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Self-Injurious Behavior: Gene–Brain–Behavior Relationships

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This paper summarizes a conference held at the National Institute of Child Health and Human Development on December 6–7, 1999, on self-injurious behavior [SIB] in developmental disabilities. Twenty-six of the top researchers in the U.S. from this field representing 13 different disciplines discussed environmental mechanisms, epidemiology, behavioral and pharmacological intervention strategies, neurochemical substrates, genetic syndromes in which SIB is a prominent behavioral phenotype, neurobiological and neurodevelopmental factors affecting SIB in humans as well as a variety of animal models of SIB. Findings over the last decade, especially new discoveries since 1995, were emphasized. SIB is a rapidly growing area of scientific interest to both basic and applied researchers. In many respects it is a model for the study of gene–brain–behavior relationships in developmental disabilities.

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Self-injurious behavior [SIB] refers to acts directed toward one's self that result in tissue damage [Tate and Baroff, 1966]. SIB by people with intellectual and other developmental disabilities has puzzled clinicians, educators and researchers over the past century [Thompson, 1999]. As many as 5%–17% of all people with intellectual and developmental disabilities engage in repetitive SIB, some very frequently [Rojahn, 1994; Colacott et al., 1998; Schroeder et al., 1999]. Compulsive SIB by people with intellectual and other developmental disabilities appears to be qualitatively different from episodic SIB by people of typical intellectual ability and with such mental disorders as

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schizophrenia, bipolar disorder, major depressive disorder, or borderline personality disorder.

Earlier attempts to understand SIB focused on the role of psychopathology, social deprivation, and homeostatic arousal regulation and the role of social and communicative functions of SIB. There is increasing evidence of diversity of both the topographical form and underlying mechanisms in SIB among people with developmental disabilities. No single cause of SIB has yet been demonstrated. Compelling evidence indicates that a great deal of SIB serves social–communicative functions [perhaps as much as 2/3 of all SIB] and arises from skill deficits [Carr et al., 1994]. Accordingly, interventions designed to address those deficits can markedly reduce SIB in many cases. There is also growing evidence of neurochemical abnormalities associated with SIB, which often co-exist with the social functions of SIB. Neurochemical differences among people who engage in compulsive SIB appear to involve dopaminergic, serotonergic, and/or endogenous opioid mechanisms, possibly exacerbated by lack of GABAergic inhibition. In addition, psychopathological traits that are commonly associated with specific syndromes (e.g., autism and Prader-Willi syndrome), some of which appear in milder forms in first-degree relatives, appear to contribute to these neurochemically driven forms of SIB.

Finally, chronic health problems (e.g., otitis media, dysmenorrhea, sleep and gastrointestinal disorders) appear to exacerbate SIB in many instances, reducing the efficacy of otherwise effective behavioral and/or pharmacological treatments. Some of these confounding health conditions appear to be iatrogenic, while others may reflect syndromically specific developmentally associated health problems (e.g.. reflux disease in Cornelia de Lange syndrome). While Lesch-Nyhan syndrome (LNS) and Rett syndrome (RS) are particularly treatment resistant, a comprehensive approach to treatment of SIB based on an understanding of the contribution of etiology, underlying social and neurochemical mechanisms, and exacerbating health conditions can markedly reduce or eliminate SIB in most other cases.

Epidemiology and Topographic Assessment of SIB

The largest epidemiological study of SIB is based on the total population data on SIB and other problem behaviors obtained from two large state-agency data sets, from New York and California [Rojahn et al., 1999]. The combined reference populations consisted of more than 130,000 individuals with mental retardation of all ages and levels of functioning. As compared to a normal curve distribution, both populations had overrepresentations of individuals with increasing deficits in functioning. The prevalence of SIB across all ages and levels of retardation was 8.0% in California and 7.9% in New York. It was found that the overall prevalence of SIB, stereotypies, aggression, and destruction was negatively related to level of functioning and expressive verbal skills but that this relationship was stronger in SIB and stereotypies than in aggression and destruction. The correlations between SIB and the presence of psychiatric diagnoses were negligible.

Most epidemiological studies on SIB have significant methodological shortcomings, one of which is the lack of well-developed survey instruments. This is an area that needs more research. A revised version of the *Behavior Problems Inventory* (BPI) is an instrument that was first developed for epidemiological research in the mid-1980s [Rojahn, 1986.] After several substantial revisions that included a new and empirically validated stereotypy section, the current BPI consists of 14 items for specific types of SIB, 24 stereotypy items, and 11 items for aggressive/destructive behaviors. Validity and reliability data indicate that the current BPI has been much improved over its predecessor.

Comorbidity Patterns of Clinical Conditions Associated with SIB

SIB is typically examined in isolation in mental retardation research studies, although there is evidence that SIB occurs in association with a wide range of clinical symptoms and conditions [Bodfish, 1999]. A complete understanding of the phenomenology of SIB will require analysis of these comorbid conditions. SIB is manifested in the context of developmental disorders, e.g., mental retardation and autism [Bodfish et al., 1995; Lewis and Bodfish, 1998]; psychiatric disorders, e.g., obsessive-compulsive disorder, anorexia, borderline personality disorder, body dysmorphic disorder, and schizophrenia [Wilhelm et al., 1999]; and neurological disorders, e.g., Tourette's syndrome [TS], neuroacanthocytosis, and chronic pain syndromes [Robertson et al., 1989]. A variety of specific genetic syndromes associated with mental retardation include SIB as part of their phenotype, e.g., Lesch-Nyhan, Prader-Willi, Smith-Magenis, de Lange, and Fragile X [Jankovic et al., 1988; Symons et al., 1999]. One potential use of the existing data on SIB comorbidity patterns is to guide the search for mechanisms that are responsible for SIB. For example, across the conditions that are known to manifest SIB, there is significant association between the presence or severity of SIB and (a) decreased cognitive skills, (b) the presence of abnormal repetitive behaviors (e.g., stereotypies, compulsive behaviors), (c) the presence of movement disorders, and (d) the presence of sleep disorders. In the developmental disorders, all these factors tend to be associated with the occurrence of SIB and each presents a potential candidate for studies of the pathophysiology and treatment of SIB.

ENVIRONMENTAL MECHANISMS AND TREATMENT STRATEGIES

Current Management and Treatment Strategies

Current best practice in the treatment of SIB involves behavior management strategies, pharmacological intervention, or, more often than not, some combination of these approaches [Cataldo and DeLeon, 1999]. Although functional analytic methods have recently helped to refine behavior analytic treatments and tailor them to specific presumed environmental determinants, the mechanisms behind pharmacological effects are not well understood. Nevertheless, through these approaches, the SIB of individuals with developmental disabilities has often been decreased dramatically. Still, numerous questions remain regarding the ability of these strategies to produce and then maintain treatment gains. Behavior management strategies are often expensive, in terms of cost and effort, and the extent to which behavior management strategies remain effective across time and conditions has not been adequately studied. Also, certain forms and patterns of SIB remain a challenge to current treatment technology. The interaction between the environmental and biological bases for SIB has, to date, been grossly under-investigated in relation to the potential impact such interdisciplinary research can have on a comprehensive understanding and efficient solution to this serious sequelae of mental retardation. Accordingly, a systematic process for integration of research strategies, if not disciplines, is now required.

Functional Analysis of SIB

Research conducted over the past 25 years indicates that SIB is, in large part, a learned behavior disorder

[Iwata, 1999]. The basic mechanisms of learning by which SIB can be acquired and maintained are described in experimental (functional analysis) methodologies. These methodologies are derived from a basic study of operant behavior in an attempt to identify the environmental determinants of specific responses that currently exist in an individual's repertoire [Kahng and Iwata, 1999]. However, functional analysis can also be used in biobehavioral studies: (1) to screen for environmental causes of biological effects; (2) to evaluate drug baselines and drug–behavior interaction; (3) to observe the transfer from biological to environmental causes of SIB or to identify biological predispositions to SIB; or (4) to assess physical anomalies.

Role of Distal Establishing Operations

Establishing operations (EOs) are antecedent events that momentarily alter the reinforcing (or punishing) effectiveness of a stimulus and the likelihood of responses associated with the contingent delivery of that stimulus [Horner, 1999]. The conditional probabilities of SIB and aggression are affected by establishing operations such as (a) change in schedule or staff, (b) fatigue, and (c) illness [Horner et al., 1997]. Distal establishing operations on SIB and aggression within instructional contexts can be treated by neutralizing routines that counter their effects or reduce the value of reinforcers associated with SIB, e.g., the schedule of reward. In order to maintain treatment in community settings, a broad range of targets and intervention outcome measures of SIB is required.

EOs can be distal (e.g., aversive stimulation at a time well in advance of the behavior's occurrence), ongoing (e.g., deprivation of food or presence of an illness), or can occur immediately preceding SIB (e.g., aversive stimulation from a demand to perform an activity). Additionally, other EOs that may influence the occurrence of SIB include deprivation of attention, restricted access to a preferred item (e.g., food or toy) or an activity (e.g., watching a video), and aversive stimulation in the form of demands. Finally, the effects of EOs are treated by (a) providing the reinforcer noncontingently, (b) providing it contingent on an alternative response (e.g., communication training), or (c) providing it contingent on the absence of SIB.

NEUROCHEMICAL SUBSTRATES OF SIB

Serotonergic Mechanisms in SIB and Related Disorders

Serotonin (5-HT) has been studied in developmental disorders since the 1950s [Cook, 1999]. Neurochemical findings of interest have included elevated platelet 5-HT levels in patients with autism and moderate to severe mental retardation [Cook and Leventhal, 1996]. It is possible, but not fully tested, that the relationships may be more to aggression, including SIB, than to the full syndrome of autism. Other 5-HT findings of interest include decreased cerebrospinal fluid 5 hydroxyindoleacetic acid (5-HIAA) in a range of patients without developmental disorders who have aggression, both self- and other-directed. Tryptophan depletion has led to an exacerbation of repetitive behaviors in autism. Serotonin synthetic capacity, as measured by [^{11}C]-α-methyltryptophan, has an abnormal developmental curve in autism relative to controls. A blunted prolactin response to fenfluramine has been seen in autism. Another interesting potential link to 5-HT is through preliminary findings related to the 5-HT transporter (SERT) promoter polymorphism and autism [Cook et al., 1997]. In samples ascertained on the basis of need for pharmacological treatment of aggression, the long form of the promoter is transmitted preferentially in two samples. In a sample of children ascertained at a younger age (e.g., age 2–3 years old), when delayed language and abnormal social skills are the primary reason for referral, the short form of the SERT was transmitted. Preliminary data suggest that restricted and repetitive behaviors may either be at a greater or lesser level, depending on the SERT promoter polymorphism transmission status, but more work is necessary to see if this is related to SIB. The pharmacological response of SIB to potent SERT inhibitors is promising. In the single published controlled trial, clomipramine, a nonselective and potent SERT inhibitor, reduced SIB [Lewis et al., 1995]. Several open trials of selective serotonin re-uptake inhibitors (SSRIs) have shown a reduction in SIB. Some but not all have reported a possible lower therapeutic window in developmental disorders when treatment with SSRIs has been used. These findings require replication in randomized, placebo-controlled trials.

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Dopaminergic Mechanisms in SIB and Related Disorders

SIB is one of a variety of abnormal repetitive behaviors that co-occur in individuals with neurodevelopmental disorders such as mental retardation, autism, and Tourette syndrome [TS] [Lewis et al., 1999]. Although relatively little is known about the neurobiological bases of these behaviors, evidence suggests that SIB reflects alterations in basal ganglia dopamine and associated neurotransmitter systems. The strongest case for dopamine (DA) mediation of SIB comes from neuropathological, neuroimaging, and neurochemical studies of individuals with Lesch-Nyhan syndrome (LNS) [Wong et al., 1996]. In individuals with mental retardation, Lewis et al. [1999] have reported significant decreases in both behavioral (e.g., blink rate) and biochemical (e.g., plasma HVA) indices of DA function consistent with a DA deficiency model of abnormal repetitive behaviors. Individuals with stereotypy, regardless of neuroleptic status, have increased dyskinesia and akathisia scores. DA antagonists appear to have some selective effects on SIB. For example, Lewis and others have data supporting the efficacy of atypical antipsychotics in treating SIB. SIB is also frequently observed in individuals with TS, a disorder linked to alterations in basal ganglia DA. Furthermore, self-injurious behaviors such as trichotillomania, onychophagia, and ritualistic self-mutilation are considered to be obsessive-compulsive spectrum disorders (OCD). OCD is now known to involve basal ganglia pathology. The comorbidity of SIB and compulsive behavior suggests a common or overlapping pathophysiology involving specific cortico–striatal–thalamic circuits.

It has been known for some time that sustained increases in DA transmis-

sion by pharmacological agents (e.g., pemoline) can result in SIB in rodents [King et al., 1998]. Moreover, animals depleted of DA by chemical lesioning early in development are much more sensitive to the SIB-inducing effects of certain dopaminergic drugs [Breese et al., 1984]. SIB has also been induced by a DA agonist in non-human primates that had sustained lesions of the ventral tegmental area (an area rich in dopamine neurons) early in development. SIB and stereotypies are also associated with early social deprivation in monkeys. Lewis et al. [1990] have reported DA receptor supersensitivity as well as significant loss of a marker for dopaminergic neurons in both the striatum and substantia nigra of early socially deprived animals.

Complex behaviors such as SIB require for their expression alterations of circuitry that involve multiple brain regions and multiple neurotransmitter systems. For example, chronic administration of opiates (e.g., methadone) and methylxanthines (e.g., caffeine) can induce SIB in rodents. Lewis et al. [1995, 1996b] have reported the efficacy of the 5-HT uptake inhibitor clomipramine in treating SIB in individuals with mental retardation, and a number of studies have demonstrated the efficacy of the opiate antagonist naltrexone. The animal and clinical findings are consistent with neuroanatomical and neuropharmacological studies that document significant interactions in striatum between DA and opioid peptides, adenosine, glutamate, and 5-HT. These studies have also traced important cortical and limbic connections to basal ganglia that are likely to mediate the expression of SIB. Neurobiological studies that further elucidate the nature of these interactions should lead to increasingly rational and selective pharmacological treatments for SIB and related repetitive behavior disorders.

Opioids, Addiction, and Stress in the Maintenance of SIB

Biological and pharmacological studies conducted during the past ten years have generated estimates that between 30% and 70% of patients with SIB have dysregulated proopiomelanocortin (POMC) or opioid systems [Sandman, 1999]. Two POMC or opiate hypotheses of SIB, increased pain tolerance and addiction to endogenous opioids, have been proposed [Sandman and Hetrick, 1995]. In studies by Sandman et al. [1990, 1997] plasma levels of highly specific immunoreactive β-endorphin (β) activity were elevated relative to the co-released peptide, ACTH, minutes after an SIB episode. Moreover, levels of β after SIB predicted subsequent response (i.e., changes in frequency of SIB) to challenges with the opiate blocker, naltrexone. An equally interesting observation in this study was the uncoupling of the adenohypophyseal POMC products β and ACTH. Disruption of the co-release of β and ACTH in the plasma is uncommon and is not evident after a variety of physical and psychological stresses. These findings suggested that a comprehensive examination of the POMC molecule and the genes that control its expression may be a productive strategy to better understand a biological pathway relevant to SIB. Sandman et al. [1999] have initiated such studies and have preliminary evidence of a mutation in the opioid region of the POMC gene.

LESCH-NYHAN SYNDROME AS A GENETIC AND NEUROBIOLOGICAL MODEL FOR STUDYING SIB

Lessons from Lesch-Nyhan Disease

The LNS is a genetically determined disorder of purine metabolism first definitively described in 1964 [Lesch and Nyhan, 1964]. The responsible gene is on the X chromosome, and the phenotype is expressed as a recessive characteristic. The molecular site of the defect is the enzyme hypoxanthine-guanine-phosphoribosyl-transferase (HPRT; EC 2.4.2.8). The most prominent metabolic consequence of this defect is an enormous overproduction of purine 5, which leads to the accumulation of large amounts of uric acid in body fluids. The patients have a remarkable disorder of central nervous system function, and they regularly display extraordinary self-mutilation and aggressive behavior. The quantities of uric acid encountered in patients with this syndrome are larger than in any other condition described, and they can lead to clinical manifestations of gout, including nephropathy. Therapy designed to target those features of the disease that are directly related to uric acid has been successful; e.g., allopurinol treatment can prevent arthritic or renal complications. Therapy aimed at the cerebral and behavioral features of this disease has been disappointing [Nyhan, 1999]. Physical restraint and the removal of teeth remain the mainstays of management. Advances in molecular biology have led to interest in new approaches, such as gene therapy [Friedmann, 1995].

Brain Imaging in SIB: Lesch-Nyhan Disease and Related Developmental Disorders With Stereotypical Behavior

There are only a few studies involving brain imaging and SIB [Wong, 1999]. Of these, primarily LNS has been studied with various brain-imaging techniques. The most notable findings include positron emission tomography studies (PET) that demonstrate decreased dopamine transporters (DAT), and decreased [^{18}F]fluorodopa measurements reflecting decreases in DOPA-decarboxylase [Wong et al., 1996]. Both findings point to a dramatic reduction in DA neurons, perhaps due to a loss of arborization. Other studies, including magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) are in progress but suggest decreases in *N*-acetyl aspartate (NAA). Most notable is a recent finding by Harris and colleagues [1999] that suggests more moderate reductions in dopamine transporters (DAT) and correlation with HPRT levels in variants of LNS (HPRT level 1.8%–20%). There was no significant difference in DAT between subjects with severe dystonia and SIB as compared to those without SIB, suggesting that DA alone may be insufficient to explain the SIB.

A related disorder characterized by stereotypical behavior is Rett syndrome (RS). As with LNS, D_2 DA receptors are not dramatically reduced. However, DAT is reduced compared to controls, but not to the same degree, as with LNS. Recent studies with [^{15}O]water PET has suggested the potential value of vasodilators such as L-arginine in therapy. A substantial number of studies have been performed with structural MRI demonstrating specific reductions in absolute and relative proportion of various structures including the basal ganglia but a lack of progression, which disfavors a degenerative process. MRS studies have also revealed decreased NAA, suggestive of decreased dendritic arborization.

Though only a small percentage self-injure, individuals with TS have been the subject of numerous brain-imaging studies. Some studies indicate elevations of D_2 DA receptors in a small subset of subjects and in some studies of monozygotic twins. Most recently, two exciting findings have been elevations of DA release following pharmacologic challenge in TS and a correlation between SERTs and vocal tics.

Neuroimaging Studies in Lesch-Nyhan Disease and Lesch-Nyhan Variants

There is a spectrum of clinical presentations of LNS depending on the extent of the HPRT deficiency [Harris et al., 1999]. The full behavioral syndrome with neurologic dysfunction, cognitive deficits, and the behavioral phenotype of compulsive SIB and aggression requires virtual absence of the enzyme. Individuals with partial variants do not self-injure and may or may not show neurological and cognitive symptoms. In classic cases, the pattern of SIB is so characteristic of the disorder that it is designated as a behavioral phenotype. Thus, Lesch-Nyhan disease has been considered a prototype to study mechanisms involved in SIB.

Harris et al. [1999] have utilized neuroimaging techniques, neuropsychological tests, and behavioral rating scales to investigate the basis of SIB in Lesch-Nyhan disease. They utilized volumetric MRI to study regions of interest, PET to investigate pre- and post-synaptic DA function, and proton spectroscopy to assess neuronal function in regions of interest. They have used PET scanning to investigate the effect of fluphenazine, a drug used to treat SIB, on DA D_1 receptor binding. They have sought to correlate neuropsychological measures with neuroimaging findings. MRI volumetric measurement of brain structures demonstrate reductions in total brain size, reduction in caudate volume ($P < .001$), and suggested maturational arrest of the brain in classical LNS. PET imaging studies indicate a significant reduction of DAT binding (64%–75% in putamen and 50%–63% in caudate) in vivo in classic LNS. Moreover, they documented that dopamine transporter binding is reduced in Lesch-Nyhan variant patients (HPRT levels 1.4%–20%) and that this reduction is correlated with the extent of the movement disorder.

To confirm that there was neuronal dysfunction in the regions of interest where dopamine function was reduced, Harris et al. [1999] carried out in vivo proton magnetic resonance spectroscopy in LNS, Lesch-Nyhan variants, and age-matched unaffected control subjects to determine brain protonated metabolite levels in the basal ganglia and related brain regions. For proton spectroscopy, multi-slice proton spectroscopic images of the brain in a standard GE 1.5-tesla MR were carried out in a scanner with a combined MR and spectroscopic imaging protocol. Spectroscopic imaging involved using a multi-slice spin-echo sequence with outer volume suppression. Four oblique slices were measured with a 15-mm thickness and a gap of 2.5 mm. The TR was 2,300 ms and TE 272 ms. The nominal voxel size was 0.8 cm^3. Voxels were chosen in the striatum (head of the caudate nucleus and putamen), thalamus, orbital medial cortex, dorsolateral prefrontal cortex, and posterior white matter, and metabolites were quantified. Multi-slice proton spectroscopic images of the brain were quantified in seven classic cases of LNS, seven variant cases, and seven age-matched controls (age range 16–24 years). NAA reductions were found in the basal ganglia (putamen) in both classic and variant cases and in the dorsolateral prefrontal cortex in variant cases. Reductions in the caudate were significant in variants in contrast to control subjects.

These MR spectroscopy findings of the NAA neuronal marker reduction are consistent with reductions of DA density with PET scanning (presumably from neuronal loss). These studies indicate the value of using complementary approaches of multiple imaging techniques, specifically, PET and MR spectroscopy in investigating this LNS.

These findings suggest that DA reduction is linked to the extent of the movement disorder but is not a sufficient explanation for SIB and that other neurotransmitters need to be examined.

Findings from these imaging studies demonstrate that HPRT deficiency results in changes in brain structure and function. Moreover, patients with partial HPRT deficiency have both neurological and cognitive deficits. DA depletion is associated with neurological deficit in our patients. These findings suggest that DA reduction is linked to the extent of the movement disorder but is not a sufficient explanation for SIB and that other neurotransmitters need to be examined.

OTHER NEUROBIOLOGICAL FACTORS IN SIB

Sleep and Cyclic Variables in SIB

Epidemiological research has identified a number of environmental and biological correlates of severe SIB that may greatly influence the development, course, maintenance, and severity of this disorder [Fisher, 1999]. Two potentially important biological factors related to SIB are sleep and cyclical variables, which include certain mood disorders and other biological processes that show periodicity and influence behavior (e.g., the menstrual cycle). Piazza et al. [1997] have conducted research studies associating SIB and sleep and cyclical variables. In one study they showed that children with severe behavior disorders were much more likely to have markedly disturbed sleep than normal age peers. In another study they showed that day-to-day fluctuations in sleep and SIB are often inversely correlated, with decreased sleep (sleep deprivation) often followed by increased SIB [Piazza and Fisher, 1991; Piazza et al., 1996]. In a series of studies, they showed that behavioral interventions designed to entrain sleep patterns in synchrony with the individual's biological clock could effectively treat sleep disorders in this population, and in rare cases, sleep treatment may significantly reduce SIB. With regard to cyclical variables in SIB, they have developed a set of procedures for detecting and testing hypotheses about cyclical SIB in nonverbal individuals and for identifying the biological processes that may be responsible for periodicity in this disorder.

Pain and SIB in Developmental Disabilities

There appear to be subgroups of individuals with developmental disabilities for whom normal pain transmission is impaired [Symons, 1999]. In many of these cases, SIB is also present [Symons and Thompson, 1997]. The link between injury and pain can be highly variable and difficult to predict. Not surprisingly then, the relation between SIB and pain in people with mental retardation and developmental disabilities is also poorly understood. There are a number of variables common to both the causes and consequences of pain, analgesia, and SIB, including the frequency, intensity, duration, and body location of stimulation. Studies designed to understand pain status and pain behaviors in individuals with severe SIB in relation to these four dimensions could assist in further refining the biobehavioral mechanisms responsi-

ble for SIB. Additionally, there appear to be subgroups of individuals with developmental disabilities for whom normal pain transmission is impaired. In many of these cases, SIB is also present [Symons and Thompson, 1997]. In autism and related pervasive developmental disorders, for example, it has long been recognized that many individuals have reduced sensation or responses to presumably painful stimuli. This observation is significant, as the estimated prevalence of SIB is approximately 40%–50% in persons with autism. In Prader-Willi syndrome (PWS), individuals have a tendency for persistent skin picking that is associated with tissue damage but little apparent pain response. Compared to matched controls, individuals with PWS have sensory nerve action potential amplitudes that, on average, are 40%–50% of normal size [Brandt and Rosen, 1998].

Dynamics of SIB

There are techniques available to assess the dynamics of the movements of SIB in situ and stereotypies in general, without interference to the client who is producing the stereotypic motions [Newell et al., 1993; Sprague et al., 1995; Newell, 1996a, 1996b]. These measures of SIB are useful because an analysis of the movement dynamics (kinematics and kinetics) would provide information relevant to both the theory and practice of SIB that is generally not available from other approaches. For example, it is valuable to know the relative size of the impact force of the self-imposed blows of SIBs and contrast them with known estimations and assessment of the blows of other contact physical activities, such as boxing and karate [Newell et al., 1999]. Comparisons between the intensity of self-injurious blows and these other activities help place notions of intensity and the clinical significance of these behaviors in a more understandable context. Furthermore, analysis of the kinematics of the movement trajectories facilitates an assessment of several motor control issues in stereotypies, including the variability of the stereotypic action, the degree of coordination in the motions of the two arms during SIB, whether the movements are essentially ballistic, or whether there is closed-loop control (feedback-based regulation) of the limb to the body. For example, for several years behavioral researchers have called for further assessment of response redistributions that may occur as a result of treatment (i.e., adaptive or maladaptive responses may change in frequency or in their relation to the target SIB following treatment) [Linscheid and Meinhold, 1990]. These types of analyses may benefit from the use of direct measures of movement dynamics in SIB.

NEURODEVELOPMENTAL UNDERSTANDING OF SIB

Studies of the Development of Stereotype and SIB in Young Children

A complementary approach to treatment of SIB and stereotyped behaviors might be to deal with these behaviors while they are emerging. There is reason to believe that most SIB and stereotyped behaviors are present in children younger than five years old. Berkson and Tupa [1999] have been studying children with severe disabilities in early intervention education programs, and they are taking a longitudinal approach. Young children also emit "proto-injurious" behaviors (i.e., behaviors that have the same form as SIB but are not injurious). The patterns are highly individual and suggest that analysis at the level of specific patterns may be important. One can also distinguish the abnormal stereotyped and SIB from the stereotyped and self-injurious behaviors that are typical of most typical infants.

From a total of 457 children in five early-intervention programs for children aged 0–3 years with significant disabilities, Berkson and Tupa [1999] were able to study 37 children who were at risk for stereotyped and/or SIB. Of these, 21 children showed proto-injurious or injurious behaviors (incidence = 4.6%). Six children showed significant SIB (incidence = 1.3%). All of these behaviors, except for self-biting, were directed at the head. Berkson and Tupa [1999] concluded that, although they also develop at later ages, severe SIBs occur prior to 3 years of age in this population.

ANIMAL MODELS OF SIB

Background: Behavioral Analyses of Animal Model Systems

Animal models of SIB require an adequate definition of the phenomenon in humans [Crnic and Nitkin, 1996; Crnic, 1999]. While the salient phenotype of individuals with mental retardation is impairment in cognitive function, other domains of behavior need to be studied, particularly in SIB. Species differences must be taken into account when establishing animal models, including differences among rodent species. While the neural development of some behavioral systems is well established, deficits in those behavioral systems cannot be used to infer involvement of particular neural systems without extensive diagnostic analysis. Detailed data analysis is an important part of this diagnostic process.

Neurobiology of the 6-Hydroxydopamine Lesioned Neonate Rat as a Model of the Dopamine Deficiency in Lesch-Nyhan Disease: Support for the D_1-Dopamine Hypothesis of SIB in the MR/DD Population

LNS and Parkinson's disease (PD) are both characterized by a loss of DA in brain, and yet each induces a unique clinical profile of motoric dysfunction and susceptibility for SIB [Breese et al., 1999]. Rats given selective 6-hydroxydopamine (6-OHDA) lesions as neonates show a marked propensity for SIB when challenged with apomorphine or L-DOPA, a response not observed in the rats lesioned as adults [Breese et al., 1984]. These results led Breese and colleagues to suggest that SIB susceptibility is dependent upon the age at which dopaminergic neurons are destroyed. Thus, the neonate-lesioned rat serves as a model [Breese et al., 1994] of the DA reduction and SIB observed in Lesch-Nyhan syndrome. Further work with this model has established that the D_1-DA receptor plays a critical role in SIB, leading to the proposal of a "D_1-DA hypothesis of SIB." In addition, the intensity of observed aberrant responses to a D_1-DA agonist can be increased by concomitant D_2-DA receptor activation, demonstrating the importance of D_1/D_2-DA receptor coupling to SIB. One use of the model has been to screen for drugs that would reduce SIB induced by DA agonists. In this regard, several drugs have been identified that could have effectiveness as therapeutic agents against SIB and aggression in patients with mental retardation and developmental disabilities (MRDD) [Schroeder et al., 1995]. Nonetheless, the critical test of the D_1-dopamine hypothesis of SIB with a D_1-DA antagonist has yet to be performed. Another major characteristic identified in the rats lesioned as neonates was the sensitization of responses to D_1-DA agonists with repeated administrations, a phenomenon referred to as "priming." Because of the direct relationship of D_1-DA receptors to SIB, considerable work has been undertaken to understand the neurobiological basis of the persistence of this sensitization phenomenon in the model [Breese et al., 1995]. One significant finding was that NMDA antagonists blocked the appearance of the sensitization if given prior to each challenge with a D_1-DA agonist. Fur-

thermore, the NMDA antagonists have been found to prevent SIB induced by DA agonists in the model. Currently an effort is underway to determine the underlying intracellular events associated with D_1-DA receptors that mediate the persistent behavioral sensitization. Specific attention is being given to protein sequences, transcription factors, and binding sites on genes as potential contributors to the permanent plasticity induced by persistent exposure of the neonate lesioned rats to a D_1-DA agonist. These basic investigations are expected to lead to identification of factors that are responsible for the D_1-DA agonist sensitization. This latter information may in turn lead to more effective treatment protocols to treat SIB.

Cellular Substrates for SIB: Insights From In Vitro Developmental Studies

Lauder [1995] used two in vitro strategies to investigate cellular mechanisms underlying abnormal striatal innervation by 5-HT and DA neurons in LNS and the 6-OHDA animal model. Lauder [1995] used skin fibroblasts obtained by biopsy from LNS patients and controls (gift of W.L. Nyhan) to test their ability to affect growth and survival of embryonic rat 5-HT and DA neurons. Conditioned medium from LNS fibroblasts or co-culture of neurons with fibroblasts inhibited survival of both 5-HT and dopamine neurons to varying degrees. However, growth of 5-HT neurons was stimulated while growth of dopamine neurons was inhibited, similar to the situation in LNS striatum. In a second set of experiments, they investigated whether striatal astrocytes from 6-OHDA animals might serve as a useful model for LNS disease. The rationale for these studies was previous evidence that neonatal 6-OHDA causes striatum to stimulate growth of transplanted embryonic 5-HT neurons [Zhou and Murphy, 1989]. Astrocytes were cultured from striatum of postnatal day (PND) 7 animals treated on PND 1 with 6-OHDA + DMI or DMI alone and co-cultured with embryonic 5-HT or DA neurons. Serotonin neurons responded to co-culture with 6-OHDA astrocytes by enhanced neurite outgrowth, whereas there was no effect on DA neurons, suggesting that these astrocytes produced increased levels of a growth factor selective for 5-HT neurons compared to DA neurons, such as S-100β [Liu and Lauder, 1992]. Other possible factors include opioid peptides, which are increased in striatum of 6-OHDA animals [Walker et al., 1991] and are able to regulate growth of 5-HT neurons [Davila-Garcia and Azmitia, 1989]. This is an attractive possibility because opioid peptides are elevated in LNS patients where they may facilitate SIB by reducing pain of self-inflicted injuries [Thompson et al., 1995]. Future studies may provide valuable insights into the etiology of LNS disease by addressing cellular and molecular mechanisms underlying the differential effects of striatal astrocytes from 6-OHDA animals on growth of embryonic 5-HT and DA neurons.

Pemoline and Other Dopaminergic Models of Self-Biting Behavior

Pemoline-induced SIB has been proposed as a useful animal model in which to study the development and regulation of similar behaviors in humans [Mueller and Hsiao, 1980; Mueller and Nyhan, 1982; Mueller et al., 1986; King, 1999]. Pemoline (2-imino-5-phenyl-4-oxazolidinone) acts at least in part through dopaminergic mechanisms [Everett, 1975; Dren and Janicki, 1977; Molina and Orsingher, 1981] where it behaves as an indirect agonist [Cromwell et al., 1996, 1997]. Pemoline shares with GBR-12909, a dopamine reuptake blocker that produces similar behavioral effects when repeatedly administered [Sivam, 1995], the effect of reducing neostriatal levels of DA and increasing the serotonin metabolite 5-HIAA [Zaczek et al., 1989; Cromwell et al., 1996; Sivam, 1996]. In addition to dopaminergic and serotonergic involvement, endogenous opioids and excitatory amino acids appear also to influence pemoline-mediated self-biting behaviors [King et al., 1998].

When administered in high doses, both pemoline and GBR-12909 reliably produce a sequence of behaviors that culminate in self-biting behavior in the rat [Genovese et al., 1969; Mueller and Hsiao, 1980; King, 1993, 1995; Sivam, 1995]. Typically, pemoline-treated animals will initially exhibit increases in locomotor and exploratory activity and proceed to display stereotyped behaviors including head bobbing, digging, sniffing, and mouth movements. Subsequently animals will begin to display self-biting behavior, typically some 12–36 hr following pemoline administration [Mueller and Hsiao, 1980; King et al., 1993]. These behaviors will spontaneously remit by 48 hr.

These behaviors were not preceded by or accompanied by an increase in grooming behaviors, but treated animals appeared unusually aggressive, as violent biting was directed toward any disturbing stimulus.

Calcium Channel Activators and SIB

To date, calcium channels have received little attention as mediators or potential therapeutic targets for SIB [Jinnah et al., 1999]. Several calcium channel subtypes are currently recognized by their different pharmacological and electrophysiological properties. The L-type calcium channel is a voltage-gated channel that is expressed throughout the brain and at high levels in the striatum, cortex, and hippocampus. Many drugs have a specific interaction with this channel, including the dihydropyridine agonist, Bay K 8644. In rodents, this drug has been reported to produce motor abnormalities that are best characterized as generalized dystonia. Jinnah et al. [1999] have recently shown that this drug will also reliably produce SIB under certain conditions in mice. These observations provide a new animal model for studying the neurobiology of SIB and implicates L-type calcium channels in the expression of SIB.

Doses of 2–12 mg/kg Bay K 8644 caused a dose-related increase in the frequency and severity of SIB in both weanling and adult mice, though young mice appeared much more susceptible to this phenomenon than older mice. The behavior typically began within 10 min of drug administration, peaked at 20–30 min, and eventually waned or disappeared by 50–120 min. Mice typically bit their forepaws, shoulders, or abdomen. These behaviors were not preceded by or accompanied by an increase in grooming behaviors, but treated animals appeared unusually aggressive, as violent biting was directed toward any disturbing stimulus. Approximately 2–4 hr after drug treatment, the mice appeared normal.

To verify that SIB was not the consequence of irritating paresthesias caused by an effect of Bay K 8644 on peripheral nerves, intracerebral microinjections were performed. Injection of 100 μg of Bay K 8644 could provoke

SIB, while the antagonist enantiomer (+) Bay K 8644 was completely inactive. Second, mice were pretreated with one of 6 L-type calcium channel antagonists 5 min before Bay K 8644 to produce SIB. In contrast, three non-dihydropyridine antagonists, diltiazem, flunarizine, and verapamil, failed to exert any protective effect. The known actions of Bay K 8644 as an L-type calcium channel agonist and the protection afforded by dihydropyridine calcium channel antagonists led Jinnah et al. [1999] to suggest that excess activity of L-type calcium channels underlies SIB in this model.

To begin to dissect the neuropharmacological basis for Bay K 8644-induced SIB, animals were pretreated with drugs influencing monoaminergic systems prior to challenge with Bay K 8644. One group of animals was treated with 2 mg of amphetamine to augment catecholamine release. The following day, these mice demonstrated moderate locomotor hyperactivity at baseline, and increased SIB after Bay K 8644. Other mice were pretreated with *p*-chlorophenylalanine to deplete 5-HT stores. These animals were indistinguishable from controls at baseline but showed markedly attenuated or exaggerated SIB after challenge with Bay K 8644. These results led Jinnah et al. [1999] to suggest that SB and SIB might be mediated by an influence of Bay K 8644 on the brain's monoaminergic systems.

Jinnah et al. [1999] provide a new tool for the investigation of the neurobiology of SIB. They also suggest that some of the many currently available calcium channel antagonists might be considered as potential therapeutic agents for these behaviors.

Behavioral Neuropharmacological Models of SIB

Despite the fact that both LNS and Parkinson's disease (PD) are recognized as being DA deficiency syndromes, there are few, if any, similarities between these disorders in the behavioral typographies manifested [Tessel et al., 1999]. For example, persons with LNS display severe SIB and aggression that are manifested early in life, while PD patients experience bradykinesia, rigidity, and tremors that most typically begin late in life. As demonstrated by the work of Breese et al. [1995], these disorders can be modeled respectively in rats by early neonatal central administration of the catecholaminergic neuronal toxin 6-hydroxydopamine (6-OHDA; LNS) or by similar 6-OHDA administrations in adult rats (PD). Both treatments markedly deplete brain dopamine tissue contents in what had been thought to be an irreversible manner. Tessel et al. [1995a, 1995b] demonstrated that at least such depletions and/or their behavioral consequences are *not irreversible*; indeed, such reversals can be generated simply by subjecting adult LNS and PD rats to one form of prolonged conditional discrimination training (fixed-ratio discriminations, FRD). Consequently, such training appears to function as a nonpharmacological, nonsurgical means to replace the lost dopamine with endogenous dopamine by "exercising" residual brain dopaminergic neurons. Recent preliminary data in Tessel's laboratories in LNS rats using in vivo microdialysis suggest that one of the earlier effects of FRD training is to increase extracellular dopamine.

SIB in Captive Monkeys: Sex, Species, Housing, and Age Effects Suggest a Gene–Environmental Interaction Hypothesis

Forty years of research on captive macaque monkeys has identified four primary factors in the etiology of macaque SIB: (1) Males are more likely to exhibit SIB than females [Sackett, 1999]. (2) Macaque species differ in their propensity for developing SIB, a phenomenon possibly correlated with species differences in social aggression. (3) Monkeys reared throughout infancy without any social contact are the most likely individuals to exhibit SIB. (4) Age is perhaps the most powerful predictor of SIB in conjunction with extended single cage housing. SIB, and even non-injurious self-abuse other than excessive self-mouthing, is not observed during infancy and is rare among young juveniles. SIB appears primarily after sexual maturity, 3–5 years of age in macaques, and is most prevalent in fully adult males at 6 years of age of more [Lichstein and Sackett, 1970; Sackett, 1999].

It is difficult to estimate the incidence of SIB either within or between captive species because of poor or no formal record keeping, definition problems, and differences in husbandry, housing, and experimental histories of animals from different facilities. Nevertheless, it is clear that most animals in the highest risk group, adult males housed in single cages, do not develop SIB. The highest estimate seems to be about 15% among the rhesus macaque males. Taken together, this research has led Sackett [1999] to suggest that SIB in macaques results from gene–environment interaction in which an extended lack of varied stimulation coupled with a fairly rare vulnerable genotype alters some perceptual, motivational, and/or emotional processes.

SUMMARY AND CONCLUSIONS

The history of research on SIB in the past 50 years is, in many respects, a model for the study of a complex disorder that is multiply caused and multiply affected by genetic, neurobiological, and environmental factors. In the 1950s the predominant emphasis was on psychodynamic interpretations [Greenacre, 1954]. In the 1960s the discovery of genetic disorders, such as Lesch-Nyhan syndrome [Lesch and Nyhan, 1964] in which SIB was a strong behavioral phenotype and the development of behavioral interventions to treat SIB, e.g. Lovaas et al. [1965], predominated. The 1970s saw the development of neurobiological animal models [Breese and Traylor, 1970], which became the theoretical basis for modeling SIB [Breese et al., 1984; Lewis and Baumeister, 1982] and for developing rational pharmacotherapies for it, e.g. Sandman et al. [1983] in the 1980s. Behavioral intervention techniques, which can be used for assessing [Iwata et al., 1982] and intervening with most forms of SIB, burgeoned in the 1980s. In the 1990s the interaction of these trends to study gene–environment interactions [Sackett, 1999], environmental effects on neurotransmitter functions [Tessel et al., 1995], and their combination [Thompson et al., 1995; Sandman et al., 1999] have predominated. The next decade holds new promise for developing a more comprehensive and theoretically driven approach to the study of this devastating disorder, its intervention, and ultimately its prevention. ■

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