The Use of Perinatal 6-Hydroxydopamine to Produce a Rodent Model of Lesch–Nyhan Disease

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Abstract Lesch–Nyhan disease is a neurologically, metabolically, and behaviorally devastating condition that has eluded complete characterization and adequate treatment. While it is known that the disease is intimately associated with dysfunction of the hypoxanthine phosphoribosyltransferase 1 (HPRT1) gene that codes for an enzyme of purine metabolism (hypoxanthine-guanine phosphoribosyltransferase) and is associated with neurological, behavioral, as well as metabolic dysfunction, the mechanisms of the neurobehavioral manifestations are as yet unclear. However, discoveries over the past few decades not only have created useful novel animal models (e.g., the HPRT-deficient mouse and the serendipitously discovered perinatal 6-hydroxydopamine (6-OHDA lesion model), but also have expanded into epigenetic, genomic, and proteomic approaches to better understand the mechanisms underlying this disease. The perinatal 6-OHDA model, in addition to modeling self-injury and dopamine depletion in the clinical condition, also underscores the profound importance of development in the differential course of maladaptive progression in the face of a common/single neurotoxic insult at different ages. Recent developments from clinical and basic science efforts attest to the fact that while the disease would seem to have a simple single gene defect at its core, the manifestations of this defect are profound and unexpectedly diverse. Future efforts employing the 6-OHDA model and others in the context of the novel technologies of genome editing, chemo- and opto-genetics, epigenetics, and further studies on the mechanisms of stress-induced maladaptations in brain all hold promise in taking our understanding of this disease to the next level.

Keywords Lesch–Nyhan disease · Rats · 6-hydroxydopamine 6-OHDA · Perinatal · Self-injurious behavior · L-DOPA · Animal models

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1 Introduction

Lesch–Nyhan disease is a rare X-linked recessive disorder that affects approximately 3 in 1 million people, almost all male (Jinnah and Friedmann 2001). A cardinal feature is excessive production of uric acid, which leads to elevated serum uric acid concentrations and its increased urinary excretion. Uric acid is near its limit of solubility in the body, and its overproduction leads to calcium precipitates in the urogenital system to cause kidney stones and renal failure; in subcutaneous tissue to cause tophi; and in the joints to cause gouty arthritis. Other clinical manifestations of Lesch–Nyhan disease include motor dysfunction (generalized dystonia), intellectual disability, and self-injurious behavior including biting, hitting, and eye poking.

Lesch–Nyhan disease appears to manifest as a spectrum of phenotypes (Fu et al. 2014). Isolated overproduction of uric acid without neurobehavioral abnormalities constitutes the mildest Lesch–Nyhan variant. The disease is caused by mutations in the hypoxanthine phosphoribosyltransferase 1 (HPRT1) gene, which encodes hypoxanthine-guanine phosphoribosyltransferase (HPRT), an enzyme involved in purine metabolism. HPRT catalyzes the conversion of the purine bases hypoxanthine and guanine into the purine nucleotide pools (Jinnah 2009). Without HPRT, hypoxanthine and guanine are not converted to nucleotides but are instead degraded to uric acid, a by-product of purine metabolism. These effects are accompanied by enhanced purine synthesis. Failed conversion of hypoxanthine and guanine and consequent enhanced purine synthesis cause excess uric acid production in Lesch–Nyhan disease.

Overproduction of uric acid in Lesch–Nyhan disease can be treated with allopurinol, a xanthine oxidase inhibitor that inhibits conversion of hypoxanthine and guanine to uric acid. Allopurinol and hydration reduce the occurrence of gouty arthritis, kidney stones, and tophi. Efficacious treatments for other aspects of Lesch–Nyhan disease have proven to be elusive.

The pathophysiologic basis of the neurobehavioral manifestations of Lesch–Nyhan disease appears to differ from somatic manifestations. Mitigation of uric acid overproduction in Lesch–Nyhan disease does not affect its neurobehavioral

manifestations. While no generally effective treatment for the neurobehavioral manifestations of Lesch–Nyhan disease has been identified to date, muscle relaxants have been used as palliative treatment for generalized dystonia (http://www.lesch–nyhan.org/en/treatment/neurological-disability/). Some neurobehavioral manifestations have been managed with behavioral therapy including therapy for short attention spans and associated learning disabilities. Overall, behavioral manifestations such as self-injury are mitigated by physical restraint which includes exclusion of sharp objects from the patient and limiting arm movement with ties or splints to control finger biting or hitting. In some cases, self-biting is managed by removing the teeth. Behavioral therapy, also employed in some cases, focuses attention on good behaviors to the exclusion of bad behaviors which are further minimized by avoiding situations in which they arise. Finally, other medications including gabapentin, carbamazepine, and diazepam have been tried in the management of self-injury with mixed or limited results. Risperidone has shown some evidence of efficacy against self-injury (Allen and Rice 1996); however, it is unclear whether any apparent effects on self-injury are non-specifically related to sedation. Given the limitations of the therapeutic approaches tried to date, new-generation treatments for behavioral symptoms remain a high priority.

The physiologic basis of the neurobehavioral abnormalities in Lesch–Nyhan disease is not fully elucidated. Dopamine pathways of the basal ganglia are affected, as demonstrated by marked (60–80 %) dopamine loss in postmortem neurochemical studies (Lloyd et al. 1981; Saito et al. 1999) and reductions in dopamine neuronal markers (Ernst et al. 1996; Wong et al. 1996) in this region. Detailed neurobiological descriptions of many other neurobiological features have been provided in extensive reviews (e.g., Papadeas and Breese 2014). However, circuit functions and definitive descriptions of maladaptive pathways are poorly understood.

2 Overview of Experimental Models

The rareness of Lesch–Nyhan disease renders studies in patients challenging and elevates the importance of experimental models in elucidating its biological aspects (Jinnah 2009). Several tissue culture and animal models that elucidate various aspects of Lesch–Nyhan disease have been developed. They have been reviewed previously by Jinnah (2009) and are summarized briefly herein.

Tissue culture models with non-neuronal cells including erythrocytes, lymphocytes, and fibroblasts derived from Lesch–Nyhan-affected patients have shed light on the metabolic and cellular impacts of HPRT deficiency. Cells deficient in HPRT accumulate purine waste products because of the failure to recycle hypoxanthine and guanine. Unexpectedly, however, purine deficiency has not been consistently associated with the failure of purine recycling (Shirley et al. 2007).

Tissue culture models with neuronal and glial cells developed as HPRT-deficient sublines of established neuroblastoma or glioma cell lines have been used to study the central nervous system dysfunction in Lesch–Nyhan disease. These models

reveal neuronal structural and chemical abnormalities including reduction in dopamine in HPRT-deficient dopamine neuron-like lines (Bitler and Howard 1986; Yeh et al. 1998; Shirley et al. 2007; Lewers et al. 2008). This dopamine deficiency is consistent with the evidence of dopamine pathway damage in patients with Lesch–Nyhan disease (Lloyd et al. 1981; Ernst et al. 1996; Wong et al. 1996; Saito et al. 1999).

Several animal models of Lesch–Nyhan disease or specific manifestations such as self-injurious behavior have also been developed. For example, self-injurious behavior is observed after high doses of chronic amphetamine, caffeine, or opiates and single-dose clonidine (Jinnah and Breese 1997; Jinnah et al. 1999a).

Introduction of the HPRT-deficient mouse in 1987 marked the first time that a genetically engineered mouse modeled a specific human disease (Hooper et al. 1987; Kuehn et al. 1987; Jinnah 2009). Like people with Lesch–Nyhan disease, the mutant mice cannot recycle hypoxanthine or guanine and exhibit increased purine synthesis (Jinnah et al. 1992, 1993). In humans, these biochemical abnormalities lead to increased uric acid with clinical consequences of gout or kidney stones (Jinnah and Friedmann 2001). In the mutant mice, in contrast, the biochemical abnormalities do not result in increased uric acid with clinical consequences because of the presence of uricase, which degrades uric acid into allantoin. Furthermore, while mutant mice, like people with Lesch–Nyhan disease, show a loss of dopamine in the basal ganglia (Jinnah et al. 1999b), they do not exhibit the motor or neurobehavioral abnormalities that people do (Engle et al. 1996; Jinnah 2009). The reason that the dopamine loss is not associated with neurobehavioral consequences in the mutant mice is unknown. Further subsequent attempts to create a mouse with comparable behavioral phenotype as Lesch–Nyhan disease has proven difficult, in part because of failure to obtain viable mice after lesioning dopaminergic neurons during development (Breese et al. unpublished observation). However, the accidental discovery of a perinatal-6-hydroxydopamine (6-OHDA)-induced Lesch–Nyhan-type behavioral profile of self-injury in adult rats provided a new avenue for research.

3 Perinatal 6-OHDA Model of Lesch–Nyhan Disease

The relevance of the perinatal 6-OHDA model to self-injurious behavior in Lesch–Nyhan disease was discovered serendipitously. Breese and colleagues initially administered 6-OHDA intracisternally to young rats in investigations designed to examine the specificity of 6-OHDA for dopamine reductions in brain. Young animals were chosen in an attempt to develop models to complement a focus in Breese's center on childhood diseases at that time. In young rats, 6-OHDA caused reductions in tyrosine hydroxylase and dopamine (Breese and Taylor 1972; Jinnah et al. 1999b)—observations that mirrored results previously found in animals administered 6-OHDA during adulthood (Breese and Taylor 1970).

From these early studies (Breese and Traylor 1972), several of the original young rats that had been perinatally treated with 6-OHDA were maintained until adulthood and challenged with the dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA)—an exposure which had previously been observed to enhance locomotor activity when given to rats treated as adults with 6-OHDA. Unexpectedly, the non-specific enhancement of locomotion was not observed in rats treated perinatally with 6-OHDA. Rather, the surprising and disturbing observation was made that all of these animals exhibited self-mutilation of the front legs and abdominal area during a time frame when hyperlocomotion was the only expected phenotype. Such an outcome had never been observed in L-DOPA-treated rats treated as adults with 6-OHDA (Breese et al. 1984).

The consistent observation of self-mutilation among rats perinatally treated with 6-OHDA and challenged as adults with L-DOPA led Breese and colleagues to abandon this model for several years. However, based on emerging biochemical evidence for dysfunction of brain neurotransmitters in Lesch–Nyhan patients (Lloyd et al. 1981), the animal model was revived. These observations in patients with Lesch–Nyhan disease were consistent with the Breese et al. (1984) publication on self-mutilation associated with perinatal depletion of dopamine with 6-OHDA. Later studies went on to show that patients with Lesch–Nyhan disease have abnormally few dopaminergic nerve terminals and cell bodies as assessed by positron emission tomography (Ernst et al. 1996). Compared with healthy control patients (n = 15), patients with Lesch–Nyhan disease (n = 12) had 31 % lower dopaminergic activity in the putamen, 39 % lower in the caudate nucleus, and 57 % lower in the substantia nigra and ventral tegmentum. These abnormalities were observed even in the youngest patients (range 10–20 years), a finding that led the investigators to conclude that the dopaminergic deficits in Lesch–Nyhan disease are developmental rather than degenerative in origin.

Together, the data from patients and the perinatal 6-OHDA model suggest that injury to dopaminergic systems early in life might underlie the self-mutilation that characterizes Lesch–Nyhan disease. Since its original development, this model has been used extensively to probe the neurobiological basis of the self-injury with a modified behavioral endpoint (first nick of skin due to biting, with immediate follow-on treatment with a dopamine D_1 receptor antagonist to prevent progression to abject self-injury (reviewed by Papadeas and Breese 2014).

Jinnah notes that no "ideal" model that replicates all features of Lesch–Nyhan disease has been developed (Jinnah 2009). Rather, the development of multiple models, each elucidating a specific aspect of this multifaceted disease and directed at answering specific research questions, has proven to be a more useful approach. Tissue culture models and the HPRT-deficient mouse model have shed light on the effects of HPRT deficiency on purine metabolism but have not helped to elucidate the basis of the neurobehavioral manifestations of the disease. The neonatal 6-OHDA model does not directly address purine metabolic effects but does help to elucidate the relationship between dopamine neuronal and basal ganglia dysfunction and self-injurious behavior and provides a useful system for probing circuits, neurotransmission, interactions with stress, and preclinical pharmacology. While

evidence from pharmacological, postmortem neurochemical, and imaging studies in humans and from animal models suggests that dopamine deficiency might underlie the self-injurious behavior across disorders (Devine 2012), a diversity of contributing mechanisms might better represent the disease. Thus, having multiple models, including the perinatal 6-OHDA model, is essential.

While Lesch–Nyhan disease is an orphan disease affecting just a few per million people, models of Lesch–Nyhan disease potentially shed light on the pathology and management of numerous disorders involving self-injury such as mental retardation and autism. In fact, the behavioral profile of Lesch–Nyhan disease and its animal models suggest that this condition is not only generalizable to the spectrum of neurobehavioral pathology in neurology and psychiatry, but may also constitute one of the most profound neuroadaptations in neuroscience. Thus, rare genetic disorders such as Lesch–Nyhan disease can have significant relevance to overall human health. The insights of these past decades of research into this disease have had general implications for neuroscience (e.g., Breese et al. 2005; Fu et al. 2014) all the while providing hope for elusive therapeutic options for patients with Lesch–Nyhan disease themselves.

4 Recent Developments

4.1 Clinical Science

Recent clinical research is consistent with the prenatal 6-OHDA model in continuing to support dopaminergic involvement in the neurobehavioral manifestations of Lesch–Nyhan disease. New clinical data also suggest an important role of epigenetics (e.g., Nguyen 2015; Trigueros Genao and Torres 2014).

4.1.1 Additional Support Consistent with Dopaminergic Involvement in Lesch–Nyhan Disease

Evidence consistent with the presence of basal ganglia dysfunction in Lesch–Nyhan disease comes from a case study in which a 29-year-old patient with refractory generalized severe dystonia and self-injurious behavior was treated with chronic bilateral globus pallidus internus deep brain stimulation (Piedimonte et al. 2015). During a 5-year follow-up period, self-injurious behavior ceased and dystonia as assessed by the Burke–Fahn–Marsden Dystonia Rating Scale and the Mean Disability Scale significantly improved. In another case report involving chronic bilateral globus pallidus internus deep brain stimulation, dystonia and self-mutilation in a 15-year-old boy ceased over several weeks after initiation of stimulation (Abel et al. 2014). After a right lead fracture, the dystonia and self-mutilation returned on the left side of the body only. These results suggest that these neurobehavioral manifestations of Lesch–Nyhan disease are lateralized. Assessment of potential laterality in the perinatal 6-OHDA model is warranted.

In a study investigating the basis of the dopamine deficiency in Lesch–Nyhan disease, substantia nigral neurons in 5 Lesch–Nyhan patients compared with 6 controls at autopsy were found to have reduced melanization and reduced tyrosine hydroxylase immunoreactivity but no signs of a degenerative process (Göttle et al. 2014). The authors suggested that the neurochemical phenotype of Lesch–Nyhan disease is not associated with neurodegeneration.

Reductions in gray matter and white matter in basal ganglia and other brain regions were observed in Lesch–Nyhan disease as revealed by observational studies using voxel-based morphometry in 21 patients with classic Lesch–Nyhan disease; 17 with Lesch–Nyhan variant disease; and 33 age-, sex-, and race-matched healthy controls (Schretlen et al. 2013, 2015). Reductions in volume versus controls were greater in patients with classic Lesch–Nyhan than in patients with Lesch–Nyhan variant disease.

Intrathecal baclofen was associated with reductions in dystonia, cessation of self-injurious behavior, and improvement in sleep that persisted through 5–16 months of follow-up in 3 patients with Lesch–Nyhan disease (Pozzi et al. 2014). The authors speculated that the results might be explained by an interaction between baclofen and dopamine complemented by baclofen-associated anxiolysis.

4.1.2 Role of Epigenetics

Lesch–Nyhan disease has been diagnosed in patients lacking an HPRT mutation, and family members with the same genetic defect can manifest with differing severities of Lesch–Nyhan disease (Trigueros Genao and Torres 2014; Ceballos-Picot et al. 2013). Epigenetic processes (that affect gene expression without affecting DNA sequence) might account for this clinical variability (Trigueros Genao and Torres 2014).

Consistent with this possibility, Nguyen (2015) recently found a wide range of amyloid precursor protein mRNA isoforms in Lesch–Nyhan patients, the implications of which are unknown, yet suggest further complexity in the full neurobiological manifestations underlying the disease. Relatedly, Kang and Friedmann (2015) recently reported genetic dysregulations common to both Alzheimer's and Lesch–Nyhan disease so the intriguing question arises as to the potential epigenetic mechanisms underlying both.

4.2 Basic Science

In recent studies, neuronal perturbations in the HPRT-deficient mouse extended outside the dopamine system to the histamine system where 1-methylhistamine and 1-methylimidazole-4-acetic acid were found to be reduced in multiple regions of brain (Tschirner et al. 2015). Whether histamine-based manipulations into the perinatal 6-OHDA self-injury might be effective or whether therapeutic

interventions could result from these new observations is unknown. In gene screening research, Torres and Puig (2015) demonstrated that HPRT actions on transcription factor genes critical to neuronal differentiation led to deregulated WNT4 from the WNT/β-caterin pathway, engrailed homeobox 2 gene, and increased tyrosine hydroxylase, DRD1, and adenosine and HTR7 serotonin receptors. Relatedly, Kang et al. (2013) demonstrated that the HPRT gene regulates a host of developmental and metabolic pathways in embryonic stem cell neuronal differentiation. The implications of these findings have yet to be determined but again suggest broad impacts of HPRT beyond its expected role. These broad impacts have been suggested by Dammer et al. (2015) who examined the proteome profiles in an HPRT deficiency model and found extensive changes in protein expression depending on whether cells were differentiated or not. They further report that not all of the identified were related to purine recycling, a finding consistent with heretofore underappreciated mechanisms that may underlie Lesch–Nyhan disease. Comparable efforts to scan the transcriptome have led to similar findings in genes and gene clusters (Dauphinot et al. 2014). One could speculate that such unexpected changes could provide links to common behavioral phenotypes across models such as the perinatal 6-OHDA model and others.

5 Future Directions

In clinical care, palliative care around minimization of injury and continued use of allopurinol to limit the consequences of the HPRT deficiency will likely remain primary and important foci. In both the clinic and research, it has been observed that stress complicates the effective management of behavior in Lesch–Nyhan patients (e.g., Anderson and Ernst 1994). Thus, a role for stress-related circuitry is apparent. In this regard, understanding the neurobiological mechanisms of stress induction of behavioral pathology (e.g., in drug addiction or induction of clinical depression) could prove useful in targeting circuits as well. It is known that select circuits engaging the amygdala and its complex circuitry along with select neurochemical systems such as corticotropin-releasing factor, serotonin, GABA, and norepinephrine are integrally involved in stress effects in other neurobehavioral pathologies (e.g., Knapp et al. 2007, 2011a, b; Huang et al. 2010). While a full understanding of the contributions of these and other systems to behavioral pathology generally is not available, it is clear that Lesch–Nyhan disease is a chronic stressful condition for patients and should be considered further. The underappreciated stress component in the animal models could also be influencing the course of the neurobiological adaptations (e.g., those mediated by corticosterone, corticotropin-releasing hormone, or others) that in turn elicit differential behavioral sensitivity. In a pemoline-induced self-injury model, for example, stress worsened the severity of injury (Muehlmann et al. 2012). Further, Stodgell et al. (1998) showed that footshock stress exacerbated self-injurious behavior in the perinatal 6-OHDA model of Lesch–Nyhan disease.

On other fronts, new technologies such as CRISPR9, while in early phases, have captured the attention of neuroscience and biology in general. It is hoped that such technologies will help hasten the elucidation of the role of genes in pathology through insertion/deletion of genes in whole animal or tissue systems. MicroRNAs, too, may help to advance Lesch–Nyhan research. Across the neurobiological spectrum, research is accelerating toward the discovery of functional microRNAs as players in the course of neurobehavioral adaptation and behavioral responsivity. With regard to Lesch–Nyhan disease, Guibinga (2015) has recently proposed a model that accommodates the idea that mRNA transcripts of the HPRT gene can exert pleiotropic effects across a variety of genes and signaling pathways that expand the suspected actions of this gene (or gene system) beyond its well-known basic metabolic housekeeping functions. Specifically, Guibinga (2015) proposes that competitive endogenous RNAs (ceRNAs) are engaged and may regulate cross talk between neural transcripts and miRNAs. A focus on genes and gene screening more generally may provide new clues to the molecular and cellular processing underlying Lesch–Nyhan disease. Moreover, differential profiles of gene expression over developmental windows post-lesion are in all likelihood critical in the course of neuroadaptations in animal models. While select genes have been examined (e.g., Torres and Puig 2015), the most prominent being the purine metabolic gene encoding the HPRT enzyme itself, comprehensive gene expression profiling across brain regions thought to be engaged in the neurobehavioral pathology of this disease has not been widely reported. Given the critical narrow window of time in which inducing the lesion will ultimately come to elicit the behavioral sensitivity in rats that models Lesch–Nyhan disease, gene screening techniques could identify gene clusters and gene expression profiles that are prominent in the underlying adaptations. Profiling soon after the perinatal 6-OHDA-induced lesion would reveal one pattern of gene expression, while profiling after pharmacological induction of hyperactivity and/or self-injurious behavior in older lesioned animals could reveal another. Both approaches could focus attention on new targets not only for therapeutics, but also for research on relevant mechanistic etiologies in this developmentally dependent pathology.

Another avenue of research that could impact both self-injury in Lesch–Nyhan disease and in other conditions characterized by self-injury is the application of contemporary technologies pertaining to chemogenetic and/or optogenetic manipulations of circuits as well as functional imaging of the consequences of these interventions (Deisseroth 2015). It is clear that circuit dysfunction is paramount in self-injury, but the nature of this dysfunction is not known. Classical thinking about dopamine D_1 or D_2 receptor pathways from the striatum has long been instructive (e.g., Surmeier et al. 2007). Assessing them directly via tracing studies, or via exciting or silencing select neuronal populations in neurobehavioral circuits suspected of regulating locomotor behavior or self-injury, constitutes an important opportunity. Combined with fMRI in rats, the optogenetic or chemogenetic approach can help to isolate and control maladaptive circuits upon which self-injurious behavior depends, and lead to discoveries of other regions, and differential connectivities among regions, that may not have been suspected.

Adeno-associated viruses (AAVs) manufactured to deliver and functionally express inhibitory halorhodopsin or excitatory channel rhodopsin to select neuronal phenotypes (e.g., subtypes of GABA output neurons of the striatum that project differentially throughout the motor integration and output circuitry) would be central players in this effort. Myriad variants of these viruses provide neuroscientists with an incredible array of tools to probe the necessity or sufficiency of select neuronal groups in specific brain regions in mediating behavioral phenotypes (Murlidharan et al. 2014; Weinberg et al. 2013). These tools could readily be employed to probe the nature of the circuit dysfunction that regulates self-injury in the perinatal 6-OHDA model. Moreover, parallel employment of these tools (or related ones described below) to the HPRT model may well help isolate common pathways and mechanisms that lead to self-injury.

Relatedly, with the advent of DREADD (Designer Receptors Exclusively Activated by Designer Drugs) (e.g., Lee et al. 2014; Urban and Roth 2015), it is now possible to modify existing brain circuits through custom-designed viral systems to respond to either peripherally or centrally administered compounds such as the designer drug clozapine-N-Oxide (CNO), which on its own has no effects in brain. New-generation DREADD-type tools are being designed to increase the sophistication and control that experimenters have in circuit discovery. Further, it is important to remember that the loss of dopamine during the development in the animal model results in a maladaptive neurobiological condition that must differ from that seen in Parkinson's disease and models thereof as the behavioral profiles of the two conditions are very different. Thus, a persistent maladaptive circuit function arising over the course of development post-6-OHDA lesion must be present, at least somewhat unique to Lesch–Nyhan disease, and should be approachable with employment of these novel tools in the model. Employing these tools in the perinatal 6-OHDA model of Lesch–Nyhan disease and associated disorders could lead to a more refined, heuristically valuable, and therapeutically relevant understanding of the behavioral components of this devastating disease.

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