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β-apptists and Tauists, it's Time for a Sermon from the Book of Biogenesis

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Mitochondria are increasingly believed to play a role in Alzheimer's disease (AD) (Swerdlow 2011b). The idea, though, that mitochondria are abnormal in AD patients is not new. Reports of perturbed mitochondrial ultrastructure and enzyme activities go back decades. More recently, investigators have begun to focus more on why mitochondria are abnormal, and how mitochondrial abnormalities may mediate neurodysfunction and neurodegeneration in the AD brain (Swerdlow 2011b).

When it comes to this line of investigation, the question of what happens to mitochondrial mass in AD is fundamental. At face value, data suggest mitochondrial mass declines in AD neurons. This is supported by studies that have used electron microscopy and PCR-based approaches (Hirai *et al.* 2001, de la Monte *et al.* 2000, Baloyannis 2006). Electron microscopy studies show numbers of normal mitochondria are reduced in AD hippocampal neurons, and genomic DNA samples prepared from AD autopsy brain tissue contain less amplifiable mtDNA than genomic DNA samples from control brains.

In this issue of the Journal of Neurochemistry, Sheng et al. provide additional insight into the AD brain mitochondrial mass deficit (Sheng *et al.* in press). The authors quantified protein levels of PGC-1α, NRF1, NRF2, and TFAM in AD autopsy brains. The PGC-1α, NRF1, NRF2, and TFAM proteins play a role in mitochondrial biogenesis, the process through which cells increase or at least maintain their mitochondrial mass by making new mitochondria (Onyango *et al.* 2010). PGC-1α is a transcriptional co-activator that plays a coordinating role in many tissues. NRF1 and NRF2 are transcription factors that directly activate the expression of a number of nuclear genes that encode mitochondrial components. TFAM associates with mtDNA itself, and helps regulate both mtDNA gene expression and mtDNA replication. Sheng et al. found each of these mitochondrial biogenesis pathway components were reduced in AD subject brains, which implies neurons in the AD brain cannot maintain their mitochondrial mass or, perhaps, possibly even downregulate their mitochondrial mass.

When it comes to AD neurodysfunction and neurodegeneration, reduced mitochondrial biogenesis in the AD brain may constitute a cause, consequence, or both. In M17 cells expressing the APP Swedish mutation (APPswe), the authors assessed the integrity of

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mitochondrial biogenesis-relevant proteins and found that relative to control cells, M17 APPswe cells contained less PGC-1α, NRF1, NRF2, TFAM, and mtDNA. M17 APPswe cell ATP levels were also reduced.

PGC-1α is activated through several pathways, including the cAMP-activated PKA pathway that features CREB (Figure 1). Levels of phosphorylated CREB, the activate form, were also reduced in the M17 APPswe cells. Administering cAMP to the cells increased mitochondrial biogenesis pathway activity. Overall, the findings of Sheng et al. suggest that at least in M17 cells APP or Aβ interfere with PKA signaling, this deactivates the mitochondrial biogenesis apparatus, and cell bioenergetic failure ensues.

The Sheng et al. study addresses several questions critical to the AD research field, but also raises additional issues and considerations. When it comes to the mitochondria-APP/Aβ nexus M17 APPswe cells, which model a specific AD variant, may tell a limited story. In this model of autosomal dominant AD, APP/Aβ perturbations presumably occur upstream of the observed mitochondrial biogenesis changes. Autosomal dominant AD cases due to APP mutation are extremely rare, though, and considerable data suggest in sporadic AD changes in mitochondrial function may actually exist upstream of APP/Aβ perturbations (Swerdlow *et al.* 2010).

Also, when it comes to the AD brain the deeper one looks into the status of mitochondrial mass the more complex the picture actually becomes. While numbers of normal mitochondria no doubt decline in many AD hippocampal neurons (Hirai et al. 2001), which the Sheng et al. study now suggests is a consequence of reduced mitochondrial biogenesis, previous studies also report that in general hippocampal neurons concomitantly accumulate degrading mitochondria. Indeed, when mtDNA contained within phagocytized mitochondria is taken into account, total hippocampal neuron mtDNA may actually increase (Hirai et al. 2001). Also, histologic surveys suggest that in the AD hippocampus the healthiest remaining neurons paradoxically display increased mitochondrial mass or increased mitochondrial mass markers (Nagy *et al.* 1999). If one considers these potentially disparate findings within the context of studies that infer neuron mitochondrial mass or mitochondrial mass markers increase with advancing age (Hirai et al. 2001, Barrientos *et al.* 1997), a case can perhaps be made that since mitochondrial function declines in both aging and AD brains, the ability to mount a compensatory mitochondrial biogenesis response constitutes a defining physiologic difference between brain aging and the AD brain (Swerdlow 2011a). While this possibility remains to be addressed, the study of Sheng et al. and other related studies indicate that as far as AD is concerned, mitochondrial biogenesis manipulation constitutes a valid, justifiable therapeutic target.

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Abbreviations used

Aβ	beta amyloid
AD	Alzheimer's disease
APP	amyloid precursor protein
cAMP	cyclic AMP
CREB	cAMP response element binding protein

mtDNA	mitochondrial DNA
NRF	nuclear respiratory factor
PGC-1α	peroxisome proliferator-activated receptor-γ coactivator-1α
PKA	protein kinase A
TFAM	transcription factor A of the mitochondria

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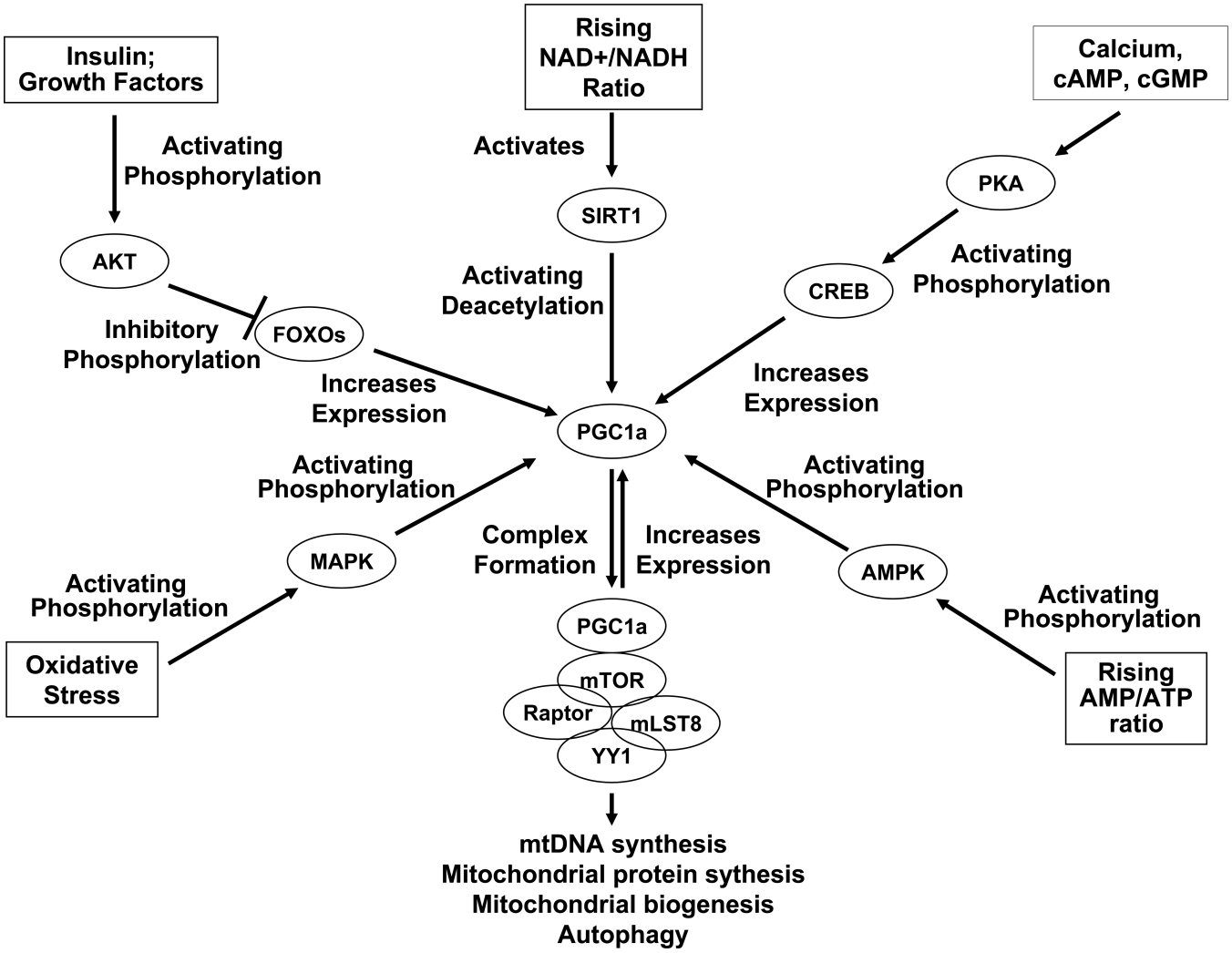

Figure 1.
Mitochondrial biogenesis regulatory pathways.