PET sheds light on Alzheimer's disease genetic risk

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Twenty-plus years of positron emission tomography (PET) data show that relative to cognitively intact controls, persons with Alzheimer's disease (AD) have reduced 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) uptake. This phenomenon is seen in brain regions containing amyloid plaques and neurofibrillary tangles, and supports the assertion that AD brains have reduced glucose consumption (1). From a diagnostic perspective, although the sensitivity of FDG PET in AD approaches that of the clinical impression, because its specificity is limited, PET is not used by itself to diagnose AD. Still, PET can refine the clinical impression, predict which patients with mild cognitive impairment (MCI) will progress to frank AD, and even help identify which normal elderly individuals are at greatest risk of cognitively declining within the next several years (1–3). In this issue of PNAS, Mosconi *et al.* (4) build upon and extend this line of work. They now report an analysis of PET scans from cognitively intact individuals with a maternal history of AD, a paternal history of AD, or no parental history of AD. PET findings were unremarkable in subjects without an affected parent and in subjects with an AD-affected father. PET scans from those with affected mothers, however, showed reduced parietal, temporal, medial temporal, frontal, and posterior cingulate glucose consumption. At face value, these data suggest that a maternally inherited genetic factor or factors influence brain metabolism.

FDG PET enables *in vivo* analysis of AD brain metabolism. With this technique, individuals are injected with FDG. A brief interval follows, during which time the injected FDG diffuses into the brain according to the blood–brain glucose gradient. Because the hexokinase-mediated phosphorylation of FDG prevents any subsequent egress from the brain and carbon dioxide cannot be released from FDG, PET can quantify the amount of FDG in the brain. With the quantitative PET approach used by Mosconi *et al.* (4), the amount of brain FDG, in conjunction with data defining rates of FDG uptake in tissue and plasma, is used to calculate a value called the cerebral metabolic rate of glucose (CMRglc). The CMRglc provides an actual measure of the brain's glucose consumption rate.

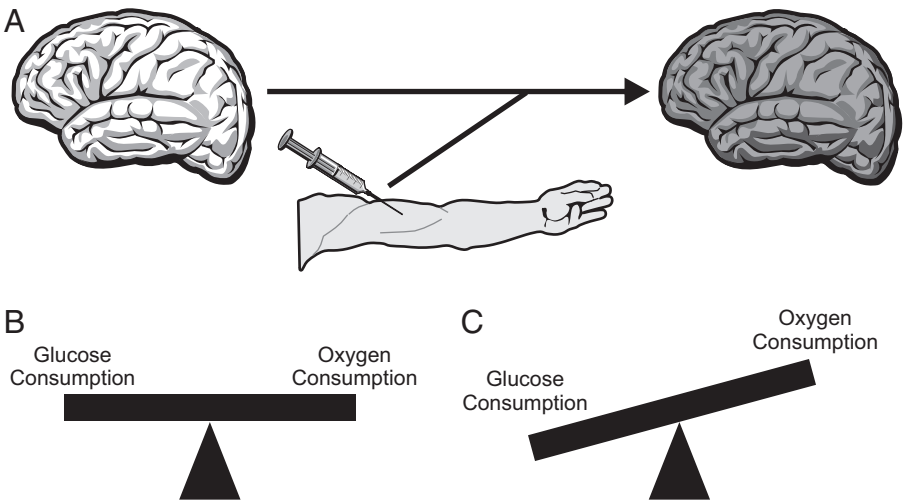

Fig. 1. Fluorodeoxyglucose PET probes brain glucose consumption. (*A*) In PET, intravenously administered fluorodeoxyglucose distributes in the brain according to the blood–brain glucose gradient. Regional reductions in fluorodeoxyglucose are held to represent areas of ''hypometabolism.'' (*B*) For the production of ATP, glucose is consumed by glycolysis, whereas oxygen is consumed through oxidative phosphorylation. The blood–brain glucose gradient is determined more by glycolysis than by oxidative phosphorylation. (*C*) In AD, PET reveals altered metabolism, but the mechanisms underlying the altered metabolism are unclear. If failing oxidative phosphorylation increases oxygen consumption, glycolysis may reciprocally decrease. This would reduce fluorodeoxyglucose uptake.

Epidemiology and neuropsychology data also indicate that having a maternal family history of longevity or AD influences longevity, cognitive aging, and AD risk more than having a paternal family history does. The Framingham Longevity Study found that offspring of long-lived mothers tend to live longer than offspring of long-lived fathers (5). In the Framingham Offspring Study, the nondemented offspring of AD-affected mothers performed less well on cognitive testing than the nondemented offspring of AD-affected fathers (6). Edland *et al.* (7) reported that, although having an AD parent confers an increased lifetime risk of AD, having an AD-affected mother confers a greater risk than having an AD-affected father.

The vast majority of those with AD have the late-onset, sporadic form in which advancing age is the single greatest risk factor. Although Mendelian inheritance patterns are not obvious in sporadic AD, the fact that children of affected individuals have an increased risk of one day developing the disease themselves means that sporadic AD is not truly sporadic (8). Various potential explanations could account for this. Parents and children typically share common environments, which could infer risk. If a parent develops AD very late in life, the children may have a greater chance of developing AD by virtue of the fact they are also at greater risk of living long. Or, genes may directly influence AD risk.

At least one gene on chromosome 19 is recognized to influence AD risk. The most studied gene at the identified locus (19q13.2) is the *APOE* gene. *APOE* encodes a protein, apolipoprotein E (ApoE), which plays a role in lipid transport. Polymorphisms in this gene define three distinct ApoE proteins (the ε2, ε3, and ε4 forms). Those with *APOE* ε4 alleles have a greater lifetime risk of AD and also develop AD at a younger age than those without *APOE* ε4 alleles (9). Cross-sectional PET studies of middle aged, nondemented individuals with *APOE* ε4 alleles show CMRglc reductions similar to those found in persons with AD (10, 11). PET studies such as this, of course, bring us back to the issue of energy metabolism in aging and AD.

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In vitro analyses of AD autopsy brain show reductions in glycolysis, pyruvate dehydrogenase complex activity, ketoglutarate dehydrogenase complex activity, and cytochrome *c* oxidase activity (12). Several of the enzymatic defects observed in AD brain are also found in noncerebral tissues. Cytochrome *c* oxidase activity, for example, is reduced in both platelets and fibroblasts obtained from AD subjects (13, 14). Patients meeting MCI syndrome criteria also have reduced platelet cytochrome *c* oxidase activity (15). Spectral data report that the low K_m cytochrome *c* binding site is altered in AD brain mitochondria (16). These findings raise the possibility that persons with AD have systemic, biochemically relevant structural differences in their cytochrome *c* oxidase from the very start of their disease, if not before. If so, it is reasonable to postulate that gene-determined alterations of the enzyme might underlie its altered function in AD (13).

Mitochondrial DNA (mtDNA) encodes three of the thirteen protein subunits that form cytochrome *c* oxidase. mtDNA does not play by the rules of Mendelian genetics, and although mtDNA is entirely maternally inherited, it is clear that diseases associated with mtDNA mutation often present as sporadic disorders. Experimental data from cytoplasmic hybrids (cybrids), in which mtDNA from AD subjects is expressed within cultured cell lines, support the idea that mtDNA may influence cytochrome *c* oxidase function in persons with AD (17). Although actual mtDNA sequence studies do argue that mtDNA in AD subjects differs from that of controls (18, 19), these differences have not been demonstrated in AD cybrids, may be somatic rather than inherited, may be consequential rather than causal, and await independent replication.

Having an AD-affected mother confers a greater risk than having an AD-affected father.

This is why the current findings of Mosconi *et al.* (4) are so compelling. Although other genetic mechanisms (such as epigenetic imprinting) could potentially account for their data, the finding that offspring of AD mothers have FDG PET scans reminiscent of AD, whereas offspring of AD fathers do not, is consistent with epidemiology, neuropsychology, and cybrid data that implicate a role for mtDNA in cognitive aging and AD.

It will not be easy to prove or disprove whether mtDNA accounts for the Mosconi *et al.* (4) data. Regardless, this report should increase interest in mtDNA as a mediator of aging success and AD risk. It will also hopefully stimulate mechanistic discussion about why glucose consumption is reduced in the AD brain. One possibility is that neuronal function becomes impaired, and this then disrupts glucose consumption. The other possibility is that neuronal bioenergetic metabolism fails, and this in turn disrupts neuronal function. The systemic and early nature of bioenergetic change in AD subjects perhaps suggests that the latter scenario is more likely.

If aerobic metabolism becomes inefficient in aging and more so in AD, then oxygen consumption may actually be increased even if glycolysis rates and aerobic ATP production are reduced (20) (Fig. 1). In the meantime, Mosconi *et al.* (4) have added a corollary to the popular aphorism stating "the apple doesn't fall far from the tree." When it comes to PET scans and AD, how far the apple falls from the tree apparently depends on what tree it falls from.

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