

A Breakthrough in Understanding the Nature of Canavan Disease, a Human Spongiform Leukodystrophy due to Inborn Errors in the Gene Encoding for Aspartoacylase

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Short Communication

Canavan disease (CD) is a rare early-onset progressive spongiform leukodystrophy in brain of both humans and animals and is due to mutations in the gene encoding for aspartoacylase (ASPA), the enzyme that hydrolyzes N-acetyl-L-aspartate (NAA) [1]. In humans, the effects of CD are generally much more profound than in rodents exhibiting this same genetic lesion. The gene for ASPA is an autosomal recessive and human or animal carriers of mutations do not appear to be affected. ASPA is expressed in oligodendrocytes and based on their large fractional cellular volume, these cells are the major source of ASPA in brain. However, ASPA has also been identified in microglia and in several other cellular brain compartments [2]. NAA is part of a very unusual tri-cellular metabolic cycle in brain as illustrated in Figure 1.

As shown in this figure, NAA is synthesized by neurons from L-aspartate (Asp) and acetyl Co-enzyme A (AcCoA) by NAA synthase [3] where glucose (Glc) is the source of the acetate (Ac) in AcCoA. NAA is the only known precursor of N-acetylaspartylglutamate (NAAG), synthesized from NAA and glutamate (Glu) in neurons

by NAAG synthase [4]. Most neurons in brain synthesize NAA and NAAG and store large quantities both substances. However, neurons cannot catabolize either of these substances. For their metabolism, upon neuron depolarization they are exported to extracellular fluid (ECF) [5]. NAA is targeted to oligodendrocytes where it is hydrolyzed by ASPA liberating Ac and Asp, and NAAG is targeted to the metabotropic Glu receptor 3 (mGluR3) on the astrocyte surface where the Glu moiety of NAAG is then cleaved by NAAG peptidase [6]. This activates astrocytes to initiate Ca⁺⁺ waves and release second messengers signaling the vascular system to increase focal blood flow. NAA is also a product of NAAG hydrolysis and is liberated to ECF and then hydrolyzed by oligodendrocyte ASPA. The tri-cellular metabolism of NAA and NAAG with two synthetic and two hydrolytic enzymes distributed between three cell types, and the mGluR3-NAAG peptidase trigger mechanism on the astrocyte surface that initiates Ca⁺⁺ waves and sends second messengers to the vascular system has been called the “operating system” of the brain. This is because failure of parts of the system has been observed to lead to grossly abnormal brain structure and function [5]. This is evident in an inborn error (IE) in a single human case of hypoacetylaspartia (HA) where NAA synthase is inactive and both NAA and NAAG are absent [7,8]. This individual is profoundly affected showing microcephaly, retardation and poor motor skills, although myelination is relatively normal. The importance of this cycle is also evidenced by the many different IE's that have been observed in human CD where ASPA is inactive to some degree and NAA cannot be hydrolyzed at the rate it is liberated to ECF [9]. In CD this leads to a buildup of both NAA and NAAG in brain ECF which is associated with an extensive spongiform leukodystrophy.

Two hypotheses had been advanced to explain how the possible buildup of NAA and NAAG in ECF might be responsible for the inability of oligodendrocytes to myelinate and/or to maintain the myelin sheaths surrounding axons in white matter in CD [1]. One was that the Ac portion of NAA was required by oligodendrocytes to build the myelin complex, and that in the absence of active ASPA, this could not be accomplished. The other was that CD was an osmotic disease and it was the buildup of NAA and NAAG in ECF that was responsible for the demyelination.

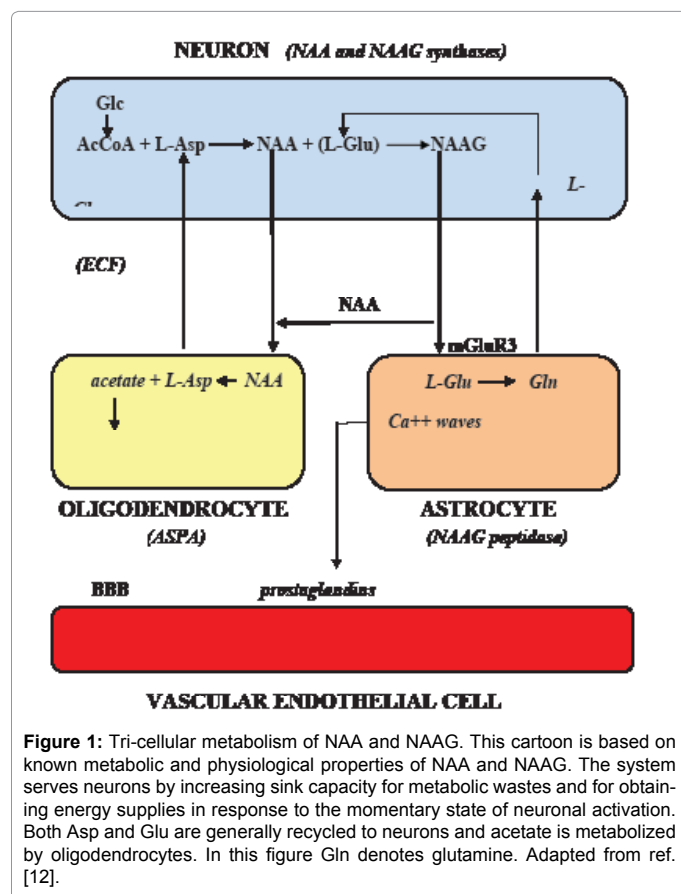


Figure 1: Tri-cellular metabolism of NAA and NAAG. This cartoon is based on known metabolic and physiological properties of NAA and NAAG. The system serves neurons by increasing sink capacity for metabolic wastes and for obtaining energy supplies in response to the momentary state of neuronal activation. Both Asp and Glu are generally recycled to neurons and acetate is metabolized by oligodendrocytes. In this figure Glu denotes glutamine. Adapted from ref. [12].

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Recent studies have shed some light on these hypotheses. An NAA synthase KO mouse similar to the human HA case was created in which NAA and NAAG were absent in brain [10]. The importance of this murine model was that it was relatively normal, clearly demonstrating for the first time that neither NAA nor NAAG were required by neurons for their survival, their ability to signal or for their myelination. Of great importance, a NAA synthase KO mouse that also had no ASPA activity has recently been generated [11]. The lack of ASPA activity alone normally results in CD in both humans and mice. However, in these CD/NAA synthase KO mice, the lack of NAA synthase resulted in no brain NAA or NAAG and remarkably, in the absence of both of these substances there was also a complete rescue of CD. This was shown by their survival, absence of spongiform vacuolization and normal motor performance. Thus, the hypothesis that CD was caused by a lack of NAA with its component Ac, considered to be required by oligodendrocytes for successful myelination, appears to be refuted. This study may also be the first recorded case of the rescue of one IE (CD) by a second IE (HA) and may reflect on the etiology of the very rare mild cases of genetically documented CD that have been reported [9].

The physiological function of NAA is as yet unclear, but it has been proposed to be a mechanism for transport of metabolic water out of neurons and into ECF for its removal from brain [12]. Whether the osmotic hypothesis, based on the abnormal buildup of NAA in ECF as being the primary cause of the leukodystrophy in CD is correct, still remains to be demonstrated. However, in the absence of any buildup of NAA and NAAG in ECF in the CD/NAA synthase KO mice that rescues CD, this is still a possibility. In addition, some animal and human CD cases have been treated with lithium and in these cases, it has been reported that NAA levels in brain rapidly returned to the normal range and that in humans there was also evidence of some improvements in both myelination and motor skills. These findings have been interpreted to suggest that lithium may act by blocking the depolarization related release of NAA to ECF, reducing its osmotic effect, and that its normalization in brain in CD represents a continued presence in neurons alone [13]. Previously, it had been proposed that if CD is an osmotic disease and that it might be treated by inhibiting NAA synthase, thus blocking the buildup of NAA and NAAG in ECF [1]. Based on the rescue of CD mice in the absence of NAA synthase any buildup of these substances in ECF [11], these authors have also proposed that a pharmacological treatment for human CD may be possible by developing specific inhibitors of this enzyme.

In summary, inborn errors in the NAA-NAAG metabolic cycle have led to a fuller understanding of the role of the tri-cellular metabolism of these substances in brain, especially in humans where such metabolic errors may profoundly affect brain development and higher cognitive and motor functions. NAA is considered to be a marker of both neuronal abundance and integrity, and changes in NAA and NAAG levels are currently evaluated in almost all cases of human brain pathology, including those exhibiting cellular and/or psychological manifestations, as well as in many human motor disorders.

Conflicts of Interest

There are none.

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