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The Genetics of Slow Tonic Neurovascular Coupling in Mammalian Brain

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ABSTRACT

Individual neurons in the central nervous system have given up their ability to reproduce or to feed themselves, and in exchange for loss of these functions, neurons are able to survive for periods of 100 years or more. Neurons are serviced by oligodendrocytes which protect, and astrocytes which serve as a conduit to provide sustenance obtained from the vascular system, to neurons and oligodendrocytes. For neurons with elongated axons, oligodendrocytes encircle, and in white matter, form lipid-rich myelin sheaths enclosing each axon in order to prevent axon to axon message interactions. Longevity of neurons is required for normal brain function in that it allows neurons to record and store information in the form of "memories" that can then be accessed over their lifetime. To do this, neurons require large amounts of energy, sometimes within seconds (rapid phasic), and at other times over minutes (slow tonic). In this commentary, the genetic mechanisms used by neurons to accomplish slow tonic delivery of energy are described.

Keywords: *Brain, Canavan disease, Genes, Genetic engineering, Neurovascular coupling*

Abbreviations Used: *Ac, acetate; AcCoA, acetylcoenzyme A; AP, action potential; Asp, aspartate; ASPA, aspartoacylase; CD, Canavan disease; ECF, extracellular fluid; Glc, glucose; Glu, glutamate; Gln, glutamine; GM, gray matter; mGluR3, metabotropic Glu receptor 3; NAA, N-acetylaspartate; NAAG, N-acetylaspartylglutamate; NVC, neurovascular coupling; WM, white matter*

INTRODUCTION

There are two mechanisms that have been identified for the supply of energy to neurons, one a slow phasic neurovascular coupling (NVC) system that increases energy supplies over 10's of seconds, and the other a fast tonic NVC system that increases energy supplies over just seconds[1]. About 50% of the brains' energy appears to be regulated by the slow tonic system. The neurotransmitter for the phasic system has been identified as glutamate (Glu), which leaks from activated glutamatergic synapses to astrocytes, and then initiates a cascade of events that rapidly increase focal blood flow. The neurotransmitter identified with the slow tonic system is N-acetylaspartylglutamate (NAAG), released non-synaptically and targeted to the metabotropic Glu receptor 3 (mGluR3)[2].In this commentary, the unusual tri-cellular N-acetylaspartate (NAA) metabolic system that produces the neurotransmitter NAAG is described, as well as the roles of at least seven genes associated with this process.

The Tri-Cellular Metabolism of NAA and NAAG

The synthesis and hydrolysis of NAA and NAAG in brain are metabolically unique in that they require three brain cell types, neurons, astrocytes and oligodendrocytes, and four enzymes differentially expressed by these cell types for completion; NAA and NAAG synthases in neurons; NAAG peptidase in astrocytes; and NAA aspartoacylase (ASPA) in oligodendrocytes [3]. The source of the acetate (Ac) moiety used by neurons to synthesize NAA is from acetyl-coenzyme A (AcCoA) derived from glucose (Glc) oxidation[4]. Neurons synthesize NAA from AcCoA and aspartate (Asp), and then synthesize NAAG from NAA and Glu[5]. Neither NAA nor NAAG can be hydrolyzed by neurons. However, NAAG, a neurotransmitter containing an NAA moiety, is released to extracellular fluid (ECF) and targeted to the mGluR3 receptor on the astrocyte surface. After docking with and signaling the astrocyte, NAAG is deactivated by NAAG peptidase, liberating NAA and Glu. Astrocytes cannot

hydrolyze NAA and it is released to ECF, enters oligodendrocytes and is hydrolyzed by ASPA producing Ac and Asp which are then completely metabolized [6]. At least seven genes are directly involved in this tri-cellular process, four associated with enzyme expression, and three associated with receptor formation, and membrane efflux and influx transporters. A description of these gene products and their metabolic functions are presented in table 1.

Table1. *Genes, with their expressed enzymes, receptors, and channels, as well as their functions in the tri-cellular metabolism of NAA. Not all of these genes have been fully characterized*

Gene #	Cell Expression	Gene Product	Gene Product Function
(1)	Neurons	NAA synthase	AcCoA + Asp to form NAA
(2)	Neurons	NAAG synthase	NAA + Glu to form NAAG
(3)	Neurons	NAA/NAAG ABCC5 exporter channel	Non-synaptic exporter of NAA/NAAG
(4)	Astrocytes	NAAG peptidase	NAAG hydrolysis to NAA and Glu
(5)	Astrocytes	mGluR3 receptor	Target of NAAG neurotransmitter
(6)	Oligodendrocytes	NAA importer channel	Importer of NAA
(7)	Oligodendrocytes	ASPA	NAA hydrolysis to Ac and Asp

The Function of the Tri-Cellular NAA System

The purpose of the tri-cellular metabolic system has been proposed to be the mechanism for control of slow tonic NVC [2]. In figure 1, the function of this system is graphically illustrated.

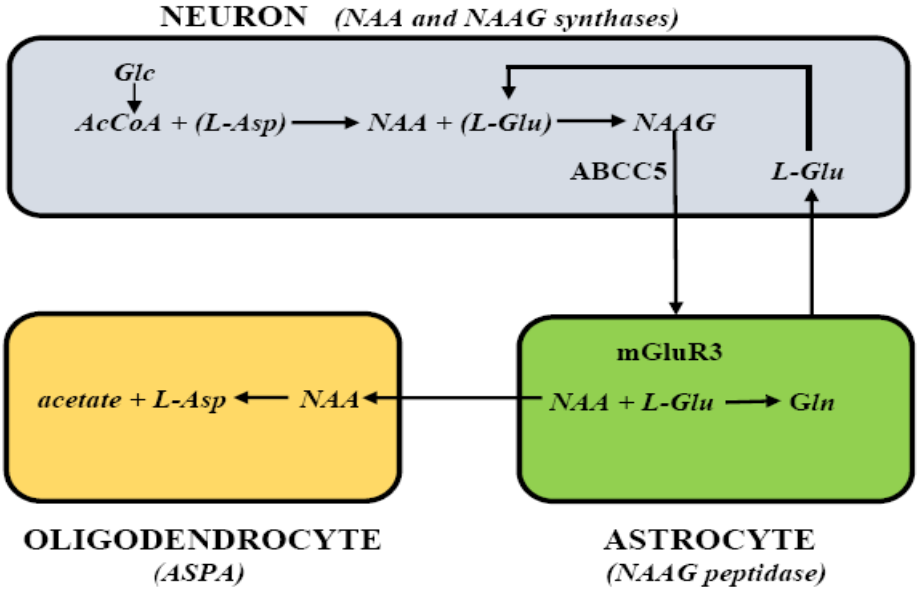

Figure1. *Cartoon of the tri-cellular metabolism of NAA and NAAG*

The tri-cellular metabolism of NAA and NAAG is unique in that it involves the expression of four different enzymes, two anabolic and two catabolic, distributed in three different cell types for its completion. NAA and NAAG are synthesized by neurons and maintained at high mM levels. NAAG can be released to ECF via the membrane ATP-binding cassette subfamily C, member 5 (ABCC5) efflux transporter and is targeted to the astrocyte surface mGluR3 receptor. Upon docking it is hydrolyzed by NAAG peptidase producing Glu and NAA. Glu can be transformed into glutamine (Gln) and recycled to neurons (Glu-Gln shuttle). NAA cannot be further metabolized by astrocytes and it is released to ECF from where it is scavenged by oligodendrocytes, hydrolyzed by ASPA and its products fully metabolized thus completing the tri-cellular metabolic sequence. From [8].

Canavan Disease

Canavan disease (CD) is an early-onset spongiform white matter (WM) disease, the etiology of which is traced to a failure of myelinating oligodendrocytes to develop or maintain neuron axon sheaths, leading to progressive failure of CNS connectivity. CD is a rare human autosomal recessive genetic disease in which inborn errors in the gene for ASPA result in reduced ASPA activity and the buildup

of NAA in ECF in both WM and gray matter (GM). A recent genetic engineering breakthrough in a CD mouse model where a normal human ASPA gene was inserted into the wrong cell, astrocytes, rescued CD and has provided encouragement for a human cure[7].

DISCUSSION

The purpose of NVC is to allow individual neurons to continuously interact with astrocytes that in turn signal the vascular system to increase blood flow and the rate of supply of oxygen and glucose (Glc). The O_2 and Glc are used to rapidly convert adenosine diphosphate (ADP) back into the energy-rich adenosine triphosphate (ATP). The ATP had been used to restore the normal plasma membrane K^+/Na^+ potential that was disturbed as a result of passage of an action potential (AP). An AP or "spike" takes about 0.5 ms to restore using ATP, and the whole spike episode lasts about 1 ms. Neurons are able to spike up to 1000 times/s, and spike frequency this is the basic mechanism that neurons use to transmit signal-encoded information as well as to search for appropriate "memories". Phasic NVC is the response to rapid neuron requirements for information and action, whereas tonic NVC is apparently used for on-going housekeeping needs such as for obtaining nutrients for building cellular metabolites used for growth and repair. Both systems may operate simultaneously in GM, but because of the paucity of synapses in WM, tonic NVC is the dominant system in WM. Thus, it becomes apparent that an absence of ASPA activity in lipid-rich, dehydrated WM can result in the pathological buildup of NAA that has been associated with the spongiform demyelination in CD.

CONCLUSIONS

In this short commentary, two proposed mechanisms used by neurons to continuously interact with astrocytes in GM and WM for supply of needed energy have been presented, as well as the possible reasons for having two different operating systems in brain. More research needs to be done and it is hoped that this commentary with stimulate further studies. Both systems are complex in nature and are important for normal brain function. In addition to CD, components of these metabolic systems have been associated with playing some role in a number of other human neuro and psychopathologies.

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