1. INTRODUCTION

1.1. Brain function

The brain is a complex information-processing organ that cannot see, smell, hear, taste or feel. For these things it relies on meaningful encoded electrophysiological signals that originate in a variety of environmental neuronal sensors and without which input, normal cognitive abilities cannot be sustained. The brain’s metabolic lifeline to the environment is the vascular system, upon which it relies for a continuous supply of nutrients, and for removal of waste products. Thus, the well being of both the brain and the whole organism depend on continuous interactions between it, its environmental sensors, and the vascular system. Superimposed on basic individual neuronal requirements for energy and waste product removal, is a very complex neuronal network that receives, interprets and responds to brain messages of both external and internal origin. At the most integrated level of neural networking is the realm of higher cognitive functions.

1.2. Brain information coding

The method used by a neuron to transmit information is by generation a series of wave-like “spikes” or depolarization’s of the plasma membrane. These spikes are interspersed with relative refractory periods during which time the membrane is re-
polarized using energy derived from ATP. The encoded information transmitted is in the
form of these spike-refractory period sequences, and at neuron-neuron synaptic interfaces
the information is translated into chemical neurotransmitters for network processing. The
spike-generation process is also metabolically costly and requires that ATP supplies be
constantly replenished or the timing of the spike-refractory periods will be altered, and
meaningful encoded information lost.

1.3. Brain-vascular system interactions, a neuron control mechanism hypothesis

There are two relatively simple substances synthesized by, and present in great
abundance in neurons in the brains of vertebrates, whose possible functions have been the
subject of research efforts over a period of many decades. One is an N-acetylated
derivative of L-aspartic acid (Asp), \( N \)-acetyl-L-aspartic acid (NAA), and the other, a
dipeptide derivative of NAA, \( N \)-acetylaspartylglutamic acid (NAAG), in which L-
glutamic acid (Glu) is joined to the Asp moiety via a peptide bond.

In this review, evidence is presented, based on results of studies in a number of
different scientific disciplines, which provides new and unique perspectives from which
to evaluate the physiological roles of NAA and NAAG, and allows development of
insights into their importance in brain function. This evidence leads to the conclusion that
NAA and NAAG operate as a linked metabolic system, which functions as a homeostatic
neuronal control mechanism that interacts with the vascular system to remove metabolic
water and supply energy in order to maintain the ability of neurons to receive and
transmit meaningful encoded information. In addition, it has become clear that any
attempt to understand the roles of NAA and NAAG separately, or to try to deduce their
linked roles based on analysis of results obtained in only a few disciplines, would
probably not be successful.

2. DISCUSSION

In this section, the elements involved in developing the neuron-vascular control
mechanism hypothesis are presented in a logical sequence, with each step evaluated by
considering what purpose is served by the particular process or metabolic step involved.
Indeed, what follows is more of a description of events than a hypothesis, a description
that leads to the conclusions that form the basis of a possible understanding the roles of
NAA and NAAG in the brain.

2.1. Neuron requirements for energy and for waste metabolic product removal

The basic function of a neuron is to communicate, and they do this by generating
intracellular electrophysiological signals in the form of action potentials or spikes. The
spikes are then translated into intercellular neurochemical signals transmitted to other
neurons at synapses, and subsequently interpreted at some level in the CNS neural
network (Clifford and Ibbotson, 2000). These energy-dependent spike trains are both
ephemeral and transient in nature, and a neuron must be able to quickly indicate its needs
for increased energy supplies, and for waste metabolic product removal in order to