The Neurobiology of Stereotypic Behaviors and Stereotypic Movement Disorders

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In the Diagnostic and Statistical Manual 4th edition (DSM-IV), stereotypic movement disorder (SMD) is defined as repetitive, nonfunctional motor behavior persisting more than 4 weeks that interferes with normal activities or results in self-inflicted bodily injury that requires medical treatment. It may be specified whether self-injurious behavior (SIB) is part of the presentation.1 By definition, compulsions, tics, a pervasive development disorder, or hair pulling (trichotillomania) do not account for these behaviors. Examples of stereotypic behaviors include hand shaking or waving, head banging, skin picking, and hitting one’s own body.

This article will review the pertinent basic and clinical literature that may help in understanding neurotransmitter mediation and functional neuroanatomy of stereotypic behaviors and SMDs. We begin with a review of neurochemical findings broken down into various sections by neurotransmitter. Each section first presents animal data, followed by a discussion of the specific disorders and relevant findings for the relevant neurotransmitter. Although pharmacologic treatment of these disorders is discussed in a separate article in this issue (pp 327-331), we briefly mention pharmacologic treatment results that may lend support to the involvement or noninvolvement of a particular neurotransmitter. In the interest of trying to understand stereotypic behaviors in general, we have broadened our discussion to include autism (a pervasive developmental disorder) and trichotillomania. Following the sections on neurobiology, functional neuroanatomical findings pertaining to stereotypic behaviors and SMDs are reviewed.

NEUROTRANSMITTERS IN STEREOTYPIC BEHAVIORS AND SMDS

Dopamine

Animal studies have investigated the role of dopaminergic transmission in stereotypic behaviors. Destruction of dopaminergic neurons during early development in the mouse, for example, leads to hypersensitivity of D1 receptors in later life. Increased stereotyped behaviors were observed in the adult animals following administration of dopamine agonists.12 Similarly, socially deprived monkeys frequently engage in self-injurious stereotypic behaviors, which have been found to increase in intensity with administration of the dopamine agonist apomorphine.9 Immunoreactivity of tyrosine hydroxylase, the limiting-rate enzyme in the synthesis of dopamine, was found to be substantially decreased in the stria-

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tum and substantia nigra of such monkeys.4

High doses of methylxanthines have also been found to increase stereotypic SIB in animal models. This effect is thought to be mediated by D2 receptors, primarily in the striatum, that are modulated by adenosine receptor blockade.5 In addition, cocaine, a potent inhibitor of dopamine reuptake,6 has been shown to increase stereotypic behaviors in animals and humans (primarily skin picking in the later).7

There are also some studies of the pharmacotherapy of stereotypies in animals with dopaminergic agents. Cats may engage in excessive licking leading to fur loss (psychogenic alopecia), and the dopamine antagonist haloperidol has shown preliminary evidence for efficacy in treating this disorder.8 Similarly, haloperidol has been reported to be effective for decreasing stereotypic behaviors in pigs.9 As discussed further in the psychopharmacological treatment of SMDs, dopamine antagonists have also been successfully used to treat stereotypic SIB in patients with mental retardation.10,11

Lesch-Nyhan syndrome (LNS) is an X-linked recessive disorder of purine synthesis with a virtual absence of hypoxanthine-guanine phosphoribosyltransferase (HPRT). Neuropsychiatric symptoms include severe self-injurious stereotypies. The underlying genetic defect is well-defined, whereas the mechanisms underlying neuropsychiatric symptoms are less clear. Early post-mortem findings in three patients with LNS demonstrated dramatically reduced levels of dopamine, homovanillic acid (a primary dopamine metabolite), and dopa decarboxylase in the basal ganglia.12 Pre-clinical studies with HPRT-deficient models13-15 and clinical studies of neurotransmitters and metabolite levels in patients with the LNS support the importance of dopaminergic mediation through findings of decreased dopamine levels, decreased dopamine storage, and decreased activity of dopamine B-hydroxylase.16,17

Positron-emission tomography (PET) techniques have shown reduced dopamine transporters in the caudate and putamen.18 Although dopamine supersensitivity has been hypothesized to play a role in SIB in LNS19 and dopamine blockers have been used for their treatment, long-term treatment with dopamine antagonists are not clearly of benefit.20,21

Tourette's disorder or syndrome (TS) is characterized by multiple motor and vocal tics, with onset during early childhood. Stereotypic SIB occurs in 13% to 53% of TS patients and has been found to have a positive correlation with severity of motor tics.22,23 Cerebrospinal fluid (CSF) studies of dopamine metabolites have been equivocal,24,25 but a postmortem study did find evidence of increased striatal dopamine transporters in TS patients.26 Functional imaging studies have confirmed an increase in striatal dopamine transporter density.27 In monozygotic twins with TS, increased caudate D2 receptor binding was associated with increased tic severity.28 Dopamine antagonists are effective pharmacological agents for treatment of tics in TS.29

Preliminary evidence suggests that atypical neuroleptics (which are both dopamine and serotonin receptor antagonists) may be useful in TS patients30 and in mentally retarded patients engaging in stereotypic SIB.31 Both preclinical and clinical studies demonstrate significant interactions between serotonergic and dopaminergic pathways.32

Serotonin

Animal research and clinical studies support a significant correlation between abnormal serotonin function and increased impulsive-aggression, including self-directed impulsive-aggressive behaviors.33-36 Administration of the 5-HT precursor 5-hydroxytryptophan has been reported to induce a complex behavioral syndrome in humans that resembles stereotypic head weaving and forepaw treading.37 Obsessive feather-picking in caged birds responded to open treatment with the serotonergic tricylic clomipramine.37 Canine acral lick dermatitis is a chronic behavioral disorder occurring in dogs. In this disorder, "compulsive" licking of an area on the paw or leg leads to fur loss and breakdown of underlying skin. In a crossover trial, acral lick dermatitis has been found to respond to clomipramine and sertraline, but not to fenfluramine and placebo.38 Serotonergic and dopaminergic pathways may interact in the production of stereotypic behaviors, as demonstrated by potentiation of apomorphine-induced stereotypic behavior following serotonin depletion in rats.39

There is increasing evidence that serotonergic pathways are important in the etiology of obsessive-compulsive disorder (OCD) and other disorders characterized by repetitive behaviors.40,41 Obsessive-compulsive behavior and SIB are at times co-expressed.42 Trichotillomania has been viewed as an obsessive-compulsive spectrum disorder, partly because as in OCD, the serotonergic tricylic clomipramine was found to be more effective than the noradrenergic tricylic desipramine.43

In patients with mental retardation, there are significant positive associations between SIB and stereotypy and compulsions.44 Few biological studies have directly explored the role of serotonin in the mediation of SIB in mental retardation, but there is increasing clinical evidence for the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of SIB occurring in patients with mental retardation.45

5-Hydroxytryptophan (a serotonin precursor) has been shown useful in only a minority of open studies.46

Serotonin may also mediate symptoms of Tourette's syndrome (TS). Decreased levels of serotonin and 5-HIAA (the primary metabolite of serotonin) were found in a postmortem analysis of subcortical brain regions of TS patients.47
Some studies have found blood tryptophan levels to be decreased, and CSF tryptophan was negatively correlated with tic severity in one study. However, tryptophan depletion did not exacerbate tics or obsessive-compulsive symptoms in a small sample of TS patients. A few controlled studies of serotonergic antidepressants have shown some benefits in TS patients. Furthermore, the addition of SSRIs to neuroleptic treatment may be useful in TS patients.

Corinna de Lange syndrome (CLS) is a rare congenital disorder with symptoms of mental retardation, excessive grooming behavior (hand-hucking and hair stroking), and self-injurious behaviors. CLS patients appear to have reduced whole blood serotonin levels. Diverse mechanisms were hypothesized to explain these findings including dysfunction in serotonin metabolism, failure to bind to platelets, or transporter abnormalities. Eger-Will syndrome (PWS) is a congenital disorder that is associated with marked hyperactivity and is the most common dymorphic form of obesity. Behavioral disturbances in PWS include self-injurious stereotypies, impulsive-aggression, and classical obsessive-compulsive symptoms. Serotonergic drugs may show efficacy in PWS, reflecting the possible role of serotonin in appetite control and eating disorders. Compulsive skin-picking, impulsive-aggression, and obsessive-compulsive related disorders. The serotonin releasing agent and reuptake inhibitor fenfluramine did not decrease SIB in PWS patients, whereas fluoxetine appears to have decreased stereotypic SIB in a number of PWS cases.

Autistic disorder (AD) is a pervasive developmental disorder characterized by impairment in social interactions, communication deficits, and restrictive and stereotyped behaviors. Stereotypic SIB is common in AD. Elevated platelet serotonin levels have been found in AD subjects, and neuroendocrine challenge studies have indicated decreased responsivity to serotonergic agents. Tryptophan depletion in AD subjects resulted in increased SIB, motor stereotypes, and anxiety. A possible link to the serotonin-transporter gene has been suggested. Both open and placebo-controlled trials with SSRIs have demonstrated efficacy in reducing symptoms such as SIB. Further supporting the role of serotonergic pathways is the finding that clomipramine was more effective than the noradrenergic tricyclic desipramine in AD. Controlled trials of fenfluramine have not demonstrated clear efficacy.

**Endogenous Opiates**

A number of authors have suggested that the endogenous opioid system may play a role in mediating self-injurious behaviors. In animal studies, opioid agonists may induce autogression and self-injury, and opioid antagonists may be particularly effective in reducing self-injurious stereotypes in younger animals. Intra-accumbens microinjections of opioid agonists in animals have biphasic effects on stereotypic behaviors. Opioids have been reported to decrease compulsive tail chasing in dogs, whereas stereotypic behaviors in swine may respond to opioid antagonists.

Two primary hypotheses have been forwarded regarding abnormal endogenous opiate function and self-injury. One hypothesis, sometimes termed the *excessive opioid hypothesis*, is that excessive opioid activity leads to stereotypic self-injury through a similar mechanism as observed in animal models. It is not posited whether an increased analgesic state is contributory. The alternative hypothesis, sometimes termed the *addiction hypothesis*, emphasizes that repetitive SIB results in release of brain endorphins, which becomes addictive to the individual, leading to reinforcement of the SIB to stimulate endogenous opiate release. Sandman found increased plasma enkephalin levels in patients with mental retardation as compared with in normal control subjects. Although these findings may support the excessive opioid hypothesis, it is also possible that decreased endogenous brain opioids ultimately leads to compensatory overproduction. Endogenous opiate levels also may vary according to how recently SIB may have been engaged. It has also been argued that opioid effects on self-injury may be primarily mediated via dopaminergic or serotonergic pathways.

Clinical reports are equivocal regarding the efficacy of opioid antagonists for the reducing stereotypic SIB in various populations. A recent placebo-controlled trial found that the opioid antagonist naltrexone sometimes increased stereotypic behavior in subjects with mental retardation and self-injurious behavior or autism. Similar to effects of naltrexone on initially increasing alcohol consumption in alcoholics before a decrease occurs, this transient increased behavior may indicate an endogenous withdrawal phenomenon and thereby implicate the brain's opiate-based reward system.

Various authors have hypothesized that increased brain opioid activity might be involved in mediating the various symptoms of autism. Studies of opioid levels in autism, however, have been inconsistent. Despite promising open trials, in controlled studies the effect of opioid blockers on target symptoms, including SIBs in autism, has been disappointing.

Abnormalities of the opioid system may also be present in TS. In fact, both opioid agonists and antagonists have been reported to be useful in some TS patients. McConville and colleagues suggest that TS patients may show dynamic fluctuation in the functional status of opioid neurotransmission rather than simple hypovocitivity or hyperactivity. The possible efficacy of naltrexone in trichotillomania. These studies suggest that further attention be paid to
the opioid system in this disorder also.

**Gamma Amino Butyric Acid (GABA)**

The role of the GABAergic system in self-injurious behavior has been inadequately studied.25,26 The anticonvulsant valproic acid, which acts to increase chloride ion flow and hyperpolarization with GABA receptor activation, was effective in reducing SIBs and aggression in patients with mental retardation and affective symptoms in an open trial.29 Valproate, however, also has serotonergic effects. The use of benzodiazepines for SIBs in mental retardation has not been well studied.

**Norepinephrine**

A primary pharmacological action of amphetamines is inhibition of norepinephrine uptake.2 Higher doses of amphetamines cause stereotypic behaviors in animals.100 Desipramine has been found to increase displacement grooming behavior in mice responding to the scent of an unkilled aggressor.101 Administration of the D2 agonist, clonidine results in decreased noradrenergic activity through stimulation of inhibitory autoreceptors. High-dose clonidine administration in mice causes severe stereotypic automutilation (self-biting).102,103 Interestingly, the clonidine effect is potentiated by pharmacological agents that selectively reduce central serotonergic activity or enhance central dopaminergic activity.104 Again, this emphasizes the importance of interactions among neurotransmitters or neuromodulators and the inherent problems of looking at any one in isolation. In fact, without clear genetic evidence, it is virtually impossible to determine whether a neurobiologic alteration is primary or a compensatory change in response to an "upstream" alteration.

Noradrenergic systems may play a role in TS. CSF norepinephrine was increased in a recent study of TS, and neuroendocrine challenge with clonidine revealed a blunted growth hormone response in a number of studies of TS.105 Clonidine may also be useful in the treatment of TS.104,105

**NEUROANATOMIC AND NEUROFUNCTIONAL ALTERATIONS ASSOCIATED WITH STEREOTYPIC BEHAVIORS AND SMDs**

Several animal studies suggest that frontal and basal ganglia regions are important in mediating stereotypic behavior.106 Weaver mice with a recessive mutation affecting cerebellar and striatal motor circuits, for example, have altered motor behavior including decreased stereotypic grooming sequences.107

In humans with OCD, there is strong evidence that prefrontal-basal ganglia-thalamic circuits are involved in repetitive thoughts and behaviors.108 Basal ganglia involvement has also been demonstrated in subjects with trichotillomania by decreased left putamen volume,109 although a PET study showed involvement of other areas, including the cerebellum.

Quantitative magnetic resonance imaging (MRI) studies in TS subjects have also indicated reduced basal ganglia volumes.26,110,111 PET studies in TS subjects have demonstrated decreased metabolic rates in ventral prefrontal and ventral striatum, with increased metabolic rates in supplementary motor, lateral premotor, and Rolandic cortices.112

Neuroanatomic and functional alterations in subjects with SMDs or stereotypic behaviors may primarily reflect the underlying disorder and may not be specifically associated with the abnormal movements themselves. For the later association to be made, it is necessary to correlate structural or functional measures with a quantitative measure of stereotypic motor behavior. This has only occasionally been done, for example, in TS patients, increased metabolism in orbitalfrontal cortex and putamen correlated with complex behavioral and cognitive features such as SIB.113 It is interesting to note the overlap among these findings, activation patterns in OCD, and structural findings in trichotillomania.

**CONCLUSION**

From neurochemical, neuroanatomic, and neurofunctional vantage points, SMDs and stereotypic behaviors are quite heterogeneous and rather poorly understood. Several neurochemical systems appear to play a role in the mediation of stereotypic movements with or without SIB. Due to the mutual interactions among many of the brain's neurochemical pathways, it is a challenging proposition to determine what neurochemical or neuroanatomic alteration is primary with regards to a behavior or disorder. This further heightens the importance of distinguishing among SMDs and making a further distinction between SMDs and stereotypic behaviors that may or may not be part of an SMD per se.

The dopaminergic, serotonergic, endogenous opiate, and noradrenergic pathways are some of the better studied neurotransmitters in this area. Alterations in all of these have been associated with various SMDs and stereotypic behaviors, yet for the most part it remains unclear as to what the biological mechanism underlying these disorders and behaviors actually is. Alterations in amount of neurotransmitter, receptor number or affinity, and response to a specific pharmacologic agent may not be primary, but rather compensatory changes. Further, the role of other messenger systems in the pathophysiologic mechanisms of psychiatric disorders are poorly understood. Further investigation of these underlying pathways may ultimately clarify how seemingly divergent biological findings and efficacious pharmacologic treatments may be related by a more basic mechanism. From a functional perspective, there are suggestions that prefrontal-basal ganglia-thalamic circuits, along with cerebellar
involvement, may be implicated in SMDS and stereotypic behaviors. Although various animal models of SIB and stereotypic movements exist, further work to elucidate the relevant neurobiology is necessary.

Further understanding in this complex area requires attention to differentiating between syndromes and behaviors, analyzing multiple neurotransmitters in tandem to better understand relationships among them, assessing secondary pathways, and utilizing neuroimaging studies with correlation analyses between functional or anatomical alterations and quantitative measures of stereotypic behaviors. Identification of genetic mutations or functionally significant polymorphisms may also be useful. Heterogeneity of these disorders and behaviors may necessitate a wide breadth of somatic modalities for effective treatment.

REFERENCES


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