Effects of ethanol and of alcohol dehydrogenase inhibitors on the reduction of N-acetylaspartate levels of brain in mice in vivo: a search for substances that may have therapeutic value in the treatment of Canavan disease

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Summary: N-Acetylaspartate (NAA) is an important osmolyte in the vertebrate brain that participates in an intercompartmental metabolic cycle. It is synthesized primarily in neurons from L-aspartate (Asp) and acetyl-CoA and, after its regulated release, it is hydrolysed by aspartoacylase in an oligodendrocyte compartment to produce Asp and acetate. NAA also gives a strong 1H magnetic resonance spectroscopic signal, which has led to its widespread use as a neuronal marker. Utilizing this noninvasive technique, the NAA concentrations in normal brain and in brains exhibiting a variety of CNS disease syndromes have been studied. In normal individuals, the concentration of NAA has been observed to be relatively stable over long periods. However, in many CNS disease processes there are long-term changes in the level of NAA that have been considered to signal changes in neuron density or function. We report that the concentration of NAA in brain is malleable and that, in addition to normal endogenous variation or changes due to disease processes, it can be modified by a variety of exogenous drugs and other substances. As a result of this investigation, we have also been able to identify a new class of NAA-active compounds—pyrazole and pyrazole derivatives—that have the ability to reduce brain NAA concentrations in normal mice. The importance
of these findings in understanding the NAA intercompartmental cycle, and its role in Canavan disease, a genetic aspartoacylase deficiency disease, are discussed.

INTRODUCTION

N-Acetyl-L-aspartate (NAA) is an important osmolyte in the vertebrate brain and eye, where its cyclical metabolism is accomplished in two separate compartments. In the brain, NAA is synthesized primarily in neurons, where it is considered to be a specific neuronal marker (Simmons et al. 1991) and, after its regulated release, is rapidly hydrolysed by aspartoacylase (N-acetyl-L-aspartate amidohydrolase, EC 3.5.1.15), which is present in oligodendrocytes (Baslow et al. 1999).

In Canavan disease (CD), a rare recessive autosomal human genetic disorder characterized by early onset and a progressive spongiform degeneration of the brain associated with CNS oedema, intramyelinic swelling and neurological symptoms, aspartoacylase activity is greatly diminished and there is a build-up of unhydrolysed NAA (Baslow and Resnik 1997). In addition, there is also evidence of loss of myelinating oligodendrocytes and, as a consequence in white matter, the loss of the axon’s myelin sheath. All of these factors indicate a progressive water imbalance in CD and suggest that the profound clinical outcome and early mortality in this disease result from a generalized osmotic imbalance and a specific metabolic failure at the neuron–oligodendrocyte interface. The genetic defects in CD are known, and may involve one or more of several alterations in a gene for the production of aspartoacylase that is located on chromosome 17, localized to the 17p13-ter region.

It has been proposed that the intercompartmental cycling of NAA may function as one of several newly identified molecular water pumps (MWPs) that, in neurons, could serve to remove metabolic and other water against a water gradient (Baslow 1998, 1999a, b; Meinild et al. 1998). In CD, where only the catabolic portion of the NAA cycle is affected, the unaffected anabolic portion results in the continuous production and release of NAA, an osmolyte that builds up in extracellular space (ECS) in the brain and which then enters the blood and is excreted by the kidneys. Increased extracellular osmotic pressure due to the unusual presence of NAA in ECS may be responsible for the initiation of the destruction of the neuron–oligodendrocyte paranodal bond and for the observed demyelination in the CD syndrome (Baslow 1999a).

A current attempt to treat CD involves intervention to restore enzyme function by genetic engineering techniques (Leone et al. 1999). An additional therapeutic possibility in CD could include finding pharmacological means to reduce the rate of synthesis and release of NAA. The content of NAA in brain appears to be quite malleable, and a number of drugs and other substances have been reported to be able to reversibly modify NAA concentrations in mammals (Baslow and Resnik 1999). One of these is ethanol (Hirakawa et al. 1994), a widely used recreational substance, also used as a drug in children exposed to ethylene glycol or methanol.