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Lesch-Nyhan Disease

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Abstract

Lesch-Nyhan disease (LND) is a rare X-linked inherited neurogenetic disorder of purine metabolism in which the enzyme, hypoxanthine-guanine phosphoribosyltransferase (HGprt) is defective. Despite having been characterized over 50 years ago, it remains unclear precisely how deficits in HGprt enzyme activity can lead to LND. Several studies have proposed different hypotheses regarding the etiology of this disease, and several treatments have been tried in patients. However, up to now, there is no satisfactory explanation of the disease and for many LND patients, efficacious treatment for persistent self-injurious behavior remains unreachable. Here, I discuss current knowledge about this mater and future directions in the field. A role for epistasis between mutated hypoxanthine-guanine phosphoribosyltransferase 1 (*HPRT1*) and amyloid precursor protein (*APP*) genes is suggested. This finding may provide new directions not only for investigating the role of APP in neuropathology associated with HGprt-deficiency in LND but also for the research in neurodevelopmental and neurodegenerative disorders in which the *APP* gene is involved in the pathogenesis of diseases and may pave the way for new strategies applicable to rational antisense drugs design.

Keywords: Lesch-Nyhan disease; *HPRT1* gene, HGprt enzyme; *APP* gene; APP-mRNA isoforms; Mutation; Epigenetics; Epistasis; Antisense drugs

Introduction

It is with great pleasure to introduce a special issue, namely ”Lesch-Nyhan Disease” which is scheduled to appear this year in Enliven: Pediatrics and Neonatal Biology. I cordially invite authors to contribute their excellent works to this exciting forum. Submissions are now open and will be fully considered for publication.

Lesch-Nyhan disease (LND) is a rare X-linked inherited neurogenetic disorder of purine metabolism affecting 1 in 380,000 people, and caused by deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGprt, EC. 2.4.2.8; MIM 300800) [1-3]. Complete or severe deficiency of HGprt activity leads to LND (MIM 300322) [1]. Classical features of LND include hyperuricemia and its sequelae (gout, nephrolithiasis, and tophi), motor disability (dystonia, chorea, and spasticity), intellectual impairment, and self-injurious behaviors such as self-biting, self-hitting, eye poking, and others. Self-injurious behavior is universal in LND. It usually emerges before 4 years of age, but may be delayed until the second decade of life. Patients with LND are unable to walk and are confined to a wheelchair. Partial deficiency of HGprt enzyme activity (MIM 300323) is characterized by consequences of overproduction of uric acid and variable spectrum of neurological manifestations, without the self-injurious behaviors: Lesch-Nyhan variants, LNVs [4,5]. The mildest variants have isolated overproduction of uric acid. These patients do not have clinically overt neurological or behavioral abnormalities, and most often are described as having HGprt-related hyperuricemia (HRH). In between the two extreme phenotypes of LND and HRH is a spectrum of phenotypes with varying degrees of neurological and behavioral abnormalities, designated as HGprt-related neurological dysfunction (HND). Patients with HND suffer from overproduction of uric acid along with some neurological or behavioral difficulties, but they do not exhibit the self-injurious behaviors seen in classic LND. Etiology involves a mutation of the housekeeping hypoxanthine phosphoribosyltransferase 1 (*HPRT1*) gene, which is on the long arm of

the X chromosome (Xq26.1). The gene has only one functional messenger RNA transcript (HPRT-mRNA) and contains 9 exons and 8 introns [4,5]. The *HPRT1* gene is on the X-chromosome; so males are affected and females in families at risk may be carriers of the mutation. Lesch-Nyhan disease historically has served as a model for exploring genotype-phenotype correlations and it was the first neurogenetic disorders for which the responsible gene was identified and is the most intensively studied genes in human genetics [5]. To date, more than 600 heterogeneous mutations in the *HPRT1* gene have been reported (see research section at http://www.lesch-nyhan.org/) [5].

Diagnosis

Diagnosis of LND is based on the following criteria: (1) biochemical: complete or severe deficiency of HGprt enzyme activity and (2) molecular: presence of a mutation in the *HPRT1* gene and (3) clinical: whether clinical symptoms are present or not [5]. Concerning the biochemical data for measurement of HGprt enzyme activity, the best results providing good correlations between residual enzyme function and clinical severity have been obtained when HGprt is studied under naturalistic conditions in living cells rather than in artificial in vitro conditions. In one assay, skin biopsies taken from patients to grow fibroblast cultures. With this assay, patients with the most severe phenotype of LND typically have <1.5% of normal enzyme activity, whereas the mildest phenotype of HRH is generally associated with >10% of more activity. Patients with intermediate phenotype of HND have activity that normally falls in between. Another good assay is based on intact erythrocytes isolated from fresh blood samples from patients. However, two unusual features of erythrocytes cause artifacts in some cases. First, erythrocytes have a lifespan of ~120 days. Second, they lack a nucleus and therefore also lack ongoing messenger RNA and protein synthesis. Thus blood samples reflect a mixture of old and new erythrocytes, so that residual HGprt enzyme activity is dependent upon the structural stability of the enzyme. The live erythrocyte assay is prone to giving artificially low activity for HGprt mutants that are structurally unstable. At the molecular level, the search for mutation in the *HPRT1* gene is usually performed using the polymerase chain reaction (PCR) followed by restriction enzymes digestion or sequencing. Prenatal diagnosis can be performed with amniotic cells obtained by amniocentesis at about 15-18 weeks' gestation, or chorionic villus cells obtained at about 10-12 weeks' gestation. Together, the disorder (LND or LNVs) involved one of the following mutations in type within the *HPRT1* gene such as single base substitution (missense mutation), deletion, duplication, and insertion [5]. Deletions, insertions and duplications are uncommon in LNVs because they most often result in a structurally abnormal protein with no functional activity. Nonsense mutations are similarly uncommon in LNVs because they result in premature termination of translation and absent enzyme activity. Missense mutations may be over-represented in LNVs, because a single amino acid substitution is more likely to permit some residual enzyme function. Here, several software programs have been designated to predict the pathogenicity of individual sequence variants. The most commonly employed include SIFT (http://sift/jcvi.org/), and PolyPhen-2 (http://genetics.bwh.havard.edu/pph2/). SIFT is based on sequence comparisons from homologous or orthologous proteins and PolyPhen-2 uses both structure and sequence information [5]. SIFT correctly classified 92.8% of pathogenic missense mutations in the *HPRT1* gene, but incorrectly classified 7.2% of the mutations as benign. PolyPhen-2 correctly classified 83.1% of known pathogenic mutations. Among those predicted to be benign, 25% were associated with the LND phenotype, and 75% with LNVs phenotype. However, there is a significant failure rate, suggesting caution in relying on their prediction for clinical prognosis of mutations in the *HPRT1* gene. These failure rates are comparable to those reported for other genes [5]. An alternative approach for examining enzyme-phenotype correlations was re-create the *HPRT1* mutations by site-directed mutagenesis, the mutant proteins were expressed and purified in vitro, and their biochemical kinetics were studied with a sensitive spectrophotometric assay. The results so obtained allowed to confirm a good correlation between clinical severity and residual HGprt enzyme activity. Concerning the clinical assessment, although patients are clustered into three distinct sub-groups (LND, HND and HRH), the clinical spectrum actually is more continuous. Some patients may fall between groups, and assignment to one group is sometimes arbitrary. The classification of these cases as HRH or HND depends on the rigor of neuropsychological testing, criteria used to define normal intelligence. Cognitive skills also change dramatically with age, and cognitive deficits are difficult to document for infants and very young children. Normal motor skills also vary dramatically with age and can be difficult to measure in infants. There are some cases in which motor skills were considered normal in the first month of life, but obvious motor delay became apparent within the first year. The occurrence of self-injury can also lead to diagnostic uncertainty. In many classic LND cases, self-injury is severe and obvious with serious tissue damage, and misclassification is unlikely. However, in some cases, self-injury is very mild. The emergence of self-injurious behaviors also is age-dependent. The average age of onset is 3.1 years but the range varies from <1 year to >20 years. The varying age at onset means that distinguishing LND from LNVs cases is subjected to error, especially for cases reported as children. Several cases initially classified as HND because of the absence of self-injurious behaviors, were reclassified as LND when self-injurious emerged later [5]. Thus, the clinical phenotype of an adult with LND or its variants can reflect an interaction between the biology of the disease and psychosocial factors that may modify the disease over time. Careful clinical assessments are essential starting points for understanding genotype-phenotype correlations.

LND Models and Therapies

Models

There is a growing need for the development of LND models to improve drug development. However, due to the rarity of the disease and the inherent difficulty in obtaining human neural tissue, many questions have been answered but many remain to be elucidated, especially the neurological and behavioral features of the disease. The earliest models used to study LND were based on non-neural cells that could be easily acquired from patients, mostly from blood or skin (fibroblasts) [6]. However, these models cannot be used to studying the neurological deficits caused by a deficit in purine recycling. Therefore, these models had been primarily used to study the general biochemical consequences of HGprt deficiency. To circumvent this cell type problem, researchers developed HGprt-deficient subclones of glioma and neuroblastom cell lines [7]. However, results obtained from these models may lose relevance, as the cells were obtained from non-patient neuronal tumors.

Despite the valuable insights that cell models have provided into mechanisms that underlie LND, they have limitations. Most significantly, there is no guarantee that any results obtained from cells in vitro are representative of the same cells in vivo. Thus, various in vivo models of LND have been generated over the years. The first animal model generated for LND was a total lack of HGprt enzyme activity mouse generated in 1987 [8], and a *HPRT1* knockout mouse model [9], and more recently, a *HPRT1* knockout rat model [10]. These models exhibited the metabolic phenotype but lacked any neurobehavioral phenotype. As a result, these models are generally used to investigate neurochemical and metabolic aspects of LND in vivo, rather than the behavioral aspects of the disease. Purely pharmacological models of self-injury have also been developed in rats such as after chronic administration of caffeine [11], or using high doses of pemoline [12]. However, only a small percentage of rats display self-injurious behavior and these tend to be mild.

Treatments

The typical neurobehavioral phenotype observed in LND patients has led to many hypotheses explaining its etiology. Up to present, there is no accepted hypothesis that explains the neurobehavioral symptoms, especially the self-injury of LND. This has made rational treatment development very difficult and has led to the absence of effective LND treatments. Among various hypotheses, the dramatically elevated levels of uric acid in blood that was the one emerged shortly after the discovery of LND. However, this hypothesis does not explain why LNVs phenotypes (>1% enzymatic activity) that have only slightly active of HGprt enzyme do not exhibit the self-injurious behavior. Furthermore, patients who are prenatally diagnosed with LND and are administered allopurinol upon birth and never have significantly elevated levels of uric acid in their blood still develop the classic LND neurobehavioral phenotype [6], suggesting a limited role of uric acid in the neurological features of LND. Today, uric acid overproduction is still treated using allopurinol, and while this effectively manages several aspects of the disease, including gout and liver failure, is not to influence the development of the neurobehavioral symptoms of LND [13]. Another hypothesis expected that failure of purine recycling would lead to a decreased concentration of purines in LND patient cells, as they compensate by increasing de novo purine synthesis, exacerbating uric acid overproduction. To address this, attempt to treat LND with replenishing the purine pool with adenine was performed [14]. The results showed that this treatment did not improve behavioral or neurological symptoms, although it did help reduce uric acid excretion and eliminate megablastic anemia, which is observed in some LND patients [15]. However, the treatment with adenine had to be abandoned due to renal failure caused by the conversion of adenine into the highly insoluble compound 2,8-dioxyadenine. As uric acid levels can usually be managed well using allopurinol alone [6], adenine therapy is no longer used in the treatment of LND. Some studies suggested that LND patients might suffer from serotonin depletion. Studies in animal models found that decreased levels of serotonin in the brain correlated with aggressive muricidal behavior, which was ameliorated by administrating 5-hydroxytrytophan, the metabolic precursor to serotonin [16]. Administration of 5-hyderoxytryptophan, carbidopa, and imipramine simultaneously abolished self-injury in LND patients [17]. However, this effect was temporary (usually only a few weeks) and could not be recaptured by a further administration of these compounds [17,18]. Finally, postmortem studies on LND brains have failed to observe any significant difference in serotonin levels in LND patients [19]. An alternate hypothesis has focused on dopamine, with evidence of a dopaminergic deficit strongly supported [20,21]. Following of this line of evidence, there have been several attempts to reduce the dopaminergic deficit by boosting dopamine production. To date, several small trials have supplemented LND patients with exogenous sources of substrate needed in the dopamine synthesis pathway such as L-3-4-dihydroxyphenylalanine (L-DOPA), is synthesized into dopamine by DOPA decarboxylase and is widely used to increase levels of dopamine in the brain, most notably to treat Parkinson's disease [22] and general dystonia [23]. However, the reported effectiveness of L-DOPA in LND has been inconsistent, ranging from slightly positive to a significantly negative effect on self-injury of LND [24]. In addition, hypothesis of dopaminergic deficiency results in increased sensitization of dopamine receptors in the remaining dopaminergic cells, and is the underlying cause of the neurobehavioral phenotypes found in LND has been also emerged [25].The treatment of dopamine hypersensitivity for LND patients by using antipsychotics such as SCH-12679, fluphenazine, haloperidol, pimozide, risperidone, and tetrabenazine have shown variable results: improving self-mutilating behavior in some patients while showing no effects in others or had to discontinue the trial due to adverse side effects [26-30]. As these drugs have multiple targets within the central nervous system, it is unclear whether the improvement in symptoms is due to the drug's effect on the dopaminergic system or not. At present, there have been no reports of any dopamine antagonists that produce broadly positive outcomes in majority of LND patients. Recently, some promising avenues to treat self-mutilating behavior and dystonia associated with LND have been discovered serendipitously rather than through rational drug design such as deep brain stimulation [31-33], and treatment with S-adenosylmethionine (SAM) [34,35]. In sum, uric acid overproduction can be managed by allopurinol treatment. Spasticity, when present and dystonia can be managed with benzodiazepines and gamma-aminobutyric acid inhibitors such as baclofen. Physical rehabilitation, including management of dysarthria and dysphagia, special devices to enable hand control of objects, appropriated walking aids, is recommended. Self-injurious behaviors must be managed with a combination of physical restraints, behavioral and pharmaceutical treatments such as elbow restraints allow hand use without the possibility of finger mutilation, and dental guards prevent cheek biting, and benzodiazepines or carbamazepine are sometimes useful for ameliorating behavioral manifestations and anxiety. With appropriate allopurinol treatment, renal function is generally preserved [36], and patients survive until second or third decade of life. Causes of death include pneumonia and other infectious diseases. In some cases, sudden and unexpected death has been reported. This appears to have a respiratory rather than a cardiogenic origin [37].

Genotype-Phenotype Correlations

It is also important to note that there are two aspects on which investigators and most publications on Lesch-Nyhan disease are currently focused: neurological impairment specially the self-injury of LND, and phenotypic diversity. What is the link between the genotype and the phenotype in LND? How the loss of HGprt enzyme function affects the brain to cause the neurobehavioral syndrome in LND/LNVs? Indeed, the genotype-phenotype correlations in LND remain incompletely characterized and sometimes conflicting such as the case with the same mutation present different clinical forms [5], and the case of LND patients for whom no mutation could be

detected in the coding region of the *HPRT1* gene [5,38-42]. The former case of discordant clinical phenotypes can be explained by several potential molecular mechanisms that may result in different levels of residual HGprt enzyme activity and thereby discordant clinical outcomes such as (a) variations in the fidelity of splicing mechanisms can result in multiple HPRT-mRNAs. Since the mechanisms responsible for splicing are inherited independently from *HPRT1*, the amount of normal HPRT-mRNAs encoding HGprt may vary among individuals carrying the same splicing mutation [5]; (b) regulatory mechanisms that control HPRT-mRNA transcription from the mutant gene or HGprt protein translation from HPRT-mRNA with aberrant regulatory signals may operate with varying fidelity among different patients with the same mutation. The outcome could be differences in residual HGprt enzyme activity and clinical phenotype. Here, quantitative studies of HPRT-mRNA or HGprt enzyme function may be useful [5,43]; (c) structural instability of the HGprt protein. For unstable proteins, enzyme function depends on the balance between elimination of damaged proteins and ongoing synthesis of new functional protein. Since mechanisms of degradation and synthesis are inherited independently from *HPRT1*, different individuals with the same mutation may have different steady-state levels of HGprt activity [5]. For the later case, there are many explanations: (a) there is a second gene that may cause clinical features closely resembling LND. This possibility is unlikely because the clinical phenotype of LND has never been associated with any other gene [42]; (b) the presence of hidden mutations in non-coding regions of the *HPRT1* gene such as introns, and promoter regions. It is known that mutations in introns or promoter regions can block the transcription of normal mRNA. If production of mRNA is impaired, there will be reduced production enzyme function, even with an entirely normal coding region for the gene. Some reports with LND patients who had single base substitutions in introns creating a false splice site and a grossly abnormal mRNA to be transcribed, and had deletions in the promoter region blocking mRNA transcription, have been described [42, 44-47]; (c) a role of epigenetic mechanisms [41] such as methylation of specific bases in the DNA that can block transcription or abnormal function of micro RNAs that targets the HPRT-mRNA could block transcription and cause reduced enzyme function. So far, there are no proven examples of epigenetic abnormalities involving abnormal methylation or micro RNAs for LND [42].

Future Directions

How the loss of HGprt enzyme function affects the brain to cause the neurobehavioral syndrome in LND/LNVs? The conflicting data between many LND models and clinical trials highlight the need for new models and new techniques for evaluating them. One of the promising avenues for generating a more accurate model of LND on a cellular scale is to use induced pluripotent stem cells (iPSCs) where differentiated patient cells are induced into a pluripotent state [48]. These iPSCs can then be differentiated into a wide range of cell types, including many subtypes of neurons, enabling the generation of patient-specific cellular models. Regarding the animal model for LND, based on the results of the mouse [9] and rat [10] *HPRT1* knockout models, it is possible that the self-injurious behavior due to a loss of HGprt enzyme activity may only occur in a central nervous system (CNS) that is more analogous to human than those found in rodents. Therefore, ideally, a new animal model for LND would be nonhuman primates, although the high costs and uncertain results of creating such a *HPRT1* knockout model. An alternate approach in which both animal and cellular models could be paired with whole-genome gene expression tools such as single-cell RNA sequencing [49] to provide unprecedented resolution of molecular changes that may be caused by HGprt dysfunction at different stages of development. However, up to date, there are no reports of iPSCs and single-cell RNA sequencing being used to probe the etiology of LND or to test potential therapeutics for LND. Recently, a report on the quantification of various beta-amyloid precursor protein (APP) messenger isoforms (APP-mRNA isoforms) in biological samples, especially for identifying the most abundant one that may decisive for the normal status or disease risk has been described [50,51]. This method was applied for identifying the defective APP-mRNA isoform in LND [50] and in a neurodevelopmental disorder resulting from a nonsense mutation in the Ox-2 antigen domain of *APP* gene [52]: APP-mRNA isoform of 624 bp, with a deletion starting after 49 bp of the 5' end of exon 3 followed by a complete deletion of exons 4-15, mutations in exon 1: c.22C>T, p.L8F, and exon 3: c.269A>G, p.Q90R encoding APP_{207} isoform, was found [51,52]. The results showed that expression of the *APP* gene is under epigenetic regulation caused by genetic and environmental factors as well as life events and aging [50,53,54], and indicated an epistasis (gene-gene interactions) between mutated *HPRT1* and *APP* genes [51]. A gene does not function by itself, but rather acts with other genes (epistasis) in a network, to influence complex traits [55]. Epistasis is important, ubiquitous and has become a hot topic in complex disease genetics, such as Alzheimer's disease (AD), schizophrenia, autism, type -2 diabetes, sporadic breast cancer, sickle-cell anemia, etc., in recent years and even common for determining phenotypes for a number of rare Mendelian diseases such as cystic fibrosis, Hirsch sprung disease, etc. [56]. However, the data supporting epistasis in complex human diseases are emerging slowly. This is due to different difficulties that we face in detecting and characterizing epistasis, such as challenges of modeling non-linear interactions, and in the interpretations of results [55,56]. Here, APP pathway is possibly implicated in the development of the neurological and behavioral features of LND/LNVs. Indeed, it was documented that (a) histopathological studies of autopsy tissues from LND patients revealed no signs suggestive of a degenerative process in any brain region [5, 57] and found a larger reduction in white matter (26% reduction) than in grey matter (17% reduction) volumes [58-60]; (b) neurochemical studies of LND brains collected at autopsy have revealed 60-80% loss of dopamine, a critically important neurotransmitter in the basal ganglia. Profound dysfunction of dopamine neurons also has been documented in imaging studies of patients with LND [5]; (c) implication of hypoxanthine excess in LND leads, directly or indirectly through its action in adenosine transport, to aberrations in neuronal development [61]; (d) adhesion of HGprt-deficient neuroblastoma as well as fibroblast from patients with LND/LNVs exhibited dramatically enhanced adhesion compared to control cells [62] and could have consequences for maturation of the CNS as seen in the smaller brain size of LND/LNVs children [58-60]; (e) AD shares gene expression aberrations with purinergic dysregulation of HGprt deficiency [63]; (f) role of *APP* is a key developmental gene related to cell-cell or cell-substrate adhesion, generation of neurons, their differentiation and migration, neurite outgrowth, regulation of synaptic function, and is important for brain morphology and highly coordinated brain function such as memory and learning [64,65]. Consequently, the type of mutation and its location in the *HPRT1* gene is an important factor for provoking disease (LND or LNVs), not only through its effect on residual HGprt enzyme

activity but also through its effect on interactions between mutated *HPRT1* and *APP* genes. The degrees of the neurological and behavioral abnormalities will depend on the functional compensation by the amount of the normal APP-mRNA isoforms and this amount, under epigenetic regulation of alternative APP pre-mRNA splicing as a result of environmental factors as well as epistasis, life events and aging may vary among individuals carrying the same mutation. This could explain the manifestation of different clinical phenotypes from different patients [66-69] and also from different affected family members [5,43,51,70] as well as the evolution of the severity of the disease from HND reported at a very young age to LND when self-injury emerged later [5]. This could explain the cases of HND with mutations predicted to cause complete loss of HGprt enzyme activity [5] and also the cases of LND that involve mutations in non-coding or promoter regions and that have an effect on the HGprt enzyme activity or do not have an effect on the HGprt enzyme activity but they have an effect on interactions between mutated *HPRT1* and *APP* genes [5].The quantitative kinetic method developed for measurement of APP-mRNA isoformsin biological samples, especially for identifying the most abundant one that may decisive for the normal status or disease risk [51] would be useful for identifying the defective APP-mRNA isoform in neurodevelopmental and neurodegenerative disorders in which the *APP* gene is involved in the pathogenesis of diseases such as autism [71,72], fragile X syndrome [72], amyotrophic lateral sclerosis [73], multiple sclerosis [74], and AD [72,75]. Once the defective APP-mRNA isoform responsible for the disease is identified, one of the potential treatment for the disease may include the inhibition or repression of translation into the damaged *APP* protein isoform from the defective APP-mRNA isoform by using antisense drugs [76].

In conclusion, *APP*, a housekeeping gene [77] and an endogenous ligand (http://www.genenames.org/genefamilies/ENDOLIG), is an important molecular hub at the center of interacting pathways and acts as a permissive factor for various neurodevelopmental and neural circuit processes [78], altered APP processing may affect brain function through a host of altered cellular and molecular events. Although LND, a quite rare disease, often is considered a relatively "simple" disorder because it is monogenic and inherited in an X-linked recessive manner permitting evaluation of single allelic defects, the unexpected and sometimes unusual mechanisms that influence genotype-phenotype relationships provide useful principles for other more complex disorders.

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