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Amyloid, Hyperactivity and Metabolism. A commentary on Vloebergh's et al.

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Abstract

Recent data suggest that amyloid precursor protein transgenic mice consume excess calories relative to nontransgenic mice, yet weight less. Potential explanations include increased locomotor activity and/or increased basal metabolism. Mechanisms that might underlie the latter explanation include transmembrane pores produced by assemblies of Aß modifying proton or ion gradients across membranes. Alzheimer's disease also results in weight loss. If amyloid were found to induce a hypermetabolic state, this would suggest an alternative mechanism for the pathology found in the disease, and provide opportunities for therapeutic strategies not yet considered.

Keywords

amyloid; body weight; hypermetabolism; activity; Alzheimer's disease

The accompanying manuscript by Vloebergs et al (2008) documents an unexpected observation of elevated caloric intake by the APP23 transgenic mouse model of amyloid deposition compared to nontransgenic mice. This is particularly surprising given that these transgenic mice have reduced body weights compared to their nontransgenic brethren. Furthermore the authors demonstrate that the changes in ingestive behavior are not secondary to impaired olfactory function. On their surface these data argue that amyloid deposition in the APP23 mouse not only impairs cognitive functions and causes a mild degree of neuron loss, but may impact more global aspects of behavior such as feeding and drinking. The authors interpret their data as being consistent with a hypermetabolic state in the transgenic mice. Another recent study similarly presented data describing increased feeding behavior by an APP/PS1 mouse based upon the TAS10 APP line (Pugh, Richardson, Bate, Upton, & Sunter, 2007). If these observations can be carried forward to AD patients, it might explain the frequent observation of weight loss in many AD cases as the dementia reaches a clinically detectable state of severity (Gillette et al., 2007).

Certainly the most intriguing aspect of the data presented by Vloeberghs et al is the idea that amyloid could be causing a hypermetabolic state. To this commentator's knowledge, all APP transgenic mouse lines that go on to develop amyloid deposits weigh less than their nontransgenic counterparts, although this fact is rarely discussed in studies evaluating these mice. We have certainly observed this in our work over the last decade with Tg2576 and APP +PS1 transgenic mice (Holcomb et al., 1998). Vloeberghs et al documents this for the APP23 line, and the TgCRND8 mouse line also exhibits lower weights at virtually all postnatal time points (Touma et al., 2004). Although the cause of this reduction in weight has never been

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explained, most assumed there was a developmental decrease in growth related processes caused either by APP over expression or by the presence of excess Aß peptide. However, the present results suggest this might not reflect abnormal growth, but excessive metabolism resulting in less energy available for growth processes. As such it could modify our collective view of the major pathologies accounting for dementia in Alzheimer's disease; for example less energy may be available to drive synaptic plasticity (or even neural activity) leading to cognitive dysfunction. Such a conception could suggest tantalizing new approaches to treating the disorder, if a hypermetabolic state were linked to excess Aß.

The first question to be considered in evaluating this possibility regards the role of Aß compared to APP overexpression. For the most part, investigators assume that the primary phenotype of APP transgenic mice derives from overproduction of Aß (based largely on the age dependence of the phenotype), but at least theoretically, most models cannot discriminate excess Aß from APP overexpression. Two approaches to resolving this issue have been tested. One is to breed the APP overexpressing mouse onto a BACE1 null background. (Ohno et al., 2004) demonstrated that the BACE1 null background protected APP mice from developing memory deficits, definitely linking this aspect of the phenotype to accumulating Aß levels in the APP mice. A second approach has been the use of gene replacement for APP and PS1 with mutated human genes. These develop amyloid deposits, but have normal levels of APP and PS1 expression (Flood et al., 2002) (Zhang, McNeil, Dressler, & Siman, 2007). A key question is whether these mice also show reduced body weight compared to nontransgenic animals with the same genetic background. Data regarding body weight have not been published in the manuscripts describing these mice, but is likely available. A similar question regards the increased spontaneous mortality observed frequently in APP transgenic mice (Carlson et al., 1997; McLaurin et al., 2006; Pugh et al., 2007). If the low weight and increased mortality phenotypes are lost in the BACE1 null background but present in the gene replacement model, it would strongly imply that accumulating Aß accounts for these components of the APP transgenic mouse phenotype.

One complication in working with APP mice which may be explained by increased rates of energy utilization regards attempts to perform caloric restriction in this model. The first report of caloric restriction in APP mice found a severe hypoglycemic reaction in the APP transgenic mice, leading to a rapid demise (Pedersen, Culmsee, Ziegler, Herman, & Mattson, 1999). Our own efforts to apply caloric restriction to the APP transgenic mice by simply restricting the amount of food consumed by a specific percentage led to unexpectedly severe weight loss, with many mice too weak to swim in the water maze tasks used to asses memory function. Only when we changed the methods of restricting diet to target specific reductions in weight did we succeed in finding benefits in terms of reduced amyloid deposition (Patel et al., 2005). Certainly if a hypermetabolic condition was present, it might explain the extreme reactions of the mice to standard caloric restriction procedures.

Accepting that the APP mice have increased metabolic demands, one question regards whether the increased demand results from enhanced basal metabolism or greater degree of physical activity. Certainly, there is evidence that APP transgenic mice do have increased rates of activity, from our early observations of larger numbers of maze arm entries(Holcomb et al., 1999; Holcomb et al., 1998), to increased open field activity (Dodart et al., 1999) through to studies performing 24 hour activity measures in home cages (Adriani et al., 2006) including the mouse strain studied in the (Vloeberghs et al., 2004). Of considerable interest is that many Alzheimer patients also demonstrate a need for increased activity, often referred to as pacing (White, McConnell, Bales, & Kuchibhatla, 2004). This can lead to attempts to escape confinement if adequate facilities are not provided to fill this need. However, the hAPP/PS1 line described by Pugh et al (2007) demonstrated reduced home cage locomotor activity at all

ages, in spite of increased food consumption and reduced body mass. Thus, increased locomotor activity is unlikely to explain all of the increased energy requirement.

Weight loss is associated with many disorders, and increased basal metabolism, especially catabolism, has been suggested as contributing to chronic obstructive pulmonary disease (Schols, 2003) , sepsis (Trager, DeBacker, & Radermacher, 2003), burn lesions (Pereira & Herndon, 2005) and cancer (Bosaeus, Daneryd, & Lundholm, 2002). Evidence exists that weight loss may be a harbinger of incipient dementia (Buchman et al., 2005; Stewart et al., 2005). The weight loss in AD is often a predictor of more rapid deterioration and, when more pronounced, mortality (Gillette et al., 2007).

There are a number of factors which might account for increased metabolic rates in general. The most common is increased thyroid hormone activity. There have been some indications this may be elevated in AD patients, but for the most part, AD patients are considered euthyroid (de Jong et al., 2006). A second possibility is increased proton leakage within the mitochondrion. Roughly 20% of oxidative metabolism is futile in that the proton gradient dissipates without generation of ATP (Hulbert & Else, 2004). In brown fat, this is accelerated via a specific uncoupling protein (UCP1) in order to generate heat and maintain body temperature. Mitochondrial damage is a common feature in AD and argued by many to be a key pathological event in the progression of the disease (Baloyannis, 2006; Moreira, Cardoso, Santos, & Oliveira, 2006; Parihar & Brewer, 2007). Although not specifically mentioned in these reviews, a greater rate of dissipation of the proton gradient across the inner mitochondrial membrane (the proton leak) could account for mitochondrial problems in AD, and possibly the APP mice. Multiple studies find that synthetic amyloid assemblies form both general membrane pores (Kayed et al., 2004) and more selective ion channels (Bhatia, Lin, & Lal, 2000). The localization of Aß within mitochondria is consistent with this possibility (Atamna & Frey, 2007)

Another possibility is increased demand for ionic pumping through Na-K ATPase or other ion transport systems. This activity utilizes roughly 20% of basal energy needs throughout the body, and as much as 60% of brain ATP is used for this function (Clausen, Van Hardeveld, & Everts, 1991). Formation of membrane pores by assemblies of Aß may deplete the normal ionic gradients established by the sodium pump and other transporters. Additionally, our work (Dickey et al., 2005) and that of others (Mark, Hensley, Butterfield, & Mattson, 1995) identified inhibition of sodium pump activity in APP mice associated with amyloid deposition and in vitro with addition of Aß. These actions of Aß assemblies may increase energy demands in the brain and possibly elsewhere (e.g. fibroblasts; (Etcheberrigaray et al., 2004), leading to increased basal metabolic rates. Failure to respond adequately to these increased demands for energy may interfere with normal cell functions, predispose cells to other toxic influences, or be directly involved in cell degeneration.

Little research has been performed regarding the presence of a hypermetabolic influence on dementia in Alzheimer patients, A single study using high quality methodology found no evidence for hypermetabolism in AD (Poehlman et al., 1997). However, considering that the first author of this paper was found guilty of multiple instances of data falsification, to the extent that he was sentenced to prison, it would seem that replication of these data will be necessary before accepting this outcome as definitive. In any case, the results of Vloeberghs et al suggest an new conceptual framework in which to consider the APP mouse phenotype. Demonstration that a hypermetabolic state exists due to excess formation of the Aß peptide may suggest alternative therapeutic strategies. While clearly further effort is required, these findings shed light an alternative strategy towards solving the vexing problem of Alzheimer's dementia.

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