nature REVIEWS DRUG DISCOVERY

SUPPLEMENTARY INFORMATION

In format as provided by the authors

Brain energy rescue: an emerging therapeutic concept for neurodegenerative disorders of ageing

Stephen C. Cunnane, Eugenia Trushina, Cecilie Morland, Alessandro Prigione, Gemma Casadesus, Zane B. Andrews, M. Flint Beal, Linda H. Bergersen, Roberta D. Brinton, Suzanne de la Monte, Anne Eckert, Jenni Harvey, Ross Jeggo, Jack H. Jhamandas, Oliver Kann, Clothide Mannoury la Cour, William F. Martin, Gilles Mithieux, Paula I. Moreira, Michael P. Murphy, Klaus-Armin Nave, Tal Nuriel, Stéphane H. R. Oliet, Frédéric Saudou, Mark P. Mattson, Russell H. Swerdlow and Mark J. Millan

https://doi.org/10.1038/s41573-020-0072-x

Supplementary Table 1 | Hormonal and energetic features of neurodegenerative disorders of ageing

Disease: monogenic (%); age of onset	Disruption of brain and whole-body energetics: supply of fuel to the brain and transformation into ATP in neurons and other cell types	References	Changes in hormones modulating energy homeostasis and neural function (plasma unless specified)	References
Alzheimer disease ~5% (usually >70 y)	Progressive ↓ brain glucose metabolism from asymptomatic to MCI to AD in hippocampus, entorhinal cortex, precuneus, posterior cingulate, temporal CX and frontal lobes; ↓CBF; ↓BBB and cellular/neuronal transport of glucose (↓ GLUT1, GLUT3, GLUT4); ↓glycolysis, ↓ hexokinase in ApoE4 vs. ApoE2; ↓ TCA cycle (↓ Pyruvate dehydrogenase, α-KGDH, Lactate dehydrogenase). ↓ mitochondrial biogenesis, fission/fusion and mitophagy; ↓PPAR/PGC-1α ApoE4 vs ApoE2; ↓ AMPK; ↓ Glucose-dependent, protective tau O-GlcNAcylation; ↓glial and oligodendrocyte lactate support of neurons; ↑ microglial glucose use (TREM2-driven) and energetic switch (oxidative phosphorylation to glycolysis). No detectable change in brain ketone uptake or metabolism nor cerebral O_2. ↓ Appetite, ↓ BMI; weight loss, poor nutrition. Obesity and type 2 diabetes are risk factors in mid-life.	[1-13]	Insulin resistance, both brain and whole body, and glucose intolerance. Aggregates of amylin in brain, neurovasculature and pancreas, with ↓ monomeric form; ↓ ghrelin, ghrelin acylation and ghrelin signaling in temporal cortex; dysregulated leptin signaling in hippocampus. Plasma: ↑ Insulin; ↑/↓ amylin; ↑/- GLP1/GIP; ↑/- ghrelin; ↓ leptin especially in women; ↑ adiponectin.	[7,14-23]
Parkinson disease ca. 5-15% (usually >60 y)	↓ Brain glucose metabolism in striatum (caudate), premotor cortex, parieto-occipital cortex and frontal cortex yet, conversely, ↑ (debated) in cerebellum and pons; SNPC not resolvable. ↓ GLUT4; ↓ glycolysis; disruption of mitochondria in SNPC, including ↓ electron transport chain activity, excess Ca^{2+}, fragmentation and ↓ mitophagy. Mutations (monogenic forms of PD) in PINK1, Parkin, LRRK2, DJ-1 (PARK7) and SCNA are associated with disruption of mitochondrial function. ↓ BMI and weight loss; ↑visceral *vs* subcutaneous fat; ↓food intake (secondary, late phase).	[1,8,11,15,24-27]	Insulin resistance (brain and systemic); ↓ Ghrelin receptor (GHSR) in SNPC (hIPS). Plasma: ↓ ghrelin; ↓/- leptin; ↑/- adiponectin.	[15,27-30]
Frontotemporal dementia ca 10-15% (~40-60 y)	↓ Brain glucose metabolism pronounced and early (predating dementia) in frontal lobes, temporal cortex, anterior cingulate cortex, striatum, insula and thalamus; ↓ CBF; mitochondrial dysfunction, fragmentation, ↓mitophagy; reduced	[8,9,31-33]	Insulin resistance. Plasma: ↑ insulin; - GLP1/GIP; ↑/- ghrelin; ↑/- leptin.	[31,34,35]

	mitochondrial signalling with endoplasmic reticulum. Binge/over-eating; ↑ BMI and weight gain; sweetness preference and ↑ carbohydrate intake; ↑ resting and total energy expenditure.			
Amyotrophic lateral sclerosis ca 10% (~50-60 y)	Complex pattern of changes in glucose metabolism differ to FTD; ↓frontal cortex, motor cortex, parietal cortex *vs* ↑ in midbrain, cerebellum, spinal cord; white matter loss linked to metabolic deficits; mitochondrial dysfunction with ↓PGC-1α, ↓oxidative phosphorylation and TCA, ↓ PPP, ↓ ATP and compromised mitochondrial quality control in skeletal muscle, spinal cord, motor neurons and cerebral neurons; metabolic changes linked to glial dysfunction, ↓astrocyte glycogen metabolism and metabolic flexibility, ↓lactate provision to neurons; ↓ oligodendrocyte lactate provision to axons with ↓ monocarboxylate transporter; ↓ myelin channel integrity. ↓ BMI and weight loss (poor prognosis), dysphagia and malnutrition (late phase); ↑ resting energy expenditure and hypermetabolism; ↑ cholesterol and dyslipidemia.	[8,31-33,36-42]	Insulin resistance and glucose intolerance, but modest and inconsistent alterations in plasma hormones; - amylin; -GLP1/GIP; ↓/- ghrelin; ↑/- leptin; ↑ adiponectin.	[31,34,43,44]
Huntington disease Inherited (ca. 8-10% are de novo mutations) (~30-50 y)	↓Glucose metabolism in frontal cortex, temporal cortex, basal ganglia (MSNs), seen before diagnosis, and also in asymptomatic mutation carriers: ↓ GLUT3-mediated neuronal glucose uptake; ↓ Glycolysis and ↓ATP; mitochondrial disruption, ↓PGCα, ↓ PPARδ; ↓TCA and oxidative phosphorylation, redox imbalance; ↓axonal delivery of mitochondria (and other cargo) to synapses; astrocyte metabolic switch to fatty acids (striatum); ↓ lactate supply to neurons. ↓ BMI, progressive weight loss, despite no initial ↓ caloric intake (and even a marked ↑ in consumption in some patients); insulin resistance.	[45-51]	Insulin resistance and glucose intolerance in some studies. Plasma: no consistent alterations in insulin; ↑/- ghrelin; ↓/- leptin; ↓/ - adiponectin	[15,52]

Except for HD, most classes of NDAs are polygenic and multifactorial: abnormalities are shown principally for idiopathic, non-familial forms of the disorders. There are several variants of FTD, mainly defined according to clinical profile. Common risk genes and symptoms are increasingly aligning FTD with ALS in a "spectrum" of disorders. The precise pattern of changes depends upon the FTD variant and specific gene mutations. For all NDAs, neurotoxic proteins (soluble forms and higher order aggregates) and their poor

clearance are incriminated in core neuropathology. Further, NDAs are all characterized by axonal-synaptic disruption, neuronal cell loss, glial dysfunction, neuroinflammation and neurovascular anomalies from blood-brain barrier breakdown to perturbed microvasculature to microvessel leakage. As described, a core feature of NDAs, starting prior to diagnosis, is defective brain energetics, glucose supply and mitochondrial generation of ATP, together with disrupted secretion and actions of hormones modulating brain energy homeostasis, food intake, synaptic function and neuronal integrity. Brain glucose metabolism is almost always measured by FDG-PET (see Box 2). All NDAs are associated with alterations in BMI and body weight[31,32,36]. Alterations shown in columns 2 and 4 are the most robust and consistently observed. Abbreviations not in main text: BBB, blood brain barrier; BMI, body mass index; CBF, cerebral blood flow; α-KGDH, α-Ketoglutarate dehydrogenase; LRRK2, Leucine-rich Repeat Kinase 2; MSN, medium spiny neuron; PARK, Parkinson-related; PGC, Peroxisome Proliferator-activated Receptor Co-activator; PINK, Phosphotensin-induced kinase; PPP – pentose phosphate pathway; SCNA, α–synuclein; SNPC, substantia nigra pars compacta and TREM2, Triggering receptor expressed on myeloid cells 2.

References

1 Aldana, B. I. Microglia-specific metabolic changes in neurodegeneration. *J Mol Biol* **431**, 1830-1842, doi:10.1016/j.jmb.2019.03.006 (2019).

2 An, Y. *et al.* Evidence for brain glucose dysregulation in alzheimer's disease. *Alzheimers Dement* **14**, 318-329, doi:10.1016/j.jalz.2017.09.011 (2018).

3 Carbonell, F., Zijdenbos, A. P., Bedell, B. J. & for the Alzheimer's Disease Neuroimaging, I. Spatially distributed amyloid-β reduces glucose metabolism in mild cognitive impairment. *Journal of Alzheimer's Disease* **73**, 543-557, doi:10.3233/JAD-190560 (2020).

4 Castellano, C.-A. *et al.* Regional brain glucose hypometabolism in young women with polycystic ovary syndrome: Possible link to mild insulin resistance. *PLOS ONE* **10**, e0144116, doi:10.1371/journal.pone.0144116 (2015).

5 Croteau, E. *et al.* Ketogenic medium chain triglycerides increase brain energy metabolism in alzheimer's disease. *Journal of Alzheimer's Disease* **64**, 551-561, doi:10.3233/jad-180202 (2018).

6 Croteau, E. *et al.* A cross-sectional comparison of brain glucose and ketone metabolism in cognitively healthy older adults, mild cognitive impairment and early alzheimer's disease. *Experimental Gerontology* **107**, 18-26, doi:10.1016/j.exger.2017.07.004 (2018).

7 Calsolaro, V. & Edison, P. Alterations in glucose metabolism in alzheimer's disease. *Recent Patents on Endocrine, Metabolic & Immune Drug Discovery* **10**, 31-39, doi:10.2174/1872214810666160615102809 (2016).

8 Briston, T. & Hicks, A. R. Mitochondrial dysfunction and neurodegenerative proteinopathies: Mechanisms and prospects for therapeutic intervention. *Biochemical Society Transactions* **46**, 829-842, doi:10.1042/bst20180025 (2018).

9 Verfaillie, S. C. J. *et al.* Cerebral perfusion and glucose metabolism in alzheimer's disease and frontotemporal dementia: Two sides of the same coin? *European Radiology* **25**, 3050-3059, doi:10.1007/s00330-015-3696-1 (2015).

10 Sweeney, M. D. *et al.* Vascular dysfunction-the disregarded partner of alzheimer's disease. *Alzheimers Dement* **15**, 158-167, doi:10.1016/j.jalz.2018.07.222 (2019).

11 Zilberter, Y. & Zilberter, M. The vicious circle of hypometabolism in neurodegenerative diseases: Ways and mechanisms of metabolic correction. *Journal of Neuroscience Research* **95**, 2217-2235, doi:10.1002/jnr.24064 (2017).

12 Wu, L., Zhang, X. & Zhao, L. Human apoe isoforms differentially modulate brain glucose and ketone body metabolism: Implications for alzheimer's disease risk reduction and early intervention. *The Journal of Neuroscience* **38**, 6665-6681, doi:10.1523/jneurosci.2262-17.2018 (2018).

13 Ryu, J. C., Zimmer, E. R., Rosa-Neto, P. & Yoon, S. O. Consequences of metabolic disruption in alzheimer's disease pathology. *Neurotherapeutics* **16**, 600-610, doi:10.1007/s13311-019-00755-y (2019).

14 Griffith, C. M., Eid, T., Rose, G. M. & Patrylo, P. R. Evidence for altered insulin receptor signaling in alzheimer's disease. *Neuropharmacology* **136**, 202-215, doi:10.1016/j.neuropharm.2018.01.008 (2018).

15 Shi, L., Du, X., Jiang, H. & Xie, J. Ghrelin and neurodegenerative disorders—a review. *Molecular Neurobiology* **54**, 1144-1155, doi:10.1007/s12035-016-9729-1 (2016).

16 Mietlicki-Baase, E. G. Amylin in alzheimer's disease: Pathological peptide or potential treatment? *Neuropharmacology* **136**, 287-297, doi:10.1016/j.neuropharm.2017.12.016 (2018).

17 McGuire, M. J. & Ishii, M. Leptin dysfunction and alzheimer's disease: Evidence from cellular, animal, and human studies. *Cellular and Molecular Neurobiology* **36**, 203-217, doi:10.1007/s10571-015-0282-7 (2016).

18 Forny-Germano, L., De Felice, F. G. & Vieira, M. N. d. N. The role of leptin and adiponectin in obesity-associated cognitive decline and alzheimer's disease. *Frontiers in Neuroscience* **12**, doi:10.3389/fnins.2018.01027 (2019).

19 Fu, W., Patel, A., Kimura, R., Soudy, R. & Jhamandas, J. H. Amylin receptor: A potential therapeutic target for alzheimer's disease. *Trends in Molecular Medicine* **23**, 709-720, doi:10.1016/j.molmed.2017.06.003 (2017).

20 Ma, J. *et al.* Peripheral blood adipokines and insulin levels in patients with alzheimer';s disease: A replication study and meta-analysis. *Current Alzheimer Research* **13**, 223-233, doi:10.2174/1567205013031602171114 34 (2016).

21 Duarte, A. I., Santos, M. S., Oliveira, C. R. & Moreira, P. I. Brain insulin signalling, glucose metabolism and females' reproductive aging: A dangerous triad in alzheimer's disease. *Neuropharmacology* **136**, 223-242, doi:10.1016/j.neuropharm.2018.01.044 (2018).

22 Bonda, D. J. *et al.* Dysregulation of leptin signaling in alzheimer disease: Evidence for neuronal leptin resistance. *Journal of Neurochemistry* **128**, 162-172, doi:10.1111/jnc.12380 (2013).

23 Yoshino, Y. *et al.* Ghrelin cascade changes in the peripheral blood of japanese patients with alzheimer's disease. *Journal of Psychiatric Research* **107**, 79-85, doi:10.1016/j.jpsychires.2018.10.011 (2018).

24 Zeng, X.-S., Geng, W.-S., Jia, J.-J., Chen, L. & Zhang, P.-P. Cellular and molecular basis of neurodegeneration in parkinson disease. *Frontiers in Aging Neuroscience* **10**, doi:10.3389/fnagi.2018.00109 (2018).

25 Matthews, D. C. *et al.* Fdg pet parkinson's disease-related pattern as a biomarker for clinical trials in early stage disease. *NeuroImage: Clinical* **20**, 572-579, doi:10.1016/j.nicl.2018.08.006 (2018).

26 Zambon, F. *et al.* Cellular alpha-synuclein pathology is associated with bioenergetic dysfunction in parkinson's ipsc-derived dopamine neurons. *Hum Mol Genet* **28**, 2001-2013, doi:10.1093/hmg/ddz038 (2019).

27 Yang, L., Wang, H., Liu, L. & Xie, A. The role of insulin/igf-1/pi3k/akt/gsk3β signaling in parkinson's disease dementia. *Frontiers in Neuroscience* **12**, doi:10.3389/fnins.2018.00073 (2018).

28 Athauda, D. & Foltynie, T. The glucagon-like peptide 1 (glp) receptor as a therapeutic target in parkinson's disease: Mechanisms of action. *Drug Discovery Today* **21**, 802-818, doi:10.1016/j.drudis.2016.01.013 (2016).

29 Suda, Y. *et al.* Down-regulation of ghrelin receptors on dopaminergic neurons in the substantia nigra contributes to parkinson's disease-like motor dysfunction. *Molecular Brain* **11**, doi:10.1186/s13041-018-0349-8 (2018).

30 Rocha, N. P. *et al.* Circulating levels of adipokines in parkinson's disease. *Journal of the Neurological Sciences* **339**, 64-68, doi:10.1016/j.jns.2014.01.021 (2014).

31 Ahmed, R. M. *et al.* Amyotrophic lateral sclerosis and frontotemporal dementia: Distinct and overlapping changes in eating behaviour and metabolism. *The Lancet Neurology* **15**, 332-342, doi:10.1016/s1474-4422(15)00380-4 (2016).

32 Jawaid, A., Khan, R., Polymenidou, M. & Schulz, P. E. Disease-modifying effects of metabolic perturbations in als/ftld. *Molecular Neurodegeneration* **13**, doi:10.1186/s13024-018-0294-0 (2018).

33 Lau, D. H. W. *et al.* Disruption of er−mitochondria signalling in fronto-temporal dementia and related amyotrophic lateral sclerosis. *Cell Death & Disease* **9**, doi:10.1038/s41419-017-0022-7 (2018).

34 Ahmed, R. M. *et al.* Eating peptides: Biomarkers of neurodegeneration in amyotrophic lateral sclerosis and frontotemporal dementia. *Annals of Clinical and Translational Neurology* **6**, 486-495, doi:10.1002/acn3.721 (2019).

35 Zanardini, R. *et al.* Serum c-peptide, visfatin, resistin, and ghrelin are altered in sporadic and grn-associated frontotemporal lobar degeneration. *Journal of Alzheimer's Disease* **61**, 1053-1060, doi:10.3233/jad-170747 (2018).

36 Vandoorne, T., De Bock, K. & Van Den Bosch, L. Energy metabolism in als: An underappreciated opportunity? *Acta Neuropathologica* **135**, 489-509, doi:10.1007/s00401-018-1835-x (2018).

37 Delic, V. *et al.* Discrete mitochondrial aberrations in the spinal cord of sporadic als patients. *Journal of Neuroscience Research* **96**, 1353-1366, doi:10.1002/jnr.24249 (2018).

38 Khalil, B. & Liévens, J.-C. Mitochondrial quality control in amyotrophic lateral sclerosis: Towards a common pathway? *Neural Regeneration Research* **12**, 1052, doi:10.4103/1673-5374.211179 (2017).

39 Tefera, T. W. & Borges, K. Metabolic dysfunctions in amyotrophic lateral sclerosis pathogenesis and potential metabolic treatments. *Frontiers in Neuroscience* **10**, doi:10.3389/fnins.2016.00611 (2017).

40 Szelechowski, M. *et al.* Metabolic reprogramming in amyotrophic lateral sclerosis. *Scientific Reports* **8**, doi:10.1038/s41598-018-22318-5 (2018).

41 Phillips, M. C. L., Murtagh, D. K. J., Gilbertson, L. J., Asztely, F. J. S. & Lynch, C. D. P. Low-fat versus ketogenic diet in parkinson's disease: A pilot randomized controlled trial. *Movement Disorders* **33**, 1306-1314, doi:10.1002/mds.27390 (2018).

42 Allen, S. P. *et al.* C9orf72 expansion within astrocytes reduces metabolic flexibility in amyotrophic lateral sclerosis. *Brain* **142**, 3771-3790, doi:10.1093/brain/awz302 (2019).

43 Ngo, S. T. *et al.* Altered expression of metabolic proteins and adipokines in patients with amyotrophic lateral sclerosis. *Journal of the Neurological Sciences* **357**, 22-27, doi:10.1016/j.jns.2015.06.053 (2015).

44 Nagel, G. *et al.* Adipokines, c-reactive protein and amyotrophic lateral sclerosis – results from a population- based als registry in germany. *Scientific Reports* **7**, doi:10.1038/s41598-017-04706-5 (2017).

45 Morea, V. *et al.* Glucose transportation in the brain and its impairment in huntington disease: One more shade of the energetic metabolism failure? *Amino Acids* **49**, 1147-1157, doi:10.1007/s00726-017-2417-2 (2017).

46 Illarioshkin, S. N., Klyushnikov, S. A., Vigont, V. A., Seliverstov, Y. A. & Kaznacheyeva, E. V. Molecular pathogenesis in huntington's disease. *Biochemistry (Moscow)* **83**, 1030-1039, doi:10.1134/s0006297918090043 (2018).

47 Polyzos, A. A. *et al.* Metabolic reprogramming in astrocytes distinguishes region-specific neuronal susceptibility in huntington mice. *Cell Metabolism* **29**, 1258-1273.e1211, doi:10.1016/j.cmet.2019.03.004 (2019).

48 Mochel, F. Triheptanoin for the treatment of brain energy deficit: A 14-year experience. *Journal of Neuroscience Research* **95**, 2236-2243, doi:10.1002/jnr.24111 (2017).

49 Agarwal, S., Yadav, A. & Chaturvedi, R. K. Peroxisome proliferator-activated receptors (ppars) as therapeutic target in neurodegenerative disorders. *Biochemical and Biophysical Research Communications* **483**, 1166-1177, doi:10.1016/j.bbrc.2016.08.043 (2017).

50 McColgan, P. *et al.* Brain regions showing white matter loss in huntington's disease are enriched for synaptic and metabolic genes. *Biol Psychiatry* **83**, 456-465, doi:10.1016/j.biopsych.2017.10.019 (2018).

51 Kedaigle, A. J. *et al.* Bioenergetic deficits in huntington's disease ipsc-derived neural cells and rescue with glycolytic metabolites. *Hum Mol Genet*, doi:10.1093/hmg/ddy430 (2019).

52 Nambron, R. *et al.* A metabolic study of huntington's disease. *PLOS ONE* **11**, e0146480, doi:10.1371/journal.pone.0146480 (2016).

Supplementary Table 2 | Hormones modulating energy intake and homeostasis via actions in the brain, and their relevance to the treatment of neurodegenerative disorders of ageing as characterized by their functional effects *in vivo*

Hormone Synthesis in periphery Synthesis in the brain	Receptors for hormone Major sites of action in brain	NDA under study Selective ligands (indication if authorized)	Influence of hormones (agonists) on food and energy intake	Central actions of hormones (agonists) and *in vivo* effects in models of NDAs	Further information (references)
Insulin Pancreatic islet beta cells. Cortex, hippocampus (low, controversial)	Insulin1R, acts via IRS 1 and 2 subunits. Heterodimerizes with insulin-like growth hormone-1R. Hypothalamus (including arcuate), cortex, hippocampus, cerebellum, SNPC, VTA, *nucleus accumbens*	MCI, AD, PD Insulin, mainly intra-nasal for NDAs. Insulin Determir and other analogues (T2D).	↓ FI and appetite; ↑ GLUT3/4 to plasma membrane; ↑ brain glucose; ↑ thermogenesis	↑ Cognition, LTP and LTD.Facilitation of - glutamatergic - synaptic plasticity (hippocampus, nucleus accumbens and VTA). Mouse models of AD: ↑ LTP; ↓ Aβ load; ↓ microglial activation.	[1-5]
Amylin Pancreatic islet beta cells. Several hypothalamic nuclei, brainstem	Amylin R1-3, heterodimerizes with calcitonin 1R (two isoforms) and RAMP1-3. Hypothalamus, amygdala, VTA, *nucleus accumbens*, cortex, brainstem, area postrema, lateral dorsal tegmental nucleus.	AD Salmon calcitonin Pramlintide (non-aggregating, non amyloidogenic analogue) (T2D)	↓ Meal size; -/↑ Satiation; ↓ Glucagon; ↓ Adiposity/body weight. Leptin sensitizer and facilitator	Complex, beneficial actions of monomeric amylin. Mouse models of AD: ↑ Cognition; ↓ Aβ load by ↑ efflux and ↓ pTau; ↓ inflammation. Conversely, aggregates of amylin are neurotoxic, pro-apoptotic, pro-inflammatory, induce microvessel damage and hyperglycemia. Amylin receptor analogue (Pramlintide) blunts disruption of cognition and neurotoxic actions of Aβ	[6-9]
GLP1 Mainly distal small intestine, ileum, colon: enteroendocrine L-cells. Hippocampus, brainstem, hypothalamus	GLP1R Hypothalamus (including arcuate), nucleus tractus solitarious, VTA, SNPC, cortex, hippocampus, brainstem, cerebellum.	AD, PD. Also Wolfram syndrome, mood disorders, schizophrenia, stroke (± T2D), epilepsy. Long-acting Exendin, Liraglutide, Lixenatide, Semaglutide (T2D). Gliptins (DPP 4 inhibitors) prevent GLP-1 breakdown	Brain: ↓ FI and appetite, possible insulin sensitizer. Pancreas: insulinotropic, ↓ Glucagon, ↓β-cell apoptosis, ↑ β-cell proliferation.	Mouse models of AD : ↑ Cognition and LTP; ↑ neurogenesis and synaptogenesis (hippocampus); ↓ Excitotoxicity; ↓ Apoptosis and synapse loss; ↓ inflammation and oxidative stress; ↓ microvessel damage, ↓ Aβ/plaques and pTau tangles. Mouse models of PD: ↑ survival and motor function; ↓ inflammation and oxidative stress; ↑ glucose tolerance; Mouse models of ALS: ↑ motor function and ↓ weight loss; ↓ apoptosis and motor neuron loss (spinal cord). Mouse models of HD:↑ survival and	[10-14]

		(T2D).		motor function; ↓ Htt accumulation in striatum, cortex and pancreas; Improved glucose regulation.	
GIP Mainly duodenum, jejunem; enteroendocrine K-cells. Hippocampus, olfactory bulb, cerebellum	GIPR Hippocampus, cortex, olfactory bulb	AD (Dual GIP-GLP-1 agonists), PD 2-Ala^2-GIP 2-Ala^2-GIP-Glu-PAL	Brain: ↓ FI alone, also appear to potentiate actions of GLP-1. Pancreas: insulinotropic; ↓ β-cell apoptosis and ↑ β-cell proliferation	Mouse models of AD: ↑ Cognition and LTP; ↑ BDNF and neurogenesis (hippocampus); ↓ α-synuclein; ↓inflammation and ↓ oxidative stress. Mouse models of PD: ↑ motor function. Dual GIP/GLP-1 agonists have superior efficacy compared to selective ligands in models of AD and PD.	[15-17]
Ghrelin Mainly stomach and duodenum: ghrelinergic cells	GHS-R1a for functionally active acetylated ghrelin Pituitary, hypothalamus (including arcuate), amygdala, hippocampus, SNPC, VTA, raphe nuclei, cortex, brainstem	None in clinical NDA trials yet. Relamorelin (gastroparesis in PD and T2D); Anamorelin (anorexia and cachexia in cancer). Acyl-ghrelin MK-0777, LY444711, HM01 (antag)	Brain: ↑ FI (appetite, reward); ↓ Energy expenditure. Pancreas: ↓ glucose-simulated insulin release. Gut: ↑ gastric emptying/motility	Mouse models of AD: ↑ Cognition and LTP; ↑ pCREB and neurogenesis (hippocampus); ↓ synapse loss and disruption of plasticity; ↓ Aβ load/toxicity and ↓ pTau; ↓Inflammation and oxidative stress; ↑ mitochondrial function; ↑ Insulin-induced glucose uptake. Mouse models of PD: ↑ Locomotion and ↑ dopamine release; ↑Mitochondrial function; ↑ PGC-1α; ↑ Sirtuin1/3; ↓Inflammation and oxidative stress. Mouse model of HD: normalization of body weight and energy expenditure; ↓ GHS-R1α levels.	[18-23]
Leptin Mainly adipose tissue; adipocytes Prefrontal cortex, other cortical regions, hippocampus	Leptin-bR ("ObR"), five other splice variants known Hypothalamic nuclei (including arcuate), cortex, hippocampus brainstem, VTA, thalamus	None in clinical NDA trials yet. Leptin; Leptin116-130 (active fragment); Metreleptin (lipodystrophy). Sensitizers like Withaferin A to reduce insulin resistance.	↓ FI and appetite; ↑ Thermogenesis, ↑ Energy expenditure	Mouse models of AD: ↑ Cognition and LTP; ↑ NMDAR- plasticity and AMPAR insertion (hippocampus); ↑ Neurogenesis and synaptic density; ↑ Mitochondrial function; ↓ Aβ aggregation/fibrils and pTau; ↓ Inflammation; ↓ Apoptosis. Mouse models of PD: ↑ pCREB and BDNF. Mouse model of ALS, leptin knock-out leads to: Slower disease progression; ↑ Body weight and fat mass; ↓ Energy output.	[24-29]
Adiponectin Mainly adipose tissue; adipocytes, also muscle cells (autocrine) Uncertain? At most, very modest expression	AdipoR1, AdipoR2, T-Cadherin Hypothalamus, brainstem, cortex, *nucleus basomagno-cellularis*	None in clinical NDA trials yet. AdipoRon, Osmotin, Arctigenin	↓ FI and appetite; ↑ Glucose uptake and glycolysis (hippocampus). Insulin sensitizer.	Mouse models of AD: ↑ cognition and LTP; ↑ neurite outgrowth and dendritogenesis; ↓ Aβ aggregation and pTau; ↓inflammation and ↓ oxidative stress.	[25,30-33]

All hormones listed (see Supplementary Table 1 for alterations in NDAs) exert actions in the brain and other organs to influence food intake and energy homeostasis: they also exert a suite of effects relevant to treatment of NDAs. These hormones enter the brain (some aided by active transport systems) from the circulation via the BBB, circumventricular organs, hypothalamic tanycytes, the choroid plexus barrier and/or other mechanisms (only for adiponectin is evidence for entry weak). Synthetic ligands act centrally to varying degrees. For some hormones, there is evidence for synthesis in the brain itself, and the contribution of central *vs* peripheral pools to cerebral effects is not always clear. GLP-1 and GIP are incretins and having effects on the pancreas in addition to the brain. The influence of hormones on food and energy balance is exerted *via* modulation of autonomic (hypothalamus), reward (VTA and limbic system) and cognitive-executive function (cortex)[32]. Details are beyond the scope of this review but ghrelin and leptin exert actions via Agouti-related peptide/neuropeptide Y-containing neurons in the arcuate nucleus that promote appetite: they also act via arcuate-localized α-melanocyte-stimulating hormone-containing neurons coupled to melanocortin 4 receptors in the paraventricular nucleus that suppress food intake. The favourable influence of hormones on neuronal integrity/survival, synaptic plasticity and cognition has been most intensively studied in hippocampus, but also cortex, striatum/SNPC and other regions. Gliptins (dipeptidyl-peptidase 4 inhibitors) prevent GLP-1 breakdown and may be beneficial for cognition in T2D (Table 3) but have not been adequately assessed in animal models of NDA. Conversely, many papers report robust actions of dual GIP/GLP-1 agonists with "superior efficacy" vs selective ligands in models of AD and PD, in which they enhance insulin sensitivity and improve glucose regulation[16,17,33]. Abbreviations not in main text: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CREB, cAMP-regulated binding element; FI, food intake; IRS, insulin receptor substrate; LTD, Long-term depression; LTP, Long-term potentiation; NMDA, N-methyl-D-aspartate; NTS, nucleus tractus solitarious; PVN, paraventricular nucleus; RAMP, Receptor-activity modifying protein: SNPC, *substantia nigra, pars compacta*; VMN, ventromedial nucleus and VTA, Ventrotegmental area.

References

1 Calsolaro, V. & Edison, P. Alterations in glucose metabolism in alzheimer's disease. *Recent Patents on Endocrine, Metabolic & Immune Drug Discovery* **10**, 31-39, doi:10.2174/1872214810666160615102809 (2016).

2 Griffith, C. M., Eid, T., Rose, G. M. & Patrylo, P. R. Evidence for altered insulin receptor signaling in alzheimer's disease. *Neuropharmacology* **136**, 202-215, doi:10.1016/j.neuropharm.2018.01.008 (2018).

3 Wijesekara, N., Gonçalves, R. A., De Felice, F. G. & Fraser, P. E. Impaired peripheral glucose homeostasis and alzheimer's disease. *Neuropharmacology* **136**, 172-181, doi:10.1016/j.neuropharm.2017.11.027 (2018).

4 Chen, Y. *et al.* Intranasal insulin restores insulin signaling, increases synaptic proteins, and reduces aβ level and microglia activation in the brains of 3xtg-ad mice. *Experimental Neurology* **261**, 610-619, doi:10.1016/j.expneurol.2014.06.004 (2014).

5 Ferrario, C. R. & Reagan, L. P. Insulin-mediated synaptic plasticity in the cns: Anatomical, functional and temporal contexts. *Neuropharmacology* **136**, 182-191, doi:10.1016/j.neuropharm.2017.12.001 (2018).

6 Mietlicki-Baase, E. G. Amylin in alzheimer's disease: Pathological peptide or potential treatment? *Neuropharmacology* **136**, 287-297, doi:10.1016/j.neuropharm.2017.12.016 (2018).

7 Wang, E. *et al.* Amylin treatment reduces neuroinflammation and ameliorates abnormal patterns of gene expression in the cerebral cortex of an alzheimer's disease mouse model. *Journal of Alzheimer's Disease* **56**, 47-61, doi:10.3233/jad-160677 (2017).

8 Fu, W., Patel, A., Kimura, R., Soudy, R. & Jhamandas, J. H. Amylin receptor: A potential therapeutic target for alzheimer's disease. *Trends in Molecular Medicine* **23**, 709-720, doi:10.1016/j.molmed.2017.06.003 (2017).

9 Mohamed, L. A. *et al.* Amylin enhances amyloid-β peptide brain to blood efflux across the blood-brain barrier. *Journal of Alzheimer's Disease* **56**, 1087-1099, doi:10.3233/jad-160800 (2017).

10 Yildirim Simsir, I., Soyaltin, U. E. & Cetinkalp, S. Glucagon like peptide-1 (glp-1) likes alzheimer's disease. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* **12**, 469-475, doi:10.1016/j.dsx.2018.03.002 (2018).

11 Athauda, D. & Foltynie, T. The glucagon-like peptide 1 (glp) receptor as a therapeutic target in parkinson's disease: Mechanisms of action. *Drug Discovery Today* **21**, 802-818, doi:10.1016/j.drudis.2016.01.013 (2016).

12 Batista, A. F., Bodart-Santos, V., De Felice, F. G. & Ferreira, S. T. Neuroprotective actions of glucagon-like peptide-1 (glp-1) analogues in alzheimer's and parkinson's diseases. *CNS Drugs* **33**, 209-223, doi:10.1007/s40263-018-0593-6 (2018).

13 Li, H. *et al.* Sodium butyrate stimulates expression of fibroblast growth factor 21 in liver by inhibition of histone deacetylase 3. *Diabetes* **61**, 797-806, doi:10.2337/db11-0846; 10.2337/db11-0846 (2012).

14 Martin, B. *et al.* Exendin-4 improves glycemic control, ameliorates brain and pancreatic pathologies, and extends survival in a mouse model of huntington's disease. *Diabetes* **58**, 318-328, doi:10.2337/db08-0799 (2008).

15 Verma, M. K., Goel, R., Nandakumar, K. & Nemmani, K. V. S. Effect of d-ala 2 gip, a stable gip receptor agonist on mptp-induced neuronal impairments in mice. *European Journal of Pharmacology* **804**, 38-45, doi:10.1016/j.ejphar.2017.03.059 (2017).

16 Jalewa, J., Sharma, M. K. & Hölscher, C. Novel incretin analogues improve autophagy and protect from mitochondrial stress induced by rotenone in sh-sy5y cells. *Journal of Neurochemistry* **139**, 55-67, doi:10.1111/jnc.13736 (2016).

17 Pathak, N. M. *et al.* Novel dual incretin agonist peptide with antidiabetic and neuroprotective potential. *Biochemical Pharmacology* **155**, 264-274, doi:10.1016/j.bcp.2018.07.021 (2018).

18 Shi, L., Du, X., Jiang, H. & Xie, J. Ghrelin and neurodegenerative disorders—a review. *Molecular Neurobiology* **54**, 1144-1155, doi:10.1007/s12035-016-9729-1 (2016).

19 Eslami, M., Sadeghi, B. & Goshadrou, F. Chronic ghrelin administration restores hippocampal long-term potentiation and ameliorates memory impairment in rat model of alzheimer's disease. *Hippocampus* **28**, 724-734, doi:10.1002/hipo.23002 (2018).

20 Santos, V. V. *et al.* Acyl ghrelin improves cognition, synaptic plasticity deficits and neuroinflammation following amyloid β (aβ1-40) administration in mice. *Journal of Neuroendocrinology* **29**, doi:10.1111/jne.12476 (2017).

21 Jeong, Y.-o. *et al.* Mk-0677, a ghrelin agonist, alleviates amyloid beta-related pathology in 5xfad mice, an animal model of alzheimer's disease. *International Journal of Molecular Sciences* **19**, 1800, doi:10.3390/ijms19061800 (2018).

22 Morgan, A. H., Rees, D. J., Andrews, Z. B. & Davies, J. S. Ghrelin mediated neuroprotection - a possible therapy for parkinson's disease? *Neuropharmacology* **136**, 317-326, doi:10.1016/j.neuropharm.2017.12.027 (2018).

23 Rudenko, O. *et al.* Ghrelin‐mediated improvements in the metabolic phenotype in the r6/2 mouse model of huntington's disease. *Journal of Neuroendocrinology* **31**, doi:10.1111/jne.12699 (2019).

24 McGuire, M. J. & Ishii, M. Leptin dysfunction and alzheimer's disease: Evidence from cellular, animal, and human studies. *Cellular and Molecular Neurobiology* **36**, 203-217, doi:10.1007/s10571-015-0282-7 (2016).

25 Forny-Germano, L., De Felice, F. G. & Vieira, M. N. d. N. The role of leptin and adiponectin in obesity-associated cognitive decline and alzheimer's disease. *Frontiers in Neuroscience* **12**, doi:10.3389/fnins.2018.01027 (2019).

26 McGregor, G. & Harvey, J. Regulation of hippocampal synaptic function by the metabolic hormone, leptin: Implications for health and neurodegenerative disease. *Frontiers in Cellular Neuroscience* **12**, doi:10.3389/fncel.2018.00340 (2018).

27 Davis, C., Mudd, J. & Hawkins, M. Neuroprotective effects of leptin in the context of obesity and metabolic disorders. *Neurobiology of Disease* **72**, 61-71, doi:10.1016/j.nbd.2014.04.012 (2014).

28 Lim, M. A. *et al.* Genetically altering organismal metabolism by leptin-deficiency benefits a mouse model of amyotrophic lateral sclerosis. *Human Molecular Genetics* **23**, 4995-5008, doi:10.1093/hmg/ddu214 (2014).

29 Fernandez-Martos, C. M., Atkinson, R. A. K., Chuah, M. I., King, A. E. & Vickers, J. C. Combination treatment with leptin and pioglitazone in a mouse model of alzheimer's disease. *Alzheimer's & Dementia: Translational Research & Clinical Interventions* **3**, 92-106, doi:10.1016/j.trci.2016.11.002 (2016).

30 Yoon, G., Shah, S. A., Ali, T. & Kim, M. O. The adiponectin homolog osmotin enhances neurite outgrowth and synaptic complexity via adipor1/ngr1 signaling in alzheimer's disease. *Molecular Neurobiology* **55**, 6673-6686, doi:10.1007/s12035-017-0847-1 (2018).

31 Ng, R. & Chan, K.-H. Potential neuroprotective effects of adiponectin in alzheimer's disease. *International Journal of Molecular Sciences* **18**, 592, doi:10.3390/ijms18030592 (2017).

32 Caron, A. & Richard, D. Neuronal systems and circuits involved in the control of food intake and adaptive thermogenesis. *Annals of the New York Academy of Sciences* **1391**, 35-53, doi:10.1111/nyas.13263 (2016).

33 Hölscher, C. Novel dual glp-1/gip receptor agonists show neuroprotective effects in alzheimer's and parkinson's disease models. *Neuropharmacology* **136**, 251-259, doi:10.1016/j.neuropharm.2018.01.040 (2018)

Supplementary Box 1 | Cellular models to study altered bioenergetics in neurodegenerative disorders of ageing

Cellular models are important in NDA research because they help identify molecular mechanisms underlying NDA, which may lead to new targets for therapeutic interventions. Cellular models also play a crucial role in the drug discovery process where they can be employed for large-scale therapeutic compound screening and drug discovery.

Traditionally, immortalized human cell lines have been the most widely used cellular model of NDA, given their robustness and amenability to expansion[1]. Immortalized cells can be easily engineered to overexpress or down-regulate genes of interest or to precisely carry disease-causing mutations through CRISPR/Cas9-mediated knock-in. The impact of mitochondrial DNA (mtDNA) on cellular disease pathways in NDA can be investigated using special immortalized cell lines or cybrids, which are depleted of mtDNA and fused with patient-derived enucleated cells[2,3]. However, the terminal growth and division cycling of immortal cells, in conjunction with their high basal need for carbon intermediates that incorporate glucose carbon means that they are best used to address specific questions of fundamental metabolism[4,5,6], and not as models of aging or to directly address neurodegenerative processes like senescence, epigenetic memory, and cell cycle regulation.

Patient-derived primary cells are an alternative cellular model for NDA. Several peripheral cell types have been used to model NDA, including skin fibroblasts and blood cells[7-10]. Unlike immortalized cell lines, primary cells are not easily amenable to expansion, a feature that makes them less valuable for high-throughput methods. Furthermore, although they may closely represent the complex genetics of NDAs[1], peripheral cells still do not faithfully reproduce the functional and metabolic features of brain cells.

Metabolic interventions may be able to increase the relevance of immortalized cells and peripheral cells for the study of the bioenergetic features of NDA. For example, glucose-free medium containing galactose blocks glycolysis and forces the cells to exclusively use mitochondrial respiration, thereby allowing for mitochondrial-related defects to become apparent[11]. By using glucose deprivation to induce metabolic stress in immortalized cells, it is possible to identify counter-regulatory strategies that could become potential treatments for NDA[12]. Inhibitors of the electron transport chain can also be employed to discover strategies to correct the mitochondrial impairment of NDA[13,14].

Besides immortalized cells and peripheral cells, a third NDA model involves cellular reprogramming technology. The most common reprogramming approach is the derivation of induced pluripotent stem cells (iPSCs)[15], which have revolutionized biomedical research because they can be derived from readily-

accessible patient material (skin, blood, hair or urine) and can be transformed into essentially any cell type in the body. The use of iPSC-derived material as NDA models enables the study of human brain cells that are normally not accessible. iPSCs can be grown in large quantities and their genome can be precisely engineered[16]. Genome editing via CRISPR/Cas9 can overcome one of the major drawbacks of iPSC models, since line-to-line variability that can potentially hamper the identification of patient-specific traits[17]. Genome editing involves either correcting the mutation in patient-derived iPSCs or introducing selected mutations into control iPSCs[18]. Gene editing is more valuable for modelling monogenic NDA like Huntington's disease (HD) compared to those caused by a complex combination of genetic and modifiable risk factors such as Alzheimer's disease (AD).

After thorough characterization and critical assessment of their whole genome, iPSCs can be differentiated into neuronal and glial cells to investigate the cellular energy homeostasis of various models NDA[19], including AD[20,21], Parkinson's disease (PD)[22-25], amyotrophic lateral sclerosis (ALS)[26,27], and HD[28-30]. iPSC-derived neural cells from familial PD patients show defective bioenergetics[23,24], altered response to oxidative stress[22], and reduced mitochondrial volume fraction[31]. iPSC-derived neurons and astrocytes generated from familial AD patients suggest oxidative stress due to mitochondrial disruption as a central disease mechanism[20]. In addition to post-mitotic neurons and glia, iPSCs can be also differentiated into neural progenitor cells (NPCs) useful for drug discovery programs targeting mitochondria bioenergetics given their proliferative properties coupled to dependence on oxidative phosphorylation[32,33].

Reprogramming technologies can bypass iPSCs to yield post-mitotic neurons directly from peripheral fibroblasts[34]. Direct reprogramming may hold specific advantages for studying NDA as it enables the retention of aging-related cellular defects that are erased during the generation of iPSCs (reviewed in Mertens et al.[35]). Studies conducted on directly reprogrammed neurons (iNs) from aging individuals and from HD patients identified cellular signatures (especially mitochondrial) that were *not* apparent in neurons obtained from iPSCs[36,37]. During the generation of iPSCs, mitochondria acquire embryonic-like features regardless of the age of the original donor[38]. Conversely, iNs retain aging-associated mitochondrial defects which become even more evident than in the original fibroblasts given the increased bioenergetic reliance of neurons on oxidative phosphorylation[39]. Nonetheless, given the lack of an intermediate proliferative state, direct reprogramming does not allow genome editing interventions and high-throughput studies. A potential strategy to overcome these technical limitations of iNs may be directly reprogrammed neural stem cells (iNSCs)[40].

A recent advance in the use of reprogramming technology for NDA research is the development of complex three-dimensional structures known as cerebral organoids or "mini-brains"[41]. iPSC-derived cerebral organoids can contain both glial and neuronal cells[42]. Microglia can also be developed within these self-assembled structures[43]. Cortical organoids may show metabolic stress, which could impair their use in disease modeling[44,45]. However, improved protocols indicate that brain organoids can allow the reproducible generation of data[44]. Cerebral organoids are starting to be used as new model systems for NDA[46]. The disease mechanisms and the effects of drugs have been modeled in organoids from AD patients[47-49]. Midbrain-specific organoids are also available to study the bioenergetics of PD[50].

Future studies will determine the comparative importance of iPSCs and directly derived neurons and organoids for advancing the understanding and therapy of NDA. This field is moving rapidly and is likely to become increasingly important in the shorter rather than long-term, both for characterisation of pathophysiological mechanisms like disruption of bioenergetics and also for drug discovery.

References

1 Andreux, P. A., Houtkooper, R. H. & Auwerx, J. Pharmacological approaches to restore mitochondrial function. *Nat Rev Drug Discov* **12**, 465-483, doi:10.1038/nrd4023 (2013).

2 King, M. & Attardi, G. Human cells lacking mtdna: Repopulation with exogenous mitochondria by complementation. *Science* **246**, 500-503, doi:10.1126/science.2814477 (1989).

3 Swerdlow, R. H. Mitochondria in cybrids containing mtdna from persons with mitochondriopathies. *J. Neurosci. Res.* **85**, 3416-3428, doi:10.1002/jnr.21167 (2007).

4 Abramov, A. Y. *et al.* Mechanism of neurodegeneration of neurons with mitochondrial DNA mutations. *Brain* **133**, 797-807, doi:10.1093/brain/awq015 (2010).

5 Kondoh, H., Lleonart, M. E., Gil, J., Beach, D. & Peters, G. Glycolysis and cellular immortalization. *Drug Discov. Today: Disease Mechanisms* **2**, 263-267, doi:10.1016/j.ddmec.2005.05.001 (2005).

6 Wilkins, H. M., Carl, S. M. & Swerdlow, R. H. Cytoplasmic hybrid (cybrid) cell lines as a practical model for mitochondriopathies. *Redox Biology* **2**, 619-631, doi:10.1016/j.redox.2014.03.006 (2014).

7 Auburger, G. *et al.* Primary skin fibroblasts as a model of parkinson's disease. *Molecular Neurobiology* **46**, 20-27, doi:10.1007/s12035-012-8245-1 (2012).

8 Huang, H.-M. *et al.* Use of cultured fibroblasts in elucidating the pathophysiology and diagnosis of alzheimer's diseasea. *Annals of the New York Academy of Sciences* **747**, 225-244, doi:10.1111/j.1749-6632.1994.tb44412.x (2006).

9 Michell, A. W., Luheshi, L. M. & Barker, R. A. Skin and platelet α-synuclein as peripheral biomarkers of parkinson's disease. *Neuroscience Letters* **381**, 294-298, doi:10.1016/j.neulet.2005.02.030 (2005).

10 Wiedemann, F. R., Winkler, K., Lins, H., Wallesch, C.-W. & Kunz, W. S. Detection of respiratory chain defects in cultivated skin fibroblasts and skeletal muscle of patients with parkinson's disease. *Annals of the New York Academy of Sciences* **893**, 426-429, doi:10.1111/j.1749-6632.1999.tb07870.x (1999).

11 Iannetti, E. F., Smeitink, J. A. M., Willems, P. H. G. M., Beyrath, J. & Koopman, W. J. H. Rescue from galactose-induced death of leigh syndrome patient cells by pyruvate and nad+. *Cell Death & Disease* **9**, doi:10.1038/s41419-018-1179-4 (2018).

12 Zhang, J. *et al.* 3-hydroxybutyrate methyl ester as a potential drug against alzheimer's disease via mitochondria protection mechanism. *Biomaterials* **34**, 7552-7562, doi:10.1016/j.biomaterials.2013.06.043 (2013).
13 Chaturvedi, R. K. & Beal, M. F. Mitochondria targeted therapeutic approaches in parkinson's and huntington's diseases. *Molecular and Cellular Neuroscience* **55**, 101-114, doi:10.1016/j.mcn.2012.11.011 (2013).
14 Joh, Y. & Choi, W.-S. Mitochondrial complex i inhibition accelerates amyloid toxicity. *Development & Reproduction* **21**, 417-424, doi:10.12717/dr.2017.21.4.417 (2017).
15 Takahashi, K. *et al.* Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* **131**, 861-872, doi:10.1016/j.cell.2007.11.019 (2007).
16 Shi, Y., Inoue, H., Wu, J. C. & Yamanaka, S. Induced pluripotent stem cell technology: A decade of progress. *Nature Reviews Drug Discovery* **16**, 115-130, doi:10.1038/nrd.2016.245 (2016).
17 Hockemeyer, D. & Jaenisch, R. Induced pluripotent stem cells meet genome editing. *Cell Stem Cell* **18**, 573-586, doi:10.1016/j.stem.2016.04.013 (2016).
18 Grobarczyk, B., Franco, B., Hanon, K. & Malgrange, B. Generation of isogenic human ips cell line precisely corrected by genome editing using the crispr/cas9 system. *Stem Cell Reviews and Reports* **11**, 774-787, doi:10.1007/s12015-015-9600-1 (2015).
19 Zink, A., Priller, J. & Prigione, A. Pluripotent stem cells for uncovering the role of mitochondria in human brain function and dysfunction. *Journal of Molecular Biology* **430**, 891-903, doi:10.1016/j.jmb.2018.02.005 (2018).
20 Kondo, T. *et al.* Modeling alzheimer's disease with ipscs reveals stress phenotypes associated with intracellular aβ and differential drug responsiveness. *Cell Stem Cell* **12**, 487-496, doi:10.1016/j.stem.2013.01.009 (2013).
21 Wang, A., Luan, H. H. & Medzhitov, R. An evolutionary perspective on immunometabolism. *Science* **363**, eaar3932, doi:10.1126/science.aar3932 (2019).
22 Nguyen, Ha N. *et al.* Lrrk2 mutant ipsc-derived da neurons demonstrate increased susceptibility to oxidative stress. *Cell Stem Cell* **8**, 267-280, doi:10.1016/j.stem.2011.01.013 (2011).
23 Ryan, S. D. *et al.* Isogenic human ipsc parkinson's model shows nitrosative stress-induced dysfunction in mef2-pgc1α transcription. *Cell* **155**, 1351-1364, doi:10.1016/j.cell.2013.11.009 (2013).
24 Sanders, L. H. *et al.* Lrrk2 mutations cause mitochondrial DNA damage in ipsc-derived neural cells from parkinson's disease patients: Reversal by gene correction. *Neurobiology of Disease* **62**, 381-386, doi:10.1016/j.nbd.2013.10.013 (2014).
25 Cooper, O. *et al.* Pharmacological rescue of mitochondrial deficits in ipsc-derived neural cells from patients with familial parkinson's disease. *Sci Transl Med* **4**, 141ra190, doi:10.1126/scitranslmed.3003985 (2012).
26 Fujimori, K. *et al.* Modeling sporadic als in ipsc-derived motor neurons identifies a potential therapeutic agent. *Nature Medicine* **24**, 1579-1589, doi:10.1038/s41591-018-0140-5 (2018).
27 Kiskinis, E. *et al.* Pathways disrupted in human als motor neurons identified through genetic correction of mutant sod1. *Cell Stem Cell* **14**, 781-795, doi:10.1016/j.stem.2014.03.004 (2014).
28 An, Mahru C. *et al.* Genetic correction of huntington's disease phenotypes in induced pluripotent stem cells. *Cell Stem Cell* **11**, 253-263, doi:10.1016/j.stem.2012.04.026 (2012).
29 Developmental alterations in huntington's disease neural cells and pharmacological rescue in cells and mice. *Nature Neuroscience* **20**, 648-660, doi:10.1038/nn.4532 (2017).
30 Guo, X. *et al.* Vcp recruitment to mitochondria causes mitophagy impairment and neurodegeneration in models of huntington's disease. *Nature Communications* **7**, doi:10.1038/ncomms12646 (2016).

31 Shaltouki, A. *et al.* Mitochondrial alterations by parkin in dopaminergic neurons using park2 patient-specific and park2 knockout isogenic ipsc lines. *Stem Cell Reports* **4**, 847-859, doi:10.1016/j.stemcr.2015.02.019 (2015).

32 Readhead, B. *et al.* Expression-based drug screening of neural progenitor cells from individuals with schizophrenia. *Nature Communications* **9**, doi:10.1038/s41467-018-06515-4 (2018).

33 Lorenz, C. *et al.* Human ipsc-derived neural progenitors are an effective drug discovery model for neurological mtdna disorders. *Cell Stem Cell* **20**, 659-674.e659, doi:10.1016/j.stem.2016.12.013 (2017).

34 Vierbuchen, T. *et al.* Direct conversion of fibroblasts to functional neurons by defined factors. *Nature* **463**, 1035-1041, doi:10.1038/nature08797 (2010).

35 Mertens, J., Reid, D., Lau, S., Kim, Y. & Gage, F. H. Aging in a dish: Ipsc-derived and directly induced neurons for studying brain aging and age-related neurodegenerative diseases. *Annual Review of Genetics* **52**, 271-293, doi:10.1146/annurev-genet-120417-031534 (2018).

36 Mertens, J. *et al.* Directly reprogrammed human neurons retain aging-associated transcriptomic signatures and reveal age-related nucleocytoplasmic defects. *Cell Stem Cell* **17**, 705-718, doi:10.1016/j.stem.2015.09.001 (2015).

37 Victor, M. B. *et al.* Striatal neurons directly converted from huntington's disease patient fibroblasts recapitulate age-associated disease phenotypes. *Nature Neuroscience* **21**, 341-352, doi:10.1038/s41593-018-0075-7 (2018).

38 Prigione, A., Fauler, B., Lurz, R., Lehrach, H. & Adjaye, J. The senescence-related mitochondrial/oxidative stress pathway is repressed in human induced pluripotent stem cells. *Stem Cells* **28**, 721-733, doi:10.1002/stem.404 (2010).

39 Kim, M. W. *et al.* Suppression of adiponectin receptor 1 promotes memory dysfunction and alzheimer's disease-like pathologies. *Sci. Rep.* **7**, doi:10.1038/s41598-017-12632-9 (2017).

40 Thier, M. *et al.* Direct conversion of fibroblasts into stably expandable neural stem cells. *Cell Stem Cell* **10**, 473-479, doi:10.1016/j.stem.2012.03.003 (2012).

41 Lancaster, M. A. *et al.* Cerebral organoids model human brain development and microcephaly. *Nature* **501**, 373-379, doi:10.1038/nature12517 (2013).

42 Kelava, I. & Lancaster, Madeline A. Stem cell models of human brain development. *Cell Stem Cell* **18**, 736-748, doi:10.1016/j.stem.2016.05.022 (2016).

43 Ormel, P. R. *et al.* Microglia innately develop within cerebral organoids. *Nature Communications* **9**, doi:10.1038/s41467-018-06684-2 (2018).

44 Velasco, S. *et al.* Individual brain organoids reproducibly form cell diversity of the human cerebral cortex. *Nature* **570**, 523-527, doi:10.1038/s41586-019-1289-x (2019).

45 Bhaduri, A. *et al.* Cell stress in cortical organoids impairs molecular subtype specification. *Nature* **578**, 142-148, doi:10.1038/s41586-020-1962-0 (2020).

46 Amin, N. D. & Paşca, S. P. Building models of brain disorders with three-dimensional organoids. *Neuron* **100**, 389-405, doi:10.1016/j.neuron.2018.10.007 (2018).

47 Choi, S. H. *et al.* A three-dimensional human neural cell culture model of alzheimer's disease. *Nature* **515**, 274-278, doi:10.1038/nature13800 (2014).

48 Gonzalez, C. *et al.* Modeling amyloid beta and tau pathology in human cerebral organoids. *Molecular Psychiatry* **23**, 2363-2374, doi:10.1038/s41380-018-0229-8 (2018).

49 Park, J. *et al.* A 3d human triculture system modeling neurodegeneration and neuroinflammation in alzheimer's disease. *Nature Neuro.* **21**, 941-951, doi:10.1038/s41593-018-0175-4 (2018).

50 Monzel, A. S. *et al.* Derivation of human midbrain-specific organoids from neuroepithelial stem cells. *Stem Cell Reports* **8**, 1144-1154, doi:10.1016/j.stemcr.2017.03.010 (2017).

Supplementary Box 2 | Microvascular changes disrupting neurovascular coupling and brain energy supply in neurodegenerative disorders of ageing

Microvascular degeneration causing progressive deterioration and leakage of the blood brain barrier is implicated in the 30% decline in pericyte number seen with age[1]. This process is exacerbated in AD, with widespread microvascular changes compromising brain structure, perfusion and function, and interfering with both pericyte and astrocyte control of cerebral vessels[1-3]. Microvascular changes in aging and AD disrupt brain glucose supply and metabolism without affecting brain oxygen metabolism, so the normally tight metabolic and neurovascular coupling is impaired[4-7]. Accordingly, deteriorating microvascular structure and blunted hemodynamic responsiveness decrease vascular delivery of fuel to the brain. However, neurovascular uncoupling may itself reflect abnormalities in synaptic function, not least the vasculature is under the control of various modes of neurotransmission. Hence, the cause and effect (perhaps circular) relationship between microvascular and neuronal changes is debated with respect to the pathogenesis of AD - and other NDAs[2,6,8]. Interestingly, microvascular changes affecting the blood-brain barrier, brain perfusion and function are more apparent in the substantia nigra and striatum in PD than in AD, and these changes are linked to a marked interference with nigrostriatal dopaminergic transmission[2]. Leakage of the blood brain barrier is linked to neuroinflammation, including neuronal network dysfunction and enhanced cognitive impairment, caused by T cell infiltration and/or viral infections outside the brain[9-11]. Given the importance of microvascular dysfunction in vascular dementia, it is important to clarify the extent to which disruption of the cerebral microvasculature and subsequent interference with neuronal energy supply contributes to the pathophysiology and progression of AD, PD and other NDAs.

References

1 Cheng, J. *et al.* Targeting pericytes for therapeutic approaches to neurological disorders. *Acta Neuropathologica* **136**, 507-523, doi:10.1007/s00401-018-1893-0 (2018).

2 Sweeney, M. D. *et al.* Vascular dysfunction-the disregarded partner of alzheimer's disease. *Alzheimers Dement* **15**, 158-167, doi:10.1016/j.jalz.2018.07.222 (2019).

3 Kimbrough, I. F., Robel, S., Roberson, E. D. & Sontheimer, H. Vascular amyloidosis impairs the gliovascular unit in a mouse model of alzheimer's disease. *Brain* **138**, 3716-3733, doi:10.1093/brain/awv327 (2015).

4 Lying-Tunell, U., Lindblad, B. S., Malmlund, H. O. & Persson, B. Cerebral blood flow and metabolic rate of oxygen, glucose, lactate, pyruvate, ketone bodies and amino acids. *Acta Neurologica Scandinavica* **62**, 265-275 (1980).

5 Ogawa, M., Fukuyama, H., Ouchi, Y., Yamauchi, H. & Kimura, J. Altered energy metabolism in alzheimer's disease. *Journal of the Neurological Sciences* **139**, 78-82, doi:10.1016/0022-510x(96)00033-0 (1996).

6 Lecrux, C., Bourourou, M. & Hamel, E. How reliable is cerebral blood flow to map changes in neuronal activity? *Autonomic Neuroscience* **217**, 71-79, doi:10.1016/j.autneu.2019.01.005 (2019).

7 Daulatzai, M. A. Cerebral hypoperfusion and glucose hypometabolism: Key pathophysiological modulators promote neurodegeneration, cognitive impairment, and alzheimer's disease. *Journal of Neuroscience Research* **95**, 943-972, doi:10.1002/jnr.23777 (2016).

8 de la Torre, J. C. Treating cognitive impairment with transcranial low level laser therapy. *Journal of Photochemistry and Photobiology B: Biology* **168**, 149-155, doi:10.1016/j.jphotobiol.2017.02.008 (2017).

9 Ransohoff, R. M. How neuroinflammation contributes to neurodegeneration. *Science* **353**, 777-783, doi:10.1126/science.aag2590 (2016).

10 Ta, T.-T. *et al.* Priming of microglia with ifn-γ slows neuronal gamma oscillations in situ. *Proceedings of the National Academy of Sciences* **116**, 4637-4642, doi:10.1073/pnas.1813562116 (2019).

11 Togo, T. *et al.* Occurrence of T cells in the brain of alzheimer's disease and other neurological diseases. *J Neuroimmunol* **124**, 83-92, doi:10.1016/s0165-5728(01)00496-9 (2002).

Supplementary Box 3 | Bioenergetics and therapeutics of ageing-related diseases of the retina: the eye as a window to the brain in neurodegenerative disorders of aging

The retina - evolutionarily and embryonically speaking an outpost of the brain - has even higher energy needs (per gram of tissue) than the brain itself, with some 10-fold greater energy consumption than the neocortex in humans[1]. The retina generates ATP principally from glucose, with an additional role for lactate and fatty acids[1-3]. Energy consumption is strikingly high in GLUT3-bearing, opsin-equipped, self-renewing, light-sensitive photoreceptors, where aerobic glycolysis is prominent which helps reduce the risk of oxidative stress. Energy requirements are also high in GLUT1-expressing retinal pigment epithelial cells that form the blood-retina barrier and promote transfer of glucose to photoreceptors. Retinal diseases, including age-related macular degeneration due to progressive loss of pigmented cells, diabetic retinopathy and glaucoma, are all strongly linked to a disruption of energy (glucose and lipid) metabolism, compromised mitochondrial ATP generation, and oxidative stress, as well as infiltration by inflammatory cells competing for glucose[4-6]. Preventing and treating the "retinal bioenergetics crisis" is attracting increasing interest to counter age-related disorders of vision, with potential approaches running from small molecules, to energy substitution to exposure to infra-red light[3,6-8] Furthermore, several "retina-specific" mechanisms to conserve energy during ageing may also be present in the brain and would therefore be therapeutic targets in NDAs[2,5,9]. Finally, as a window on the brain, the eye is attracting attention in NDA, especially AD, because many ocular manifestations - like the accumulation of neurotoxic proteins - parallel those seen centrally, and can be monitored by a broad array of techniques potentially modifiable by novel therapeutics[10-12].

References

1 Country, M. W. Retinal metabolism: A comparative look at energetics in the retina. *Brain Research* **1672**, 50-57, doi:10.1016/j.brainres.2017.07.025 (2017).

2 Léveillard, T. & Sahel, J.-A. Metabolic and redox signaling in the retina. *Cellular and Molecular Life Sciences* **74**, 3649-3665, doi:10.1007/s00018-016-2318-7 (2016).

3 Vohra, R. *et al.* Lactate-mediated protection of retinal ganglion cells. *Journal of Molecular Biology* **431**, 1878-1888, doi:10.1016/j.jmb.2019.03.005 (2019).

4 Joyal, J.-S. *et al.* Retinal lipid and glucose metabolism dictates angiogenesis through the lipid sensor ffar1. *Nature Medicine* **22**, 439-445, doi:10.1038/nm.4059 (2016).

5 Murphy, M. P. & Hartley, R. C. Mitochondria as a therapeutic target for common pathologies. *Nature Reviews Drug Discovery* **17**, 865-886, doi:10.1038/nrd.2018.174 (2018).

6 Léveillard, T., Philp, N. & Sennlaub, F. Is retinal metabolic dysfunction at the center of the pathogenesis of age-related macular degeneration? *International Journal of Molecular Sciences* **20**, 762, doi:10.3390/ijms20030762 (2019).

7 Maloney, D. M., Chadderton, N., Palfi, A., Millington-Ward, S. & Farrar, G. J. in *Retinal Degenerative Diseases* 275-279 (Springer International Publishing, 2019).

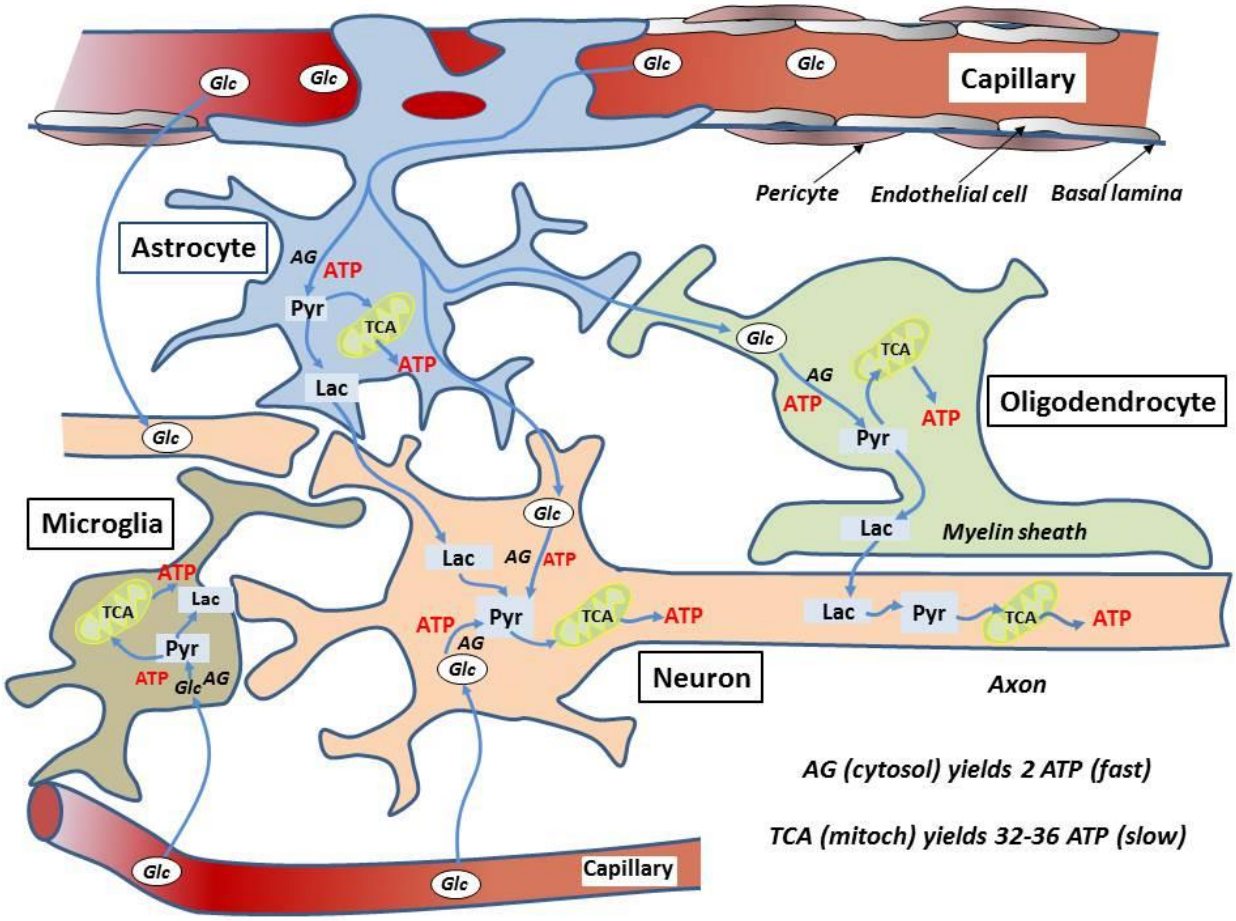
8 Sivapathasuntharam, C., Sivaprasad, S., Hogg, C. & Jeffery, G. Improving mitochondrial function significantly reduces the rate of age related photoreceptor loss. *Experimental Eye Research* **185**, 107691, doi:10.1016/j.exer.2019.107691 (2019).

9 Ferrington, D. A. *et al.* Altered bioenergetics and enhanced resistance to oxidative stress in human retinal pigment epithelial cells from donors with age-related macular degeneration. *Redox Biology* **13**, 255-265, doi:10.1016/j.redox.2017.05.015 (2017).

10 Koronyo, Y. *et al.* Retinal amyloid pathology and proof-of-concept imaging trial in alzheimer's disease. *JCI Insight* **2**, doi:10.1172/jci.insight.93621 (2017).

11 Lim, M. A. *et al.* Genetically altering organismal metabolism by leptin-deficiency benefits a mouse model of amyotrophic lateral sclerosis. *Human Molecular Genetics* **23**, 4995-5008, doi:10.1093/hmg/ddu214 (2014).

12 Chiquita, S. *et al.* The retina as a window or mirror of the brain changes detected in alzheimer's disease: Critical aspects to unravel. *Molecular Neurobiology* **56**, 5416-5435, doi:10.1007/s12035-018-1461-6 (2019).



Supplementary Figure 1 | Schematic depiction of energy supply and interrelationship between neurons and other cell types making up the neurovascular unit. Distribution of glucose (Glc) to and between various cell types following its capture from brain capillaries. Glucose reaches neurons and oligodendrocytes *via* astrocytes which possess end-feet attached to the capillary walls: it may also enter all cells types by free diffusion through the extracellular space. Astrocytes also provide energy to neurons and oligodendrocytes as lactate (Lac) which is generated from glucose via aerobic glycolysis (AG). Oligodendrocytes themselves deliver lactate to axons. The outer wall of brain capillaries is partially covered by contractile pericytes which control capillary diameter. Endothelial cells line the lumen. For details of glucose handling and ATP generation by individual components of this neurovascular unit, see Figure 1 of the main paper.