavioral function than the absolute level of either. This argument suggests that inaccurate conclusions may result from associations derived from considering one of these peptides and not the other.

Disruption of the co-expression of ACTH and BE can be attributed to lesions of the medial basal hypothalamus (Barna, Koenig, & Davis, 1992), stress-induced increases in circulating levels of corticotrophic releasing hormone (Sasaki et al., 1987; Hendris, 1989; Laatikainen, Virtanen, Kaaja, & Salminen-Lappalainen, 1991; Hargreaves, Flores, Dionne, & Mueller, 1990) and mutations that alter the three dimensional conformation of the POMC molecule (Rosenblatt & Dickerson, 1997). The most likely source of dysregulation of POMC expression, however, is the pattern and order of proteolytic processing of POMC by the prohormone convertases, PC1 and PC2. The PC's are members of a family of subtilisin-like enzymes that convert the biologically inactive POMC molecule into bioactive peptides (Seidah & Chretien, 1992; Seidah et al., 1991). PC1 has relatively limited processing properties compared with the wider processing properties of PC2, but both liberate several interesting, smaller peptides from the large precursor POMC molecule.

Both convertases are present in the fetus by midgestation but the great differences in the distribution of PC1 and PC2 that are evident prenatally begin to disappear as organisms reach adulthood (Zheng, Streck, Scott, Seidah, & Pintar, 1994). Because all elements of this POMC-PC-peptide system unfold early in fetal life, uncoupling of POMC fragments or abnormal concentration of POMC products may be evidence of disturbances expressed during the prenatal period (Bicknell, Savva, & Lowry, 1996) with potentially profound influences on development. Previously we (Barron & Sandman, 1983) reported that subgroups of individuals exhibiting SIB had a highly significant risk of prenatal complications.

There is no direct parallel to our studies of the biological basis of *sequential patterns* of SIB. Other research, including our previous studies, has focused either on the relations between POMC and diagnostic classes or on the relation of POMC with simple measures of *rate and/or frequency* of behavior (Sandman et al., 1990a; Sandman et al., 1997; Sandman et al., 2000). These studies have reported that dysregulation in the opioid region of POMC is manifested among autistic subgroups including those with SIB by (i) elevated resting levels of the C-terminal fragments (Leboyer et al., 1994; Leboyer et al., 1999; Cazzullo et al., 1999) but not N-terminal fragments of POMC; (ii) elevation of the intact BE₁₋₃₁ after a stressful challenge (Sandman et al., 1997), and (iii) uncoupling of BE₁₋₃₁ and ACTH after challenge and at rest (Bouvard et al., 1995; Leboyer et al., 1994; Leboyer et al., 1999; Sandman et al., 1997; Sandman et al., 2003). The present study differs from these studies because of the focus on the role of a biological system in maintaining a complex chain of sequentially-dependent behavioral events. The dynamics of a sequential behavioral pattern are unique and are not related to the frequency or rate of behavior or to other subject characteristics as reported here and in other studies (Marion et al., 2003; Kroeker et al., 2004). The patterns reported here were not the result of clustered “bouts” of SIB. The temporal lag employed in the generation of the sequential patterns militated against the inclusion of bout-like events in the analysis. Moreover, formal analysis of behavioral bouts determined with survival curves in a subgroup of subjects, did not support any relation with the POMC molecule.

The present findings extend previous reports by indicating that the temporal associations between behavioral events are related to the level of POMC dysregulation. The association between a complex pattern of human behavior and POMC activity is the strongest we have observed, persists over time and is most robust among subjects identified as having severe and clinically significant SIB episodes. These results are consistent with our working hypothesis (Sandman & Touchette, 2001; Marion et al., 2003; Kroeker et al., 2004) that the temporally dependent phenotype of self-injury reflect primitive patterns that are governed by internal or biological factors and in this case, by POMC.

The role of POMC in the maintenance of temporally dependent patterns of SIB was established further in a subgroup of subjects by introducing a centrally acting pharmacological probe that blocked the POMC opiate fragment. Naltrexone interrupted the pattern of self-injuring incidents in individuals who had high levels of BE immediately after SIB. Because opiates, in addition to their analgesic properties, also have euphoric effects, we have presumed that one consequence of SIB is the pleasure derived from an acute increase in BE (Sandman et al., 1995; Sandman et al., 1999). SIB patterns are difficult to interrupt, perhaps because the behavioral rituals associated with them are pleasurable and therefore reinforcing. In support of this argument, the temporally dependent patterns of self-injury were decreased when a centrally-acting pharmacological probe was introduced that blocked the immediate biological and reinforcing consequences of the POMC-opioid system.

Optimal response to opiate blockade, however, was observed in subjects with both morning (chronic) POMC dysregulation and elevated (acute) BE after SIB. This finding is consistent with rodent (Shen & Crain, 1992; Crain & Shen, 1995) and primate (Crockett et al., 2007) models demonstrating that chronic exposure to, and/or acute elevation of, opioids results in supersensitivity to the effects of opiate antagonists (Schaefer & Michael, 1990).

We found that POMC is one biological system associated with the unique sequentially dependent SIB phenotype and we proposed that both the chronic and acute activity of the endocrine stress system maintains and motivates this maladaptive behavior. Morning POMC levels are temporally stable biological patterns (Sandman et al., 2002) perhaps reflecting

biological traits and therefore, a predisposition to SIB. The functional significance of POMC imbalance in this population is unknown but the relative elevation of BE (or the imbalanced expression of BE due to decreased levels of ACTH) may reflect reduced pain perception (partial analgesia) which could contribute to the development of SIB (Sandman et al. 1995; Sandman et al., 1999). Consistent with this possibility is that one distinguishing feature of SIB is the raised threshold for painful stimulation among affected subjects (Ludäscher et al., 2007; Schroeder, Oster-Granite, & Thompson, 2002). For these individuals, extreme self-stimulation may be the only means for securing necessary arousal. In addition, the acute elevation of opioid levels immediately after SIB may reflect the direct biological consequences of the behavior. As described above, one consequence of SIB may be the euphoric effect related to the increase in BE (Sandman et al., 1995; Sandman et al., 1999). Modifying this behavior is notoriously difficult perhaps because of these dual processes. Thus treatments must be directed to both the chronic condition, which is responsible for the elevated pain threshold, and the acute condition which associates pleasure with the behavioral act.

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FIGURE 1.

Presents the mean z-score distributions for the relations between SIB and both antecedent (before) and subsequent (following) behavioral events. For instance, the probability that an SIB even either preceded or followed another SIB event was highly significant (the dotted lines depict the $p < .01$ level of significance). Staff interaction was significantly less probable both before and after an SIB event. [SIB (self injurious behavior), Staff Prox (Proximity of Staff to subject), Restraint (presence or absence of restraining devices), Peer (presence or absence of peer interactions), Agitation (hyperactivity, temper tantrums), Stereo (Stereotypy-repetitive body movements), Null (30 second periods without recordable events)].

FIGURE 2.

Panel A illustrates that increases in morning E (higher log values) are associated significantly higher transitional probabilities for SIB (greater degree of contagion). Panel B presents the same data for a subgroup of 23 of the same subjects tested nine to twelve months after the initial evaluation (presented in Panel A). Panel C is a subgroup of subjects from Panel A who were selected by staff at the beginning of the study as exhibiting the most severe SIB.

FIGURE 3.

An increase in E within five minutes of an observed self-injury predicts a positive response (decreased SIB contagion) to subsequent treatment with Naltrexone.