Neurodegeneration, Sleep, and Cerebral Energy Metabolism: A Testable Hypothesis

Mortimer Mamelak, MD, FRCPC

ABSTRACT

Varying degrees of metabolic arrest are used by many living species to survive in a harsh environment. For example, in hibernating mammals, neuronal activity and cerebral metabolism are profoundly depressed in most regions of the brain and limited energy resources are deployed to maintain vital cell functions. Gathering evidence suggests that energy resources are also limited in both Alzheimer's and Parkinson's diseases, and that this promotes metabolic stress and the degenerative process. Key steps in this process are energy requiring, and this further compromises cell energy reserves. It may be possible to slow the progress of these diseases by inducing slow-wave sleep (SWS) at night with gammahydroxybutyrate. Patients with these diseases sleep poorly and generate little SWS. SWS and hibernation are thought to be on a continuum of energy conservation. Thus, the induction of SWS may retard the degenerative process by depressing cell metabolism and by directing energy utilization to vital cell functions. In this way, GHB-induced SWS may duplicate the effects of hibernation and extend biologic time. *(J Geriatr Psychiatry Neurol* 1997; 10:29–32).

Varying degrees of metabolic arrest are used by many living species to survive in a harsh environment. For example, in hibernating mammals, neuronal activity and cerebral metabolism are profoundly depressed in most regions of the brain, and limited energy resources are deployed to maintain vital cell functions. Gathering evidence suggests that energy resources are also limited in both Alzheimer's and Parkinson's diseases, and that this promotes metabolic stress and the neurodegenerative process. Key steps in this process are energy requiring, and this further compromises cell energy reserves. It may be possible to slow the progress of these neurodegenerative disorders by inducing a partial metabolic arrest at night during sleep with gammahydroxybutyrate (GHB). This agent induces rapid eye movement (REM) and slow-wave sleep without the development of tolerance to these actions in time. Patients with either Alzheimer's or Parkinson's disease sleep poorly and generate little slow-wave sleep. Slow-wave sleep and hibernation are thought to be on a continuum of energy conservation. Thus, the induction of slow-wave sleep with GHB may alleviate cellular stress, and the concomitant depression of metabolism may slow the degenerative process. In this way, the induction of slow-wave sleep with GHB may duplicate the effects of hibernation and extend biologic time.

Metabolic arrest is used by many living species to survive in a harsh environment. Turtles, for example, are remarkable for their tolerance of total anoxia.[1,2] *Pseudemys scripta* can endure 48 hours in an atmosphere composed of 100% nitrogen and can survive anerobic dives of up to 2 weeks. Other species of turtle bury themselves in the mud of the ocean floor for 2 or 3 months at a time. How do they survive? The tissue most sensitive to oxygen lack is the brain, where energy must be continuously expended to maintain the integrity of the cell membrane and its potentials. Although a number of biologic mechanisms are utilized by the turtle brain to cope with anoxic conditions, one important adaptation is the suppression of spontaneous neuronal activity and the consequent reduction in cerebral energy utilization. Relatively little energy expenditure at rest appears necessary for the maintenance of cell membrane gradients.[3] Resting energy utilization seems to be devoted largely to other cellular processes such as cell maintenance and repair, axoplasmic transport, and in neuronal perikarya, protein synthesis. Hibernating mammals are also able to survive extremes of low temperature and starvation. Neuronal activity is depressed during hibernation, but

Received June 20, 1996. Received revised October 29, 1996. Accepted for publication October 30, 1996.

From the Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada.

Reprint requests: Dr. Mortimer Mamelak, Department of Psychiatry, Baycrest Centre for Geriatric Care, 3560 Bathurst St., Toronto, ON M6A 2E1.

brain energy reserves in the form of high levels of glycogen, adenosine triphosphate, and creatine phosphate are maintained despite a profound decline in most regions of the brain in cerebral blood flow and in cerebral metabolism as measured by the relative cellular accumulation of 2-deoxyglucose.[4–6]

In man, slow-wave sleep has certain features in common with hibernation, and indeed, hibernation is considered by some biologists to be an extension and intensification of nonrapid eye movement (NREM) sleep.[4]

Glucose utilization measured by 2-deoxyglucose uptake during slow-wave (NREM stages 3 and 4) sleep in young men is reduced by as much as 40% throughout the gray matter of the brain.[7,8] Lesser reductions in glucose utilization are observed in stage 2 NREM sleep.[9] These sleep-associated reductions in glucose utilization are thought to parallel the decline in single-cell neuronal activity and rate of synaptic activity during NREM sleep.[7,8] A recent study has also demonstrated that a very substantial 25% decrease in the cerebral metabolic rate for oxygen occurs during slow-wave sleep in man.[10]

What is the function of slow-wave sleep and what purpose is served by reducing the cerebral metabolic rate during this state? Does NREM sleep, and slow-wave sleep in particular, protect the brain from unfavorable conditions that, in this case, are internally generated by the excessive metabolic demands of the waking brain? A normal brain generates 20% to 25% of the body's energy daily, even though the brain constitutes only 2% of the body's weight.[11] It has been demonstrated that toxic and endocrine agents that threaten the brain's energy supply reflexly induce comatose states and a fall in the cerebral metabolic rate that is thought to protect the brain from this hazard.[12] NREM sleep and the accompanied reduction in cerebral metabolic rate may also be a response to metabolic conditions that threaten the brain's energy reserves after a long day of wakefulness.

The duration of slow-wave sleep in man declines with age. About 20% of the sleep of children and adolescents is occupied by slow-wave sleep, and the amplitude of their slow delta waves commonly exceeds 200 μV.[13,14] Although the absolute number of delta waves appears to remain fairly constant with age, their amplitude progressively falls below the 75-μV criterion required to identify them as slow waves.[15] Thus, as the brain ages, more time is spent in NREM stages 1 and 2 sleep, and perhaps more important, sleep efficiency falls and more time is spent awake.[14] These developments suggest that the amplitude of the diurnal variation in glucose utilization and the magnitude of the corresponding decline in nocturnal cerebral metabolism falls with age, and that brain energy conservation during sleep becomes progressively less effective. This failure may even be more extreme in the case of patients with Alzheimer's or Parkinson's disease in whom the decline in slow-wave sleep is more precipitous and who spend far more of their time awake at night than do the normal elderly.[15–17] The breakdown of sleep is one of the earliest features of these two common neurodegenerative disorders.

Selective neuronal vulnerability is the hallmark of each of these disorders.[18] In Alzheimer's disease, the most vulnerable neurons are the pyramidal cells that provide long corticocortical and hippocampal projections. These neurons are likely to utilize glutamate as a neurotransmitter and to receive extensive glutamatergic inputs. Parkinson's disease involves the dopaminergic nigrostriatal neurons. The specific factor that initiates the degeneration in each of these neuronal systems is not known, and for this reason, studies on the biochemical and cytologic changes in these conditions cannot always specify the step in the degenerative cascade that the changes represent. Nevertheless, certain themes recur, and a conceptual framework for the metabolic evolution of both conditions appears to be emerging. Thus, it has been proposed that energy production reserve is compromised in these conditions, and that this in turn promotes metabolic stress or limits the capacity of neurons to cope with metabolic stressors.[19]

For example, in Alzheimer's disease, the elevated levels of heat shock protein and the cytokine interleukin-1 that are found in the brain are cited as evidence for metabolic stress.[20–23] Although low levels of both are found in normal brain, both of these agents are overexpressed when the brain is exposed to ischemia, trauma, free radicals, and other toxic insults. Both heat shock proteins and interleukin have been shown to activate the gene for the amyloid precursor protein and to induce the production of amyloid precursor protein mRNA. These observations suggest that the increased synthesis of amyloid precursor protein in Alzheimer's may be a response to ongoing cellular stress.

Other studies in Alzheimer's have focused on the genesis of the neurofibrillary tangles, another hallmark of the disease but not specific to it. Thus, a novel microtubule-associated protein kinase that is strongly inhibited by adenosine triphosphate (ATP) has stirred great interest, and it has been proposed that low ATP levels in cerebral neurons that are energy deficient, perhaps due to mitochondrial aging, activate microtubule-associated protein kinase to phosphorylate the microtubule protein tau, and set in motion the sequence of metabolic events that lead to neurofibrillary tangles.[24,25] A similar process may account for the aberrant neurofilament phosphorylation observed in Alzheimer's disease. Some evidence that ATP generation is compromised in Alzheimer's disease, comes from in vivo studies with nuclear magnetic resonance spectroscopy, although the findings with this technique have not been entirely consistent.[26–28] Defective oxidative metabolism in Alzheimer brain with reduced concentrations of key enzymes like pyruvate dehydrogenase and alpha ketoglutarate dehydrogenase has also been cited as evidence for impaired energy production.[29] Studies in primate brain demonstrate impairments with age in the mitochondrial

enzymes that mediate oxidative phosphorylation even in healthy animals.[30] As well, reduced temporoparietal glucose utilization has been a consistent observation. This reduction has even been observed in subjects predisposed to the disease who do not yet manifest its clinical symptoms.[31] The reduction in glucose utilization has been proposed as a marker for vulnerability to Alzheimer's disease. However, the reason for the reduction in glucose utilization is by no means clear, and it need not immediately be secondary to decreased energy formation. Neuronal loss and synaptic degeneration, particularly along the long corticocortical and hippocampal projection neurons, appears to be a key feature of Alzheimer's disease, and the loss of these neurons may account for the reduced cerebral metabolic rate for glucose. The reasons for this loss remain unknown, but it has been proposed that there is excessive activation of the neuronal signal-transduction system in this disease, and this process can lead to cell death.[23] Excitatory amino acid-induced cell death may be cited as one cause of this phenomenon. This activation is enhanced in energy-deficient cells, and it has been shown, for example, that in such energy-deficient neurons, the excitatory amino acid neurotransmitter glutamate causes persistent receptor activation and becomes neurotoxic.[18] Defective mitochondria and aging may also promote tissue breakdown through free radical formation and lipid peroxidation.[30] An increase in lipid peroxidation has been demonstrated in Alzheimer's disease.[32]

The search for the cause of Parkinson's disease may be somewhat closer to a conclusion. Gathering evidence implicates a defect in complex 1 of mitochondrial energy metabolism in the pathogenesis of this illness.[18,33,34] The toxic free-radical metabolite of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP), 1-methyl-4 phenylpyridium (MPP+), has been shown to be a specific inhibitor of mitochondrial complex 1, and postmortem studies of complex 1 activity in Parkinson's disease have shown reduced levels in the substantia nigra, but not in the other brain regions. Thus, it has been argued that mitochondrial dysfunction in Parkinson's disease impairs ATP generation, and that this promotes cell membrane failure and the intracellular accumulation of sodium and subsequently the excessive accumulation of intracellular calcium. Impaired ATP generation impedes the ATP-dependant extrusion of calcium and its storage in the endoplasmic reticulum. High intracellular calcium levels may then activate metabolic intermediates of the signal transduction system, and again, as in Alzheimer's disease, set in motion a cascade of events that leads to cell death. Increased lipid peroxidation in the substantia nigra of patients with Parkinson's disease provides additional evidence that free radical damage is a factor in this condition.[35]

If, as has been proposed, NREM sleep and slow-wave sleep in particular serve to conserve cerebral energy, then the breakdown of NREM sleep with age and the specific failure to generate slow-wave sleep may further compromise cerebral energy resources. Indeed, around-the-clock utilization of energy at waking levels may challenge the energy production capacity of the nervous system and limit its ability to maintain cell functions such as repair, transport, secretion, and protein synthesis in addition to the very critical function of preserving the integrity of cell membranes. Low energy reserves may impair the capacity of the brain to respond to augmented demands in the face of toxic insults. No matter what the initiating cause of Parkinson's or Alzheimer's disease, the breakdown of sleep and the failure of energy conservation during sleep add an additional metabolic burden.

Can this be corrected? One possibility is the nocturnal use of gammahydroxybutyrate. This remarkable compound has been shown to induce NREM and REM sleep and to specifically induce high-voltage slow-wave sleep.[37] Patients with narcolepsy have used this agent nightly for many years without the development of tolerance. Gammahydroxybutyrate, or its congener butyrolactone, has been shown to reduce cerebral glucose utilization in a dose-related manner, and even to conserve and protect cerebral ATP levels in the face of hypoxia.[38,41] Indeed, studies have demonstrated that gammahydroxybutyrate can function as a neuroprotective agent against ischemia.[40] Studies of the gammahydroxybutyrate actions in brain also demonstrate a protective effect against lipid peroxidation.[41] Other work has demonstrated that gammahydroxybutyrate blocks excitotoxic damage to the brain induced by kainic acid, and thus that it may be able to act more generally against excitotoxic glutamatergic damage.[42]

If energy depletion contributes to the deterioration of the brain in Alzheimer's disease or Parkinson's disease, any intervention that reduces energy demand by inhibiting neuronal activity may slow the progress of these illnesses. Under conditions of metabolic depression, cell energy reserves are more likely to be devoted to maintenance of cell membrane potentials and membrane integrity, and less vital processes may not as readily proceed. The manufacture of amyloid protein and the phosphorylation of tau, for example, both of which require ATP, might not proceed with the same velocity when neuronal metabolism is depressed. Similarly, the activation of the signal-transduction system may also not proceed as readily under conditions of partial metabolic arrest.

Current treatment approaches to Alzheimer's and Parkinson's diseases aim at improving the function of remaining neurons or at regenerating fresh neurons. It may be simpler to prevent their degeneration in the first place. Many living species promote their survival by using varying degrees of metabolic arrest to protect their tissues from extreme conditions and, in this way, extend biologic time.[43] It may be possible to duplicate this phenomenon clinically in man with the use of gammahydroxybutyrate.

References

1. Lutz PL, LaManna JC, Adams MR, Rosenthal M. Cerebral resistance to anoxia in the marine turtle. *Respir Physiol* 1980; 41:241–251.
2. Sick TJ, Rosenthal M, LaManna JC, Lutz PL. Brain potassium homeostasis, anoxia and metabolic inhibition in turtles and rats. *Am J Physiol* 1982; 243:R281–R288.
3. Mata M, Fink DJ, Gainer H, et al. Activity-dependent energy metabolism in rat posterior pituitary primarily reflects sodium pump activity. *J Neurochem* 1980; 34:213–215.
4. Heller HC, Krilowicz BL, Kilduff TS. Neural mechanisms controlling hibernation. In: Malan A, Canquilhem B, eds. *Living in the cold. 2nd International Symposium*. London: John Libbey Eurotext Ltd., 1989:447–459.
5. Frerichs KU, Kennedy C, Sokoloff L, Hallenbeck JM. Local cerebral blood flow during hibernation, a model of natural tolerance to cerebral ischemia. *Cereb Blood Flow Metab* 1994; 14:193–205.
6. Pakhotin PI, Pakhotina ID, Belousov AB. The study of brain slices from hibernating mammals in vitro and some approaches to the analysis of hibernation problems in vivo. *Prog Neurobiol* 1993; 40:123–161.
7. Buchsbaum MS, Gillin JC, Wu J, et al. Regional cerebral glucose metabolic rate in human sleep assessed by position emission tomography. *Life Sci* 1989; 45:1349–1356.
8. Maquet P, Dive D, Salmon E, et al. Cerebral glucose utilization during sleep-wake cycle in man determined by positron emission tomography and [^{18}F]2-fluro-2-deoxy-D-glucose method. *Brain Res* 1990; 513:136–143.
9. Maquet P, Dive D, Salmon E, et al. Cerebral glucose utilization during stage 2 sleep in man. *Brain Res* 1992; 571:149–153.
10. Madsen P, Schmidt J, Wildschiodzt G, et al. Cerebral O_2 metabolism and cerebral blood flow in humans during deep and rapid eye movement sleep. *J Appl Physiol* 1991; 70:2597–2601.
11. Stryer L. *Biochemistry*. 3rd Ed. New York: W.H. Freeman, 1988:627–645.
12. Pazdernik T, Cross R, Nelson S, et al. Is there an energy conservation "system" in brain that protects against the consequences of energy depletion? *Neurochem Res* 1994; 19: 1393–1400.
13. Williams RL, Karacan I, Hirsch CJ. *EEG of human sleep. Clinical Applications*. New York: Wiley, 1974.
14. Feinberg I. Schizophrenia: caused by a fault-in programmed synaptic elimination during adolescence? *J Psychiatr Res* 1983; 17:319–334.
15. Bliwise DL. Sleep in normal aging and dementia. *Sleep* 1993; 16:40–81.
16. Vitiello MV, Prinz PN, Williams DE, et al. Sleep disturbances in patients with mild-stage Alzheimer's disease. *J Gerontol* 1990; 45:M131–M138.
17. Prinz P, Poceta S, Vitiello MV. Sleep in the dementing disorders. In: Boller F, Grafman J, eds. *Handbook of neuropsychology*. Vol. 4. Amsterdam: Elsevier Science, 1990:335–347.
18. Hof PR, Morrision JH. The cellular basis of cortical disconnection in Alzheimer's disease and related dementing conditions. In: Terry R, Katzman R, Bick KL, eds. *Alzheimer disease*. New York: Raven Press, 1994:197–229.
19. Beal MF. Does impairment of energy metabolism result in excitotoxic neuronal death in neurodegenerative illnesses. *Ann Neurol* 1992; 31:119–130.
20. Hoyer S. Brain oxidative energy and related metabolism, neuronal stress and Alzheimer's disease: a speculative synthesis. *J Geriatr Psychiatry Neurol* 1993; 6:3–13.
21. Hamos JE, Obias B, Pulashi-Salo D, et al. Expression of heat shock proteins in Alzheimer's disease. *Neurology* 1991; 4:345–350.
22. Royston MC, Rothwell NJ, Roberts GW. Alzheimer's disease: pathology to potential treatments? *Trends Pharmacol Sci* 1992; 13:131–133.
23. Mrak RE, Sheng JG, Griffin WST. Glial cytokines in Alzheimer's disease: review and pathogenic implications. *Hum Pathol* 1995; 26:816–823.
24. Horsburgh K, Saitoh T. Altered signal transduction in Alzheimer disease. In: Terry RD, Katzman R, Bick KL, eds. *Alzheimer disease*. New York: Raven Press, 1994:387–404.
25. Bush ML, Miyashiro JS, Ingram VM. Activation of a neurofilament kinase, a tau kinase, and a tau phosphatase by decreased ATP levels in nerve growth factor-differentiated PC-12 cells. *Proc Natl Acad Sci U S A* 1995; 92:1861–1865.
26. Pettegrew JW, McClure RJ, Kanfer JN, et al. The role of membranes and energetics in Alzheimer Disease. In: Terry RD, Katzman R, Bick KL, eds. *Alzheimer disease*. New York: Raven Press, 1994:369–386.
27. Brown GG, Levine SR, Gorell JM, et al. In vivo ^{31}P NMR profiles of Alzheimer's disease and multiple subcortical infarct dementia. *Neurology* 1989; 39:1423–1427.
28. Murphy DGM, Bottomley PA, Salerno JA, et al. An in vivo study of phosphorous and glucose metabolism in Alzheimer's disease using magnetic resonance spectroscopy and PET. *Arch Gen Psychiatry* 1993; 50:341–349.
29. Blass JP, Gibson GE, Sheu KR, Black RS. Mitochondria, aging, and neurological disease. In: Zatta P, Nicolini M, eds.Non-neural cells in Alzheimer's disease. Singapore: World Scientific, 1995:95–107.
30. Bowling AC, Mutisya EM, Walker LC, et al. Age-dependent impairment of mitochondrial function in primate brain. *J Neurochem* 1993; 60:1964–1967.
31. Reiman EM, Caselli RJ, Yun LS, et al. Preclinical evidence of Alzheimer's disease in persons homozygous for the ϵ4 allele for apolipoprotein E. *N Engl J Med* 1996; 334:752–758.
32. Markesbery WR, Ehmann WD. Brain trace elements in Alzheimer disease. In: Terry RD, Falzman R, Bick KL, eds. *Alzheimer disease*. New York: Raven Press, 1994:353–367.
33. Furtado JCS, Mazurek MF. MPTP-induced neurotoxicity and the quest for a preventive therapy for Parkinson's disease. *Can J Neurol Sci* 1991; 18:77–82.
34. Schapira AHV, Cooper JM, Dexter D, et al. Mitochondrial complex 1 deficiency in Parkinson's disease. *J Neurochem* 1990; 54:823–827.
35. Fahn S, Cohen G. The oxidant stress hypothesis in Parkinson's disease: evidence supporting it. *Ann Neurol* 1992; 32:804–812.
36. Mamelak M. Gammahydroxybutyrate: an endogenous regulator of energy metabolism. *Neurosci Biobehav Rev* 1989; 13:187–198.
37. Wolfson LI, Sakurada O, Sokoloff L. Effects of butyrolactone on local cerebral glucose utilization in the rat. *J Neurochem* 1977; 29:777–783.
38. MacMillan V. The effects of gamma-hydroxybutyrate and gamma-butyrotactone upon the energy metabolism of the normoxic and hypoxic rat brain. *Brain Res* 1978; 146:177–187.
39. Lavyne MH, Hariri RJ, Tankosic T, Babiak T. Effect of low dose butyrotactone therapy on forebrain neuronal ischemia in the unrestrained, awake rat. *Neurosurgery* 1983; 12:430–434.
40. Meerson F, Kagan V, Prilipko L, et al. Inhibition of lipid peroxidation action with ionol and gammahydroxybutyric acid in emotional pain stress. *Biull Eksp Biol Med* 1979; 88:404–406.
41. Azczek R, Nelson M, Coyle J. Kainic acid neurotoxicity and seizures. *Neuropharmacology* 1981; 20:183–189.
42. Hochachka PW, Guppy M. *Metabolic arrest and the control of biological time*. Cambridge: Harvard University Press, 1987.