be able to shift the circadian clock. This pathway could also be manipulated to ameliorate seasonal affective disorder [18]. A drug that made one happier and more alert by specifically activating a few thousand retinal ganglion cells would be a remarkable advance indeed.

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Glucose Metabolism: A Sweet Relief of Alzheimer's Disease

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Patients and individuals at risk for Alzheimer's disease show reduced glucose metabolism in the brain. A new study takes advantage of a fly model of Alzheimer's disease to demonstrate that enhancing glucose uptake in neurons has strong neuroprotective effects involving improved proteostasis.

Although the brain constitutes only 2% of the total body mass, it is one of the major energy-demanding organs in the human body. Glucose is an essential energy substrate to sustain neuronal activity and is taken up via glucose transporters expressed in the brain endothelium, astrocytes and neurons [1]. Accumulating evidence suggests that impaired cerebral glucose metabolism is an invariant pathological feature of Alzheimer's disease (AD). This

phenomenon is proposed to contribute to disease progression and the manifestation of clinical symptoms, even decades before the occurrence of cognitive dysfunction and histopathological alterations [1]. Although an experimental reduction of glucose uptake in the brain has been reported to enhance the progression of AD in mouse models, the therapeutic potential of targeting glucose transporters has not been defined. A new study from Linda Partridge's group [2], published in this issue of *Current Biology*, now demonstrates that neuronal overexpression of glucose transporter-1 (GLUT-1) in a *Drosophila* model of AD alleviates neurodegeneration and behavioral alterations. Remarkably, improved glucose metabolism in the nervous system prolonged lifespan and reduced proteostasis alterations.

AD is the most common type of senile dementia worldwide that is characterized by progressive loss of synaptic function followed by neuronal death. These events are mediated in part by the abnormal deposition of misfolded amyloid-β peptide (Aβ) and the accumulation of the hyperphosphorylated form of the microtubule-associated protein Tau in the brain of affected patients [3]. Besides aging, type 2 diabetes mellitus involving insulin resistance is considered a risk factor in developing AD. Importantly, a diminution of glucose uptake in the brain is an early and accurate biomarker of neuronal atrophy and dysfunction in AD [4]. Glucose metabolism, as assessed by positron emission tomography, is substantially reduced in the hippocampus and brain cortex of familial AD subjects [1]. Furthermore, altered glucose uptake is also observed in the brain of patients with mild cognitive impairment, considered a prodromal stage of AD [5]. Similar alterations are also a salient feature of various mouse models of familial AD [6,7], supporting the idea that altered glucose uptake contributes to disease progression. Several carriers facilitate the transport of glucose across the blood–brain barrier. In the human brain, GLUT-1 is expressed mainly in glia and endothelial cells and GLUT-3 in neurons, playing an essential role in the modulation of brain glucose uptake and possibly AD development [1]. Importantly, experimental evidence demonstrated that GLUT-1 deficiency in endothelial cells accelerates AD pathology in mouse models, enhancing neurodegeneration, Aβ deposition and cognitive decline [8]. However, whether strategies to restore glucose levels in the brain could prevent the progression of AD remained unclear.

Here, Niccoli *et al.* [2] shed light on the effectiveness of increasing glucose uptake in neurons using a genetic approach in a fly model of AD. The authors selectively overexpressed GLUT-1 in a controlled manner in adult neurons of transgenic *Drosophila* expressing a mutant form of Aβ42. Remarkably, overexpression of GLUT-1 in the brain of these fly mutants increased lifespan and ameliorated the cardinal features of AD [2]. These protective effects were also achieved even after the neuropathological process had begun, suggesting the therapeutic potential of a sudden increase in glucose uptake in the brain in the context of AD. Glucose metabolism and insulin signaling regulate energy homeostasis, controlling different brain circuits involved in learning and memory [1]. To increase the translational potential of the study, the authors tested the significance of administrating the anti-diabetic agent metformin to the AD fly model. Metformin is a gold-standard drug for the treatment of type 2 diabetes mellitus and stimulates glucose uptake. Consistent with previous results in mouse models of AD [9], metformin also delayed the progression of experimental AD in flies, phenocopying the results observed upon GLUT-1 overexpression. Metformin increased the lifespan and rescued the behavioral deficits of experimental AD, increasing the clinical relevance of the current study.

The exact molecular mechanisms underlying the effects of increased glucose uptake in AD models remain to be determined. Importantly, the main risk factor of AD is aging, a process associated with a reduced buffering capacity of the proteostasis network that may contribute to the abnormal deposition of protein aggregates [10,11]. One of the main nodes of the proteostasis network that is altered in AD is the unfolded protein response (UPR), an adaptive reaction against endoplasmic reticulum (ER) stress [12,13]. Several studies suggest that ER stress is linked to abnormal glucose metabolism and insulin resistance in peripheral organs [14,15]. Remarkably, Niccoli *et al.* [2] discovered a new neuroprotective mechanism connecting GLUT-1 expression and the engagement of the UPR. The UPR represents a major repair reaction that aims to reduce the load of unfolded proteins at the ER. In doing so, this pathway reinforces many aspects of the secretory pathway, including protein folding, quality control mechanisms, and the degradation of misfolded proteins [14]. However, chronic ER stress results in cell death by apoptosis. The UPR is initiated by the activation of specialized stress sensors, including inositol-requiring protein 1α (IRE1α), protein kinase RNA-like ER kinase (PERK) and activating transcription factor 6 (ATF6). Under resting conditions, these sensors are kept in an inactive state through the binding of the ER chaperone BiP (also known as 78 kDa glucose-regulated protein, Grp78). Under conditions of ER stress, BiP is released from these sensors, allowing them to trigger the downstream outputs of the UPR [16]. Of note, overexpression of GLUT-1 or treatment of flies with metformin was associated with a reduction in BiP levels and, as a consequence, activation of the IRE1 and ATF6 arms of the UPR. Moreover, the authors reported that genetic reduction of BiP activity also rescued Aβ toxicity and that this occurs through upregulation of the UPR in AD flies [2]. Consistent with these observations, previous studies have shown that overexpression of the transcription factor XBP1, a downstream target of IRE1, protects against Aβ toxicity and Tau overexpression in fly models of AD [12]. Altogether, these results depict an intimate crosstalk between energy control mechanisms and the regulation of neuronal proteostasis. Thus, targeting glucose uptake in the brain may affect two principal features of AD — cognitive decline and proteostasis dysfunction.

Importantly, recent advances in the field have uncovered a novel activity of the ER proteostasis network in modulating neuronal plasticity and synaptic function. Strategies that alleviate chronic ER stress

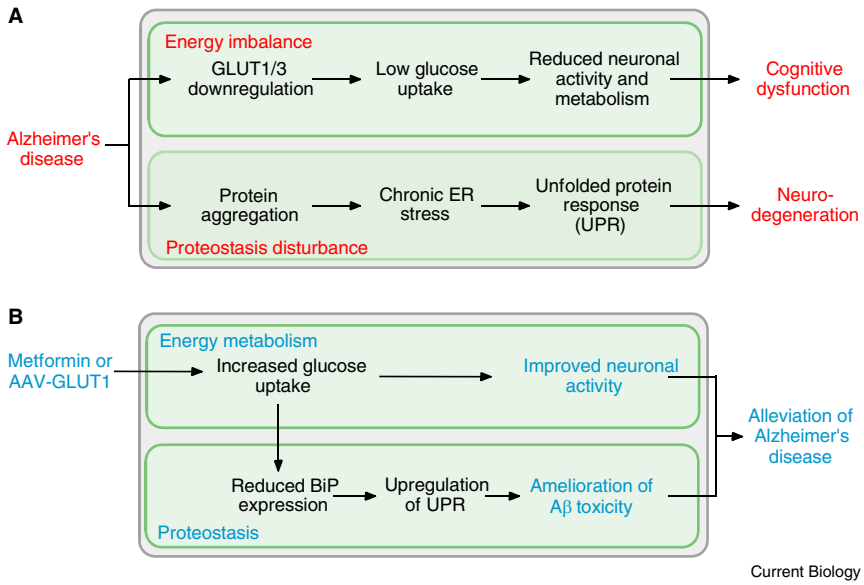

Figure 1. Improving glucose uptake in the brain protects against Alzheimer's disease (AD).
(A) The neurodegenerative process of AD involves progressive neuronal dysfunction and the abnormal deposition of aggregated proteins. Low glucose uptake or reduction of glucose levels in the brain is an early event in AD, leading to cognitive dysfunction and neurodegeneration. The occurrence of chronic endoplasmic reticulum (ER) stress contributes to neuronal damage in AD possibly by activating cell death mechanisms governed by the unfolded protein response (UPR). (B) Experimental strategies to enforce glucose uptake in fly models of AD by overexpressing glucose transporter 1 (GLUT-1) delay disease progression, associated with enhancement of adaptive mechanisms mediated by the UPR, possibly due to reduced expression of BiP, a well-known negative regulator of UPR stress sensors. Since the anti-diabetic drug metformin has similar protective effects, strategies to deliver GLUT-1 into the brain of AD patients, including gene therapy using the injection of adeno-associated vectors (AAV), might improve cognitive function and reduce abnormal protein aggregation.

signals have strong neuroprotective effects in mouse models of AD, improving synaptic function [17,18]. Moreover, we recently uncovered a physiological function of XBP1 in the nervous system in the control of learning and memory-related processes [19]. This novel activity of XBP1 in the brain was mapped to the transcriptional control of brain-derived neurotrophic factor (BDNF), a key component in memory consolidation. Of note, BDNF also regulates energy homeostasis, increasing the expression of glucose transporters. Altogether, the study from Niccoli *et al.* [2] highlights the potential of enforcing glucose uptake in the brain as a strategy to improve cognitive function that may in the long term reduce protein aggregation in AD by restoring proteostasis.

Further studies are needed to validate the impact of modulating glucose uptake in the brain of mammalian models of AD. Since the fundamental mechanisms linking energy control and glucose homeostasis in the brain are highly conserved in evolution, the current study in *Drosophila* promises great translational potential. The use of gene therapy to deliver glucose transporters into the hippocampus and other brain areas affected in AD could emerge as an attractive strategy to reverse the alterations observed in glucose uptake in AD patients (Figure 1). This approach is predicted not only to boost energy metabolism and improve mitochondrial function, but also to improve the buffering capacity of the cell against abnormal protein aggregation. The neuropathological cascade of AD begins many years before clinical onset. Since a reduction in glucose uptake in the brain is an early biomarker of AD, defining the mechanism that underlies this energy failure may assist with the design of hopefully preventative strategies for this fatal disorder.

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Perceptual Inference: A Matter of Predictions and Errors

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A recent study finds that separate populations of neurons in inferotemporal cortex code for perceptual predictions and prediction errors, supporting predictive coding theories of perception.

More than a century ago, Helmholtz described perception as a process of unconscious inference — that is, an attempt to infer the most likely causes of our sensory inputs given our prior knowledge of the world. In recent decades, interest in this perspective has been rekindled by new insights from computer science and neuroscience, leading to theories on how the brain could accomplish such inferences. One highly influential theory is 'predictive coding' [1,2], according to which cortical regions constantly generate hypotheses (or 'predictions') about the likely causes of their inputs. For instance, when presented with the stimulus in Figure 1A, a cortical region specialised in processing simple geometrical shapes may generate the hypothesis of a white triangle partially occluding three black circles [3]. In addition to representing these predictions, each cortical region also encodes how they differ from current sensory inputs: these 'prediction errors' allow for efficient updating of hypotheses. This coding scheme can account for many properties of how neurons behave in early visual cortex [2,4], and has received indirect support from neuroimaging [3,5–8] and electrophysiology [9,10] in humans, and from electrophysiology in monkeys [11].

To date, however, there has been a noticeable lack of evidence for a central tenet of predictive coding theory, and one that distinguishes it from other theories of perceptual inference [12] — that predictions and prediction errors are explicitly and separately represented within a given cortical region (Figure 1B). Consistent with the theory, a new study published in this issue of *Current Biology* [13] measuring single unit responses in macaques reports encoding of predictions and prediction errors by separate neural populations in inferotemporal cortex (IT).

In their study, Bell *et al.* [13] presented monkeys with images of faces and fruits, while a latent variable — not revealed to the monkeys — determined the relative probability of each image category. Despite the implicit nature of this manipulation, neural responses in IT (known to be involved in processing complex visual stimuli) were strongly modulated by image predictability. First, averaged over all face-responsive cells, neural firing rates were higher for unexpected *versus* expected faces, consistent with the encoding of prediction errors. Second, multivariate analyses revealed that population activity encoded the probability of a face occurring, even before an image was presented. Thus, IT encodes both predictions about upcoming sensory input, and the mismatch between these predictions and the input that was actually received (Figure 1C).

One strong prediction made by predictive coding theories is that these two signals, predictions and prediction errors, are represented in separate populations of neurons. One way to establish this would be to record from neurons in different cortical layers: in the theory, predictions generated by a cortical region are sent back to explain its inputs from lower-level regions, and thus they should reside in the feedback-providing deep layers; prediction errors, on the other hand, are sent forward as input to higher-level regions, and thus should reside in the superficial layers [1,14]. Bell *et al.* [13] did not measure the cortical depth of the neurons from which they recorded, but they did address this issue in a different way: by examining the relationship between the signals across neurons. Although the strength of neurons' face (relative to fruit) preference correlated positively with both their encoding of the *a priori* likelihood of a face appearing (the prediction) and their enhanced response for unexpected *versus* expected faces (the prediction error), there was strikingly no correlation between prediction and prediction error encoding across neurons.