Gene–Diet Interactions in Brain Aging and Neurodegenerative Disorders

Mark P. Mattson, PhD

While there are many examples of people who live for 100 years or more with little evidence of a decline in brain function, many others are not so fortunate and experience a neurodegenerative disorder, such as Alzheimer disease or Parkinson disease. Although an increasing number of genetic factors that may affect the risk for neurodegenerative disorders are being identified, emerging findings suggest that dietary factors play major roles in determining whether the brain ages successfully or experiences a neurodegenerative disorder. Dietary factors may interact with disease-causing or predisposing genes in molecular cascades that either promote or prevent the degeneration of neurons. Epidemiologic findings suggest that high-calorie diets and folic acid deficiency increase the risk for Alzheimer disease and Parkinson disease; studies of animal models of these disorders have shown that dietary restriction (reduced calorie intake or intermittent fasting) and dietary supplementation with folic acid can reduce neuronal damage and improve behavioral outcome. Animal studies have shown that the beneficial effects of dietary restriction on the brain result in part from increased production of neurotrophic factors and cytoprotective protein chaperones in neurons. By keeping homocysteine levels low, folic acid can protect cerebral vessels and prevent the accumulation of DNA damage in neurons caused by oxidative stress and facilitated by homocysteine. Although additional studies are required in humans, the emerging data suggest that high-calorie diets and elevated homocysteine levels may render the brain vulnerable to age-related neurodegenerative disorders, particularly in persons with a genetic predisposition to such disorders.

For author affiliation, see end of text.
Dietary restriction induces a mild cellular stress response in neurons as a result of its effects on energy availability and activity in neuronal circuits. Neurons respond to this stress by increasing the production of proteins that enhance cellular stress resistance; examples include neurotrophic factors, protein chaperones (such as heat-shock proteins), and antiapoptotic proteins (such as Bcl-2). A similar mechanism may stimulate neurogenesis and synaptic plasticity. Peripheral effects of dietary restriction may also benefit the brain. For example, enhanced insulin sensitivity and decreased homocysteine and cholesterol levels would be expected to prevent age-related damage to cerebral blood vessels and may also have more direct beneficial effects on neurons and glia.

higher calorie intake (6, 7). Of interest, the risks for Alzheimer disease and Parkinson disease were more strongly correlated with calorie intake than with weight or body mass index. One interpretation of the latter finding is that persons who have a metabolic constitution that allows them to maintain a normal body weight, even with a high caloric intake, may be at increased risk for Alzheimer disease and Parkinson disease.

A longitudinal, prospective, population-based study evaluated 2459 community-dwelling Yoruba residents of Nigeria and 2147 community-dwelling, genetically related African-American residents of Indianapolis (8). The age-adjusted incidence of dementia was significantly higher in the Indiana cohort, which suggests the involvement of environmental factors in disease risk; different caloric intake in the two study samples (low in Nigeria and high in Indiana) is one possible factor. Although not established in the latter study, one clear difference between the two study samples was caloric intake (low in Nigeria and high in Indiana).

Strong evidence that caloric intake may affect the risk for neurodegenerative disorders comes from animal studies. Rats maintained on dietary restriction for 2 to 4 months exhibit increased resistance of hippocampal neurons to degeneration caused by the amnestic toxin kainic acid; this resistance led to a profound deficit in learning and memory in rats fed ad libitum but little or no memory deficit in rats maintained on dietary restriction (9). In another study, the vulnerability of hippocampal and cortical neurons to excitotoxicity and apoptosis was decreased in presenilin 1 mutant mice maintained on dietary restriction (10). In a model of Parkinson disease, the vulnerability of midbrain dopaminergic neurons to MPTP toxicity was decreased and motor function was improved by dietary restriction (11). Of interest, dietary restriction not only is neuroprotective; it also stimulates neural stem cells in the brain to produce new nerve cells (12) and might thereby promote the reconstruction of neuronal circuits damaged by injury or disease.

Recent studies of rodents have revealed cellular and molecular mechanisms underlying the beneficial effects of dietary restriction on the brain (Figure). Dietary restriction increases the production of neurotrophic factors, particularly brain-derived neurotrophic factor in many different regions of the brain (12, 13). Brain-derived neurotrophic factor can enhance learning and memory, can protect neurons against oxidative and metabolic insults, and can stimulate neurogenesis; these actions may protect neurons against age-related neurodegenerative disorders. Dietary restriction also induces the production of protein chaperones, such as heat-shock protein 70 and glucose-regulated protein 78, which are known to help cells resist various insults (11, 14). Therefore, it appears that dietary restriction promotes neuronal survival, plasticity, and even neurogenesis by inducing a mild cellular stress response that involves activation of genes that encode proteins designed to promote neuronal growth and survival (Figure).

**Dietary Folate, Homocysteine, and Neurodegenerative Disorders**

Levels of homocysteine in the blood increase with age, and persons with elevated homocysteine levels are at increased risk for vascular disease, heart attack, and stroke (15). Many patients with Alzheimer disease and Parkinson disease have elevated homocysteine levels; a recent prospective study of the Framingham Heart Study cohort revealed that persons with elevated homocysteine levels are at increased risk for Alzheimer disease (16). Cells produce homocysteine from the amino acid methionine; homocysteine is metabolized by remethylation to methionine by enzymes that require folic acid and cobalamin (vitamin B12) or is converted to cysteine by cystathionine β-synthase, a pyridoxine (vitamin B6)-dependent enzyme. Patients with a genetic deficiency of cystathionine β-synthase exhibit a clinical phenotype that includes mental retardation, cerebral atrophy, and seizures.

Folic acid deficiency can result in hyperhomocysteinemia.
Dietary Interventions To Promote Successful Brain Aging

Neurodegenerative disorders are proving very difficult to treat, and this fact emphasizes the importance of identifying ways to prevent these diseases. The emerging epidemiologic and experimental data described earlier, together with the fact that dietary restriction consistently increases life span in all mammals studied to date, provide a strong rationale for future studies in humans to determine whether dietary restriction will reduce the risk for age-related neurodegenerative disorders. Dietary restriction may not only benefit obese persons (body mass index > 25 kg/m²); it may also reduce the risk for disease in persons whose body weights are within the “normal” range (body mass index between 20 and 25 kg/m²). The current average daily calorie intake of Americans is approximately 2700 for women and more than 3000 for men. When a person reaches a low body mass index (≈20 kg/m²), a daily calorie intake in the range of 1600 to 2200 calories would be expected to promote optimal health. However, randomized, controlled trials with well-defined end points are required to establish an optimum range of calorie intake before recommendations can be confidently made.

Because homocysteine level has been established as an independent risk factor for cardiovascular disease and stroke (15), it is important that homocysteine levels be measured and that (if levels are elevated) diet be appropriately modified to reduce homocysteine levels. Plasma homocysteine concentrations typically range between 5 and 15 μmol/L. The risk for cardiovascular disease, stroke, and Alzheimer disease increases considerably when homocysteine levels are greater than 10 μmol/L; it is reasonable to expect the same is true for Parkinson disease. Dietary supplementation with 400 μg of folic acid can decrease homocysteine levels by 2 to 5 μmol/L in most persons; thus, a folic acid concentration of 15 μmol/L could mean a two- to fourfold decrease in risk for Alzheimer disease. More information on homocysteine and folate can be found at the Web site of the American Heart Association (http://circ.ahajournals.org/cgi/content/full/99/1/178).

An increasing number of genetic factors that either cause or increase the risk for neurodegenerative disorders are being identified. Genetic mutations can cause rare forms of Alzheimer disease (amyloid precursor protein, presenilin 1, and presenilin 2), Parkinson disease (α-synuclein and parkin), Huntington disease (huntingtin), and amyotrophic lateral sclerosis (Cu/Zn-superoxide dismutase). Data from transgenic mice expressing a disease-causing mutation suggest that the course of some of these inherited disorders can be modified by dietary factors (10) (Duan W, Mattson MP. Unpublished data). On the other hand, dietary restriction had no beneficial effect on disease onset and actually accelerated disease progression in Cu/Zn-SOD mutant mice (21). Dietary modifications may be particularly useful in persons who may have a genetic predisposition for a neurodegenerative disorder. Examples include persons with an 84 allele of apolipoprotein E who are at increased risk for Alzheimer disease (2) and those with the C677T polymorphism in methyl tetrahydrofolate reductase who have elevated homocysteine levels (22).

Although we have focused on dietary restriction and

### Table 1. Evidence That Calorie Intake Affects the Risk for Alzheimer Disease and Parkinson Disease

<table>
<thead>
<tr>
<th>Finding</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-calorie intake is associated with reduced risk for Alzheimer disease.</td>
<td>7</td>
</tr>
<tr>
<td>Low-calorie intake is associated with reduced risk for Parkinson disease.</td>
<td>6</td>
</tr>
<tr>
<td>Caloric restriction preserves memory in aging rodents.</td>
<td>25</td>
</tr>
<tr>
<td>Dietary restriction protects neurons in rodent models relevant to Alzheimer disease.</td>
<td>9, 10</td>
</tr>
<tr>
<td>Dietary restriction protects dopaminergic neurons and improves motor function in animal models of Parkinson disease.</td>
<td>11</td>
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<tr>
<td>Caloric restriction has antiaging effects.</td>
<td>26</td>
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</tbody>
</table>

### Table 2. Evidence That Elevated Homocysteine Levels and Low Folate Levels May Increase the Risk for Alzheimer Disease and Parkinson Disease

<table>
<thead>
<tr>
<th>Finding</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Folate levels are decreased and homocysteine levels increased in patients with Alzheimer disease.</td>
<td>17</td>
</tr>
<tr>
<td>Persons with elevated homocysteine levels are at increased risk for Alzheimer disease.</td>
<td>16</td>
</tr>
<tr>
<td>High homocysteine levels are associated with poorer cognitive function.</td>
<td>27</td>
</tr>
<tr>
<td>Homocysteine levels are increased in patients with Parkinson disease.</td>
<td>28</td>
</tr>
<tr>
<td>Elevated homocysteine levels endanger neurons in mouse models of Alzheimer disease and Parkinson disease; folic acid is neuroprotective.</td>
<td>18, 19</td>
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Dietary factors may influence the health of the brain. For example, animal studies have suggested that creatine, antioxidants (such as vitamin E and flavonoids), and anti-inflammatory agents have neuroprotective actions. On the other hand, emerging evidence suggests that consumption of diets high in saturated fats and cholesterol can increase the risk for Alzheimer disease and amyotrophic lateral sclerosis (23). Collectively, the available data suggest that a brain-healthy diet is very similar to a heart-healthy diet. Specific dietary components may affect brain functions. For example, data suggest that tryptophan (a precursor of the neurotransmitter serotonin) can affect mood, whereas dietary choline (a precursor of acetylcholine) can affect learning and memory (24).

While the emerging data suggest that dietary factors can affect the risk for age-related neurodegenerative disorders (Tables 1 and 2), it is unclear whether they will have any major effect on the course of these disorders in symptomatic patients. No current evidence shows that dietary restriction or folic acid supplementation will benefit symptomatic patients, and we have not found any clear benefit of short-term dietary restriction (days to weeks) in animal models of neurodegenerative disorders (9). However, as methods for early diagnosis of Alzheimer disease and Parkinson disease improve, it will be of considerable interest to perform clinical trials of caloric restriction in patients who are in early preclinical stage of the disease. Clinical trials of folic acid in patients with Alzheimer disease are in progress and should provide an answer as to whether this approach will be beneficial.

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References