Journal of Neuroscience Research 66:851–856 (2001)

Brain Metabolism and Brain Disease: Is Metabolic Deficiency the Proximate Cause of Alzheimer Dementia?

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The potential of impairments in oxidative/energy metabolism to cause diseases of the brain had been proposed even before the major pathways of oxidative/energy metabolism were described. Deficiencies associated with disease are known in all the pathways of oxidative/energy metabolism and are associated with some of the most common disorders of the nervous system, including Alzheimer's disease (AD) and Parkinson's disease. A common mechanism in these conditions appears to be a downward mitochondrial spiral, involving abnormalities in energy metabolism, calcium metabolism, and free radicals (reactive oxygen and nitrogen species). In AD, the spiral appears to interact with abnormalities in the metabolism of the Alzheimer amyloid precursor protein (APP) and its Aβ fragment. Several lines of evidence indicate that the mitochondrial spiral may be a proximate cause of the clinical disabilities in AD. Decreases in cerebral metabolic rate (CMR) characteristically occur in AD and in other dementias. Inducing decreases in CMR leads to clinical disabilities characteristically associated with AD and with analogous problems in experimental animals. Treatments directed toward normalizing CMR appear to help at least some patients. Further studies of this possibility and of treatments designed to ameliorate the mitochondrial spiral may prove useful for treating AD and perhaps some other dementing disorders. J. Neurosci. Res. 66:851–856, 2001.

Key words: brain; metabolism; disease; mitochondria; Alzheimer's disease

Recognition of the close dependence of brain function on continuous, efficient utilization of oxygen quickly led investigators to postulate that impairment of cerebral oxidative metabolism might be an important cause of diseases of the brain. This suggestion had been made even before the major pathways of brain metabolism were elucidated. Judah Quastel, one of the founders of modern neurochemistry, stated that hypothesis clearly in the early 1930s:

> The mental symptoms accompanying anoxaemia (as, for instance, that following ascent to high altitudes) are well known. They include loss of judgement and memory, disorientation for time, irritability, and emotional instability. Abnormal mental symptoms accompany carbon monoxide poisoning, and there seems to be little question that anoxaemia of the brain leads to irrational behavior. Anoxaemia may not only be created by lack of oxygen, however, but by conditions set up which render the oxygen unavailable for oxidative purposes. Hence disturbances in the nervous system which result in diminished rates of oxidation will be as productive of mental disorder as lack of oxygen alone (Quastel, 1932).

For the next 40 years, many investigators did not accept that idea. They recognized, correctly, that cutting off the supply of oxygen or glucose killed brain cells, for instance in strokes. They thought, correctly, that measurable falls in adenosing triphosphate (ATP) typically are associated with cell death. However, they assumed, incorrectly, that an impairment of oxidative/energy metabolism severe enough to have any physiological effect would kill cells. That error arose in part because the other functions of mitochondria were not yet appreciated, including their important role in modulating intracellular signal transduction.

Work over the last 30 years has proved Quastel's insight to be prescient. Deficiencies in all the major pathways of oxidative/energy metabolism have been found in patients with brain diseases (Table I). Many of the most common and important diseases of the brain have been found to be associated with deficiencies in these pathways (Table II). The study of oxidative/energy metabolism in diseases of the brain has become a booming area of investigation.

That a variety of clinical syndromes can be associated with disorders of oxidative/energy metabolism is in ac-

Contract grant sponsor: NIH; Contract grant number: AG 14930; Contract grant sponsor: Overbrook Foundation; Contract grant sponsor: Institute for Aging; Contract grant sponsor: Winifred Masterson Burke Relief Foundation.

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Received 19 May 2001; Revised 5 September 2001; Accepted 5 September 2001

TABLE I. Brain Disorders Associated With Deficiencies in Oxidative/Energy Metabolism*

Pathway	Disorder(s)
Glycogenolosis	Delirium, stupor and coma, MD
Glycolysis	Tremors, hypotonia
PDHC	MD with lactic acidosis, SNE, ataxias, HD, AD
Krebs' tricarboxylic acid cycle	MD with lactic acidosis, ataxia, PD, PSP, AD
Electron transport	Mitochondrial encephalomyopathies, HD, PD, AD
Gluconeogenesis	Lactic acidosis, delirium, stupor and coma
Carnitine acetyltransferase	Ataxia
Glutamate dehydrogenase	Ataxia (OPCA, MSD/PSD)

*MD, mental deficiency; SNE, subacute necrotizing encephalopathy of Leigh; HD, Huntington's disease; AD, Alzheimer's disease; PD, Parkinson's disease; OPCA, olivopontocerebellar atrophy; MSD, multiple system disorder; PSD, Parkinson's spectrum disorder; PSP, progressive supranuclear palsy.

TABLE II. Common Brain Diseases With Deficiencies in Oxidative/Energy Metabolism

Disorder	Nature of metabolic deficiency
Delirium	Hypoxia (anoxic, histotoxic, anemic, etc.), hypoglycemia
Wernicke-Korsakoff	Thiamin deficiency: PDHC, KGDHC, transketolase
Pellagra	Niacin deficiency: NAD/NADP-dependent enzymes
Alzheimer's disease	PDHC, KGDHC, COX
Parkinson's disease	Complex I, KGDHC
Huntington's disease	Caudate metabolism, PDHC
Cerebrovascular disease	Decreased O_2, decreased glucose, increased lactate
Schizophrenia?	mtDNA defects?

cordance with current knowledge on genetic brain diseases, i.e., "inborn errors of metabolism" (Scriver et al., 2001). The previously assumed tight association between specific genetic-biochemical defects and specific clinical syndromes has not been borne out by more recent and more extensive studies (Wallace, 1999; Blass and McDowell, 1999; Blass, 2000, 2001; Scriver et al., 2001; Gravel et al., 2001). The earlier view appears to have been due in part to systematic ascertainment errors, which arose because relatively few patients and controls could be studied by the low-throughput methods then available. Screening of larger populations has shown that even classical, hexosaminidase A-deficient Tay-Sachs disease can be associated with at least five distinct syndromes (Gravel et al., 2001). They include schizophrenia and motor neuron disease as well as "classic" Tay-Sachs disease with severe brain damage in infancy and death by 4 years of age. Genetically determined deficiencies of hexosaminidase A occur even in clinically normal people. In general, mutations that lead to functionally milder metabolic deficiencies tend to be associated with milder clinical disorders of later onset, but the relationships are not quantitatively tight (Wallace, 1999; Blass and McDowell, 1999; Blass, 2000, 2001; Scriver et al., 2001; Gravel et al., 2001). As yet, the conventional explanations for the variation of clinical phenotype associated with similar genotypes tend to include relatively vague statements about "genetic background" and "environmental influences" (Wallace, 1999; Blass and McDowell, 1999; Blass, 2000, 2001; Scriver et al., 2001; Gravel et al., 2001). The state of knowledge regarding disorders of oxidative/energy metabolism is similar to that in other metabolic disorders, in which the mechanisms linking different clinical expressions to similar molecular abnormalities are poorly understood (Wallace, 1999; Blass and McDowell, 1999; Blass, 2000, 2001).

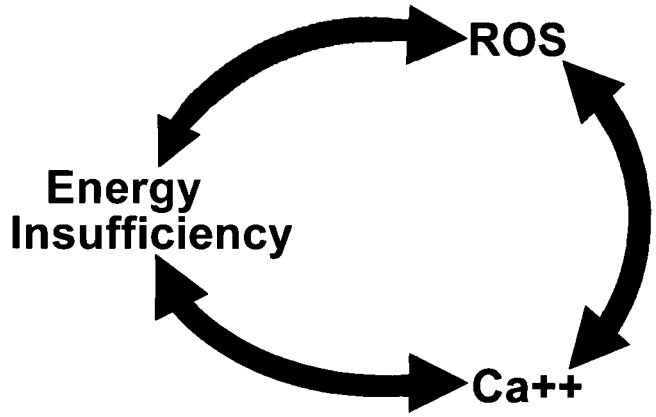

Fig. 1. The mitochondrial spiral. Impairments of energy metabolism, alterations in cellular calcium homeostasis, and excess free radicals (ROS) interact with each other in mitochondria; inducing any one of them leads to abnormalities in the other two. The interaction can set up a deleterious, downward cycle (Blass, 2000).

THE MITOCHONDRIAL SPIRAL

Impairments of oxidative/energy metabolism have a number of consequences in common. One of these is the "mitochondrial spiral" diagrammed in Figure 1 (Blass, 2000). In disorders of oxidative metabolism, abnormalities are typically found in mitochondrial energy metabolism, in calcium metabolism, and in free radicals [reactive oxygen species (ROS) or reactive nitrogen species (RNS)]. These three interact with each other, so that an abnormality in any one of the components of the mitochondrial spiral can be predicted to lead to abnormalities in the other two. A downward spiral is often the result.

Mitochondria are critical subcellular organelles not only for the production of energy but also because they modulate a variety of signaling systems. For instance, mitochondria take up and release calcium; they have a critical role in reducing cytoplasmic calcium in pathological states. Mitochondria are a major source of ROS and RNS, and these radicals have a critical role in modulating cellular functions. For instance, without NO we could not dilate our blood vessels and therefore

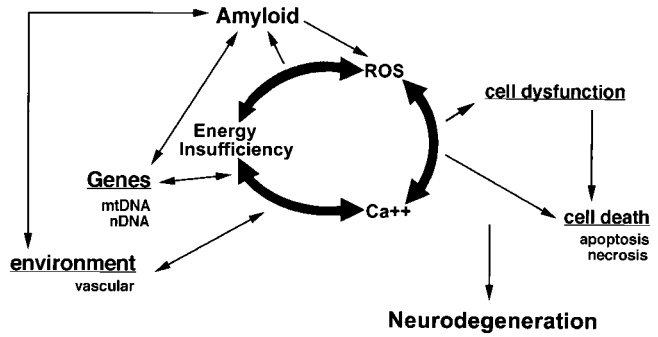

Fig. 2. The mitochondrial spiral in Alzheimer's disease (AD). Either genetic or nongenetic factors can lead to the mitochondrial spiral and to the accumulation of AD amyloid in the brain. Whether the same genes can lead directly to both abnormalities is not known. Vascular disease, which is the most common cause of death in the developed world, is a clinically prominent abnormality, which can lead to increased expression of the AD amyloid precursor protein (APP) and to the mitochondrial spiral. AD amyloid appears to act on cells through free radical mechanisms (Hensley et al., 1996); impairment of oxidative/energy metabolism can lead to increased expression of APP (Kalaria et al., 1993).

could not reproduce our species, at least not by traditional methods. Mitochondrial abnormalities can lead to cell death, both by necrosis and by apoptosis. Mitochondrial proteins such as cytochrome c and apoptosis-inducing factor (AIF) have been shown to play critical roles in apoptotic cell death. Although the mitochondrial spiral itself and a number of its consequences are common to many brain diseases, the precise way in which the spiral interacts with disease-specific abnormalities can obviously vary from disease to disease.

An example is the way in which the mitochondrial spiral may interact with amyloid in Alzheimer's disease (AD). Figure 2 diagrams a possible relationship. Amyloid is thought by many but not all investigators to play a critical role in the pathophysiology of AD. Both genetic and nongenetic factors can lead to increased production of amyloid. Prominent among the nongenetic factors is vascular compromise, as demonstrated in both humans and animal models (Kalaria et al., 1993). Both genetic variations and nongenetic factors can lead to the mitochondrial spiral, and vascular compromise is again prominent among the latter. Whether some of the same genes can lead directly to mitochondrial compromise and directly to amyloid accumulation is uncertain (Sheu et al., 1999). The probable reason why vascular disease is potentially so important in inducing both AD amyloid disease and the mitochondrial spiral is that vascular disease is so common in our species as we age, at least with a modern Western diet. Extensive experimental work by a number of investigators, including Mattson and Markesbery and their coworkers (Hensley et al., 1996), indicates that amyloid (Aβ) can directly induce the mitochondrial spiral. An important way in which it can do so is through free radicals, which can arise when metals are bound to the peptide. Addition of free radical scavengers dramatically reduces the toxicity of amyloid in vitro (Hensley et al., 1996).

Accumulating data from a number of sources indicate that the accumulation of amyloid is not, by itself, adequate to cause dementia (Snowden, 1997; Davis et al., 1999; Wolf et al., 1999). The widely publicized "Nun Study" gave particularly clear results. This is a meticulous clinical and neuropathological study of a community of older religious Sisters in Chicago. Many of the nuns whose brains showed the full *neuropathological* picture of AD, including a high density of neuritic amyloid plaques, were mentally entirely intact during life. They included Sister Mary, who died while mentally sharp on detailed testing when she was 101 years old (Snowden, 1997). (It has been argued that Sister Mary would have been demented if she had lived to age 106 or 110 years. That possibility cannot be checked experimentally. Whether one believes it is a matter of judgment.) The view that amyloid and neuritic plaques in AD are the seminal event in the disease has recently been reviewed (Selkoe, 2001). The neuropathologic data are consistent with the view that neuritic plaques in AD may play a role analogous to that of atherosclerotic plaques in myocardial infarction. Atherosclerotic plaques predispose to the formation of clots, but it is the clotting off of circulation that is the proximate cause of the infarction. We (Blass and McDowell, 1999; Blass, 2000, 2001) and others (Butterfield et al., 1998) have proposed that amyloid plaques may be an important biological risk factor for AD rather than the proximate cause of the clinical signs and symptoms.

The Alzheimer amyloid peptide is, among other things, an antioxidant, because of the properties of its Met_{35} (Butterfield et al., 1998). Expression of the amyloid precursor protein (APP) increases after a variety of insults (Kalaria et al., 1993), suggesting that APP may be an "injury-response protein." These observations suggest that APP expression may increase to protect against oxidative stress. Of course, every reducing agent is potentially an oxidizing agent after it has been converted to the oxidized form. Accumulations of APP or of amyloid in the oxidized form could be a source of free radical damage in AD. That would be consistent with the experimental results and proposal of Butterfield et al. (1998). The situation would then be analogous to the inflammatory cascade. Inability to mount an inflammatory response is life threatening, but excess inflammation has to be treated, for instance, in osteoarthritis.

Another important observation from the Nun Study is that clinically significant dementia is much more likely to develop in people who have both cerebrovascular disease and AD lesions than in people who have AD lesions alone (Hensley et al., 1996). That observation suggests that impaired oxidative/energy metabolism has an important role in the development of the clinical disability. This has contributed to the hypothesis, discussed in more detail below, that the "mitochondrial spiral" is a proximate cause of the clinical dementia in AD.

TABLE III. Koch's Postulates Adapted for Metabolic Disease

1. The metabolic abnormality occurs in the disease state
2. Inducing the metabolic abnormality causes a clinical disorder that mimics the disease state
3. Inducing the metabolic abnormality in experimental animals leads to animal models of the disease
4. Treatment to normalize the metabolic abnormality ameliorates the clinical state

IS THE MITOCHONDRIAL SPIRAL THE PROXIMATE CAUSE OF DEMENTIA IN AD?

Causation is a complicated issue in biology, as has been pointed out by, among others, Aristotle. In the Nineteenth Century, Robert Koch stated four requirements to establish a convincing relationship between an infectious agent and a clinical disease. The following discussion attempts to adapt Koch's Postulates to degenerative disease and specifically to AD (Table III).

Does the Abnormality Accompany the Disease?

Reduction in oxidative/energy metabolism accompanies AD dementia, essentially invariantly. The reductions in cerebral metabolic rate for glucose (CMR_{glu}) and O_2 (CMR_{O2}) and in cerebral blood flow (CBF) are one of the best-documented abnormalities in AD and, indeed, in other dementias as well. They were demonstrated as early as the 1950s by invasive methods and have been reproduced extensively by modern methods, including positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI; Ibáñez et al., 1998). Reduction in CMR characteristically occurs not only in AD but also in most, if not all, of the other nosological entities that cause dementia (Blass and McDowell, 1999; Blass, 2000, 2001). Molecular genetic and family studies have made it possible to identify individuals at high risk for AD before they show clinical signs that can be detected by sensitive neuropsychological tests or evidence of brain atrophy on MRI (Kennedy et al., 1995; Reiman et al., 1996; Johnson et al., 2001). Reductions in CMR occur in these individuals *before* neuropsychological or imaging evidence of AD (Kennedy et al., 1995; Reiman et al., 1996; Johnson et al., 2001). This robustly replicated observation refutes the earlier hypothesis that the reductions in CMR in AD are due to reductions in "brain activity" or to brain atrophy. The temporal relationship—reductions in CMR prior to the development of clinical disabilities—is consistent with the reductions in CMR being a cause of the clinical disabilities. Impairment of oxidative energy metabolism leads to increased expression of the Alzheimer APP (Blass et al., 2000) and to cytoskeletal disorganization, including the appearance of epitopes associated with paired helical filaments/tangles (Blass et al., 1990; Cheng and Mattson, 1992). Impairments of oxidative/energy metabolism are classical causes of premature death of neurons (Blass, 2001). The mechanisms by which abnormalities of oxidative/energy metabolism can contribute to the formation of neuritic plaques and brain atrophy in AD have been reviewed elsewhere (Gibson et al., 1998; Blass et al., 2000; Gibson, 2001).

Defects in AD brain mitochondria have been robustly demonstrated in AD, as discussed elsewhere (Blass and McDowell, 1999; Gibson et al., 2000; Blass, 2000, 2001; Brown et al., 2001). We have proposed that circulatory impairments in the supply of glucose and O_2 to the brain may interact synergistically with inherent impairments in the ability of the brain to oxidize substrate in causing the clinical abnormalities in AD (Blass et al., 2000).

The decrease in CMR is generally proportional to the degree of clinical disability, in studies of groups of patients or in serial studies of single patients (Wolf et al., 1999; Ibáñez et al., 1998). The degree of intrinsic mitochondrial abnormality is also proportional to the degree of clinical disability (Gibson et al., 2000; Brown et al., 2001). This result has been found with two different mitochondrial markers. One is the activity of the α-ketoglutarate dehydrogenase complex (KGDHC) in individuals who possess the *APOE4* susceptibility gene for AD (Gibson et al., 2000). The other is a measure of the amplification of the CO1 gene on mtDNA (Brown et al., 2001).

Does Inducing the Abnormality Lead to the Clinical Signs and Symptoms of the Disease?

Extensive documentation over at least 50 years proves that inducing impairments in brain oxidative/energy metabolism induces abnormalities in memory, judgment, and other higher brain functions that parallel those in AD and other dementias (Gibson et al., 1981; Blass and Gibson, 1999). The effects of reduced oxygen tension in inspired air were studied early and in great detail (Gibson et al., 1981), because of the importance of that knowledge for military aviation in World War II (Fig. 3). Confusion can also be induced by limitations in the supply of sugar (e.g., hypoglycemia) or by vitamin deficiencies that impair the brain's ability to oxidize substrate (e.g., thiamin deficiency), among other causes (Gibson et al., 1981, 1998; Blass and Gibson, 1999; Blass et al., 2000).

Impairing cerebral oxidative/energy metabolism can induce delirium or dementia or both, depending on how severe the metabolic impairment is and for how long it lasts (Gibson et al., 1981; Blass and Gibson, 1999). Delirium is often referred to in neurology as "metabolic encephalopathy" and is characteristically associated with decreased cerebral oxidative/energy metabolism (Gibson et al., 1981; Blass and Gibson, 1999). Delirium and dementia are clinically related conditions. Engel and Romero (1959) conceptualized delirium and dementia as two extremes on a spectrum of "cerebral insufficiency." They put forward this simplifying formulation although they were aware that a variety of etiologies and of nosological entities has been described that can give rise to delirium or to dementia or to both. (Analogously, it is useful to think of febrile seizures as a clinical entity, even though there are many causes of fever.) Engel and Romano (1959) proposed that delirium is functional brain failure and by definition re-

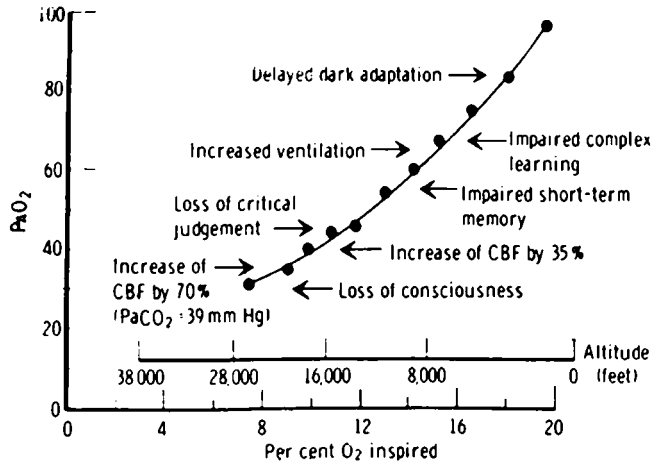

Fig. 3. Neurological and psychological effects of hypoxia on humans. This figure, reproduced from the book "The diagnosis of stupor and coma" by Plum and Posner (1980), illustrates the progressive impairment of higher mental functions in humans as the tension of inspired oxygen falls.

versible, whereas dementia is anatomic brain failure and by definition irreversible. In practice, the conditions often overlap. Patients with dementias are particularly susceptible to delirium, even if the dementia is so mild that it is "subclinical" (Gibson et al., 1981; Blass and Gibson, 1999). Chronic delirium can be very difficult to distinguish from dementia. The "reversible dementias" about which much was written some years ago are chronic delirious states.

Impairment of oxidative/energy metabolism can also induce neuropathological changes, which are also known to occur in AD. These include loss of neurons, increased expression of APP, and cytoskeletal abnormalities (Kalaria et al., 1993; Blass et al., 1990, 2000; Blass and McDowell, 1999). The neurons in layers III and V of temporal cortex are selectively vulnerable (i.e., are particularly prone to be lost) in AD, and these neurons are normally enriched in a mitochondrial constituent that is deficient in AD, namely, KGDHC (Ko et al., 2001). This observation has led us to propose that variability in the composition of mitochondria among different kinds of brain cells and among different kinds of neurons may contribute to the selective vulnerability characteristic of AD, and by implication perhaps in other disorders displaying selective vulnerability as well (Ko et al., 2001).

Does Inducing the Abnormality in Experimental Animals Lead to Animal Models of the Disorder?

Common conditions that can induce delirium/dementia in human patients induce analogous conditions in experimental animal models (Gibson et al., 1981; Siegel et al., 1999; Blass and Gibson, 1999). They include, for instance, different forms of hypoxia and of hypoglycemia, ammonia toxicity, deficiencies of vitamins B_1 (thiamine) and B_3 (niacin), and a number of other metabolic insults discussed in detail elsewhere (Siegel et al., 1999). The animals in which these conditions have been experimentally induced have trouble in performing tasks that require learning and skills, including motor skills. These experimental conditions are discussed in standard textbooks (Siegel et al., 1999).

Does Treating the Abnormality Ameliorate the Signs and Symptoms of the Disease?

Two groups have reported that increasing blood glucose improves memory in patients with AD (Craft et al., 1992; Manning et al., 1993). In those studies, blood sugar was clamped at about 220 mg/dl. Craft et al. (1992) have presented evidence that this highly replicable effect is mediated by insulin. That proposal deserves further testing.

At the Burke Medical Research Institute in New York, we have been testing the ability of a patented mixture of glucose and intermediates of the Krebs tricarboxylic acid cycle to ameliorate the clinical illness in ordinary clinical use. In the initial open trial in seven patients, the outcome measure used was the Mini Mental State Examination (MMSE), a standard and robust screening tool for dementia (Anthony et al., 1982). The treated patients improved on average by more than 4 points, and the difference was significant by paired *t*-test. The first attempt at a double-blind study was not truly double blind, because the staff could tell whether the patients were on active preparation or placebo. The results of this effectively open trial agreed qualitatively with those of the intentionally open trial. Patients taking the active, foul-tasting preparation also deteriorated less than those taking the placebo on another standard neuropsychological test used in testing therapies for AD, namely, the ADAS-COG. A true double-blind trial is in progress.

The assumption underlying the Burke trials is that ameliorating the metabolic defect may well help AD patients, *if* the metabolic defect is a proximate cause of their clinical disability. That may be true even if some other abnormality, such as amyloidosis, is a more "fundamental" cause of the disease. An analogy is the use of aspirin or other anticlotting agents to prevent thromboses in patients with atherosclerosis, while at the same time trying to reduce their cholesterol levels.

IMPLICATIONS

A variety of data supports the assumption that the impairment in oxidative/energy metabolism in AD is a proximate cause of the dementia. These data should encourage efforts to ameliorate this abnormality in a clinically useful way.

Several other dementing disorders are also associated with decreases in brain oxidative/energy metabolism (Browne et al., 1997; Mizuno et al., 1998; Albers et al., 2000). Global cognitive impairment with normal cerebral oxidative/energy metabolism appears to be rare. These observations lead to the speculative hypothesis that impairment of brain oxidative/energy metabolism is the proximate cause of many disorders that impair mentation.

Further studies are needed to test this hypothesis, not only in dementias but also in other chronic impairments of mentation, including certain forms of madness. Intensive studies of oxidative/energy metabolism in neurological and psychiatric disorders may yet aid us to provide better help for people suffering from these conditions.

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