BJP British Journal of Pharmacology

DOI:10.1111/bph.12531
www.brjpharmacol.org

Themed Issue: Mitochondrial Pharmacology: Energy, Injury & Beyond

REVIEW

Changes in mitochondrial function are pivotal in neurodegenerative and psychiatric disorders: How important is BDNF?

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Keywords
mitochondria; BDNF; calcium; glucocorticoids; neurogenesis; plasticity; neurodegenerative diseases; psychiatric disorders

Received
2 August 2013
Revised
8 November 2013
Accepted
11 November 2013

The brain is at the very limit of its energy supply and has evolved specific means of adapting function to energy supply, of which mitochondria form a crucial link. Neurotrophic and inflammatory processes may not only have opposite effects on neuroplasticity, but also involve opposite effects on mitochondrial oxidative phosphorylation and glycolytic processes, respectively, modulated by stress and glucocorticoids, which also have marked effects on mood. Neurodegenerative processes show marked disorders in oxidative metabolism in key brain areas, sometimes decades before symptoms appear (Parkinson's and Alzheimer's diseases). We argue that brain-derived neurotrophic factor couples activity to changes in respiratory efficiency and these effects may be opposed by inflammatory cytokines, a key factor in neurodegenerative processes.

LINKED ARTICLES
This article is part of a themed issue on Mitochondrial Pharmacology: Energy, Injury & Beyond. To view the other articles in this issue visit http://dx.doi.org/10.1111/bph.2014.171.issue-8

Abbreviations
CORT, corticosterone; CUMS, chronic unpredictable mild stress; ETC, electron transport chain; GRs, glucocorticoid receptors; IMM, mitochondrial inner membrane; IMS, intermembrane space; IMS, mitochondrial inner membrane space; MRs, mineralocorticoid receptors; mtPTP, mitochondrial permeability transition pore; NT, neurotrophins; OMM, outer membrane mitochondrial

Mitochondria

The brain is at the absolute limit of its energy supply

The human brain receives ~15% of cardiac output at rest and has only a few minutes autonomy. Table 1 shows some of the strategies used to optimize oxygen use. In the heart, McCormack and Denton (1990) showed that calcium coupled cardiac work to metabolism by activating the three rate-limiting Krebs cycle enzymes: pyruvate, NAD^+-isocitrate and 2-oxoglutarate dehydrogenases. Energy production is therefore tightly coupled to work requirements, without depleting ATP. This also occurs in the brain, but here the main use-dependent neurotrophin, brain-derived neurotrophic factor (BDNF), also has a role in changing mitochondrial efficiency, but these effects may be countered by inflammatory cytokines.

Mitochondrial electron transfer chain

Brain mitochondria are essential for neurotransmission, short- and long-term neuronal plasticity, cellular resilience to stress and behavioural adaptation (Mattson *et al.*, 2008). Dysfunction in these metabolic processes contributes to a wide variety of diseases, including psychiatric disorders (Table 1; Quiroz *et al.*, 2008; Cheng *et al.*, 2010a). The electron transport chain (ETC) produces energy and is organized in five protein complexes located in the mitochondrial inner membrane (IMM). Three of these complexes (I, II and III) pump protons (H^+) across the inner membrane, establishing the electrochemical gradient, which is then used by complex V

Table 1

Strategies to optimize oxygen use

(A) The brain is at the absolute limit of its energy supply
- Maximum firing rate may be 100–300 Hz (mean 4 Hz)
- Breakdown of 40 $\mu mol \cdot g^{-1} \cdot min^{-1}$ ATP, of which 75% is used for signalling (action potential firing, related ion channel flux and transmitter recycling) and 10% for maintaining the membrane potential of neurons (3% glia)

(B) Strategies used by the brain to run at maximal efficiency
- 30% of neurons may fire at 1 Hz, but only 5% at 100 Hz, with redistribution of firing rates
- Differentiation of the roles of AMPA receptors (fast transmission, low affinity) and NMDA receptors (slow transmission, high affinity, coincidence detection)
- Both GABA and glutamate are also fuels for Krebs cycle
- Glucocorticoids fulfil a role as stress hormones but also change metabolism
- However, blood flow only increases ~50% in response to increased demand limiting oxygen delivery
- Activity-dependent neurotrophins (BDNF) may couple respiratory efficiency to demand (see text)

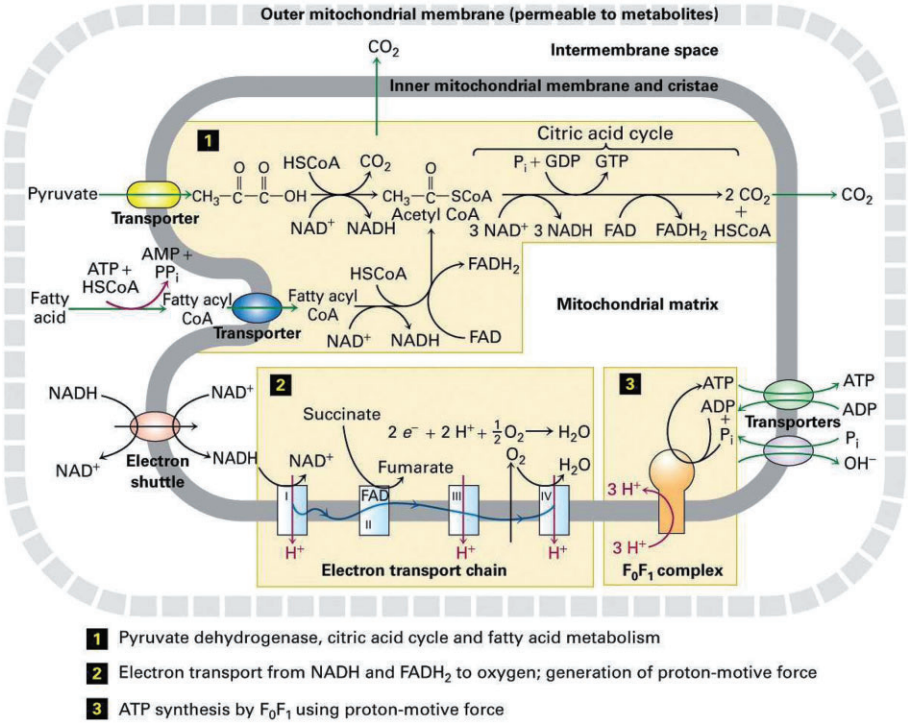

Figure 1

Mitochondrial ATP synthesis via the electron transport chain (Alberts *et al.*, 2002).

(ATP synthase) to produce ATP. The overall process involves the transport of electrons from reduced nucleotides (NADH + H^+ and $FADH_2$) to molecular oxygen, which is converted into H_2O_2 (Figure 1; Alberts *et al.*, 2002). In relation to the respiratory chain, complex I (NADH + H^+ dehydrogenase/ubiquinone or coenzyme Q_{10}) plays a major role in the control of ATP synthesis; deficiencies in this mitochondrial complex have been associated with disease states such as neuromuscular neuropathies and Leber's hereditary optic neuropathy (Ben-Shachar and Karry, 2008). The ETC is also of major importance in terms of maintaining membrane potential ($\Delta\psi_m$; Fox *et al.*, 1993), controlling intracellular Ca^{2+} homeostasis (Baydoun *et al.*, 1988; 1990), initiation of apoptosis and the regulation of the production of reactive oxygen species (ROS; Wallace *et al.*, 1995), including superoxide (O_2^{-}), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\bullet}$) and singlet oxygen ($O^{\bullet}$); once again, changes in one or more of these mitochondrial parameters/functions have been implicated in the onset of various diseases, including neurodegenerative (Table 2; Manji *et al.*, 2012).

Mitochondrial DNA

The unique property of mitochondria is the possession of their DNA (mtDNA), which is maternally inherited, and

Table 2
Mitochondrial-related diseases

Inherited diseases	Acquired diseases	Neurodegenerative diseases
Kearns–Sayre syndrome	Diabetes	Alzheimer's disease
Leber's hereditary optic neuropathy	Cancer	Parkinson's disease
Mitochondrial encephalomyopathy, lactic acidosis and stroke-like syndrome	Hepatitis C virus-associated hepatocarcinogenesis	Bipolar disorder
Myclonic epilepsy and ragged-red fibres	Non-alcoholic steatohepatitis	Schizophrenia
Leigh syndrome sub-acute sclerosing encephalopathy	Sarcopenia	Ageing and senescence
Neuropathy, ataxia, retinitis pigmentosa and ptosis	Exercise intolerance	Huntington's disease
	Chronic fatigue syndrome	Amylotrophic lateral sclerosis
Myoneurogenic gastrointestinal encephalopathy (Cohen and Gold, 2001)	(Pieczenik and Neustadt, 2007)	(Cassarino and Bennett, 1999; Pieczenik and Neustadt, 2007; Manji *et al.*, 2012)

therefore, they have the power to mutate and pass on that change. They have the ability to signal a change in their functional state to the nucleus through a system known as retrograde signalling and cause adjustments in the cell so as to accommodate the change (Butow and Avadhani, 2004; Pieczenik and Neustadt, 2007). In contrast to nuclear DNA, mtDNA is compact, lacks introns, contains greater than 90% sequence-encoding genes and is lacking in repairing mechanisms and histones. The latter suggests that mtDNA is likely to be more susceptible or sensitive to damage, including mutations of nuclear material especially in relation to oxidative changes, ROS and products of lipid peroxidation. Essential mitochondrial functions including oxidative phosphorylation, Ca^{2+} buffering and signalling, and apoptosis will also be influenced by mutations to mtDNA, resulting in the onset of diseases including those associated with the CNS. In relation to the above mitochondrial functions and related essential intracellular processes, it is now clear that organelle dysfunction is linked to a wide range of human disease conditions (Wallace, 2005).

In general terms, diseases associated with organelle dysfunction relate, firstly, to classic mitochondrial disorders resulting from mutations of nuclear genes that directly affect mitochondrial gene expression or ATP production via oxidative phosphorylation or mtDNA [i.e. rearrangement mutations – inherited (primarily insertions) or spontaneous (primary deletions); polypeptide gene missense mutations; and protein synthesis (rRNA and tRNA) gene mutations; Holt *et al.*, 1988] and, secondly, to other diseases caused by mitochondrial dysfunction resulting from nuclear gene mutations that cause disruption of non-respiratory function. The latter can be related to neurodegenerative diseases caused by nuclear gene mutations that regulate organelle morphology and dynamics plus subcellular distribution of mitochondrial subunits associated with the key processes of organelle fission and fusion. This type of regulation involving mtDNA and the above processes is likely to have major effects on the physiological function of neurons and, hence, have a major role in the onset and development of diseases of the CNS, such as Parkinson's disease (PD) and Alzheimer's disease (AD; Bingwei, 2009).

Mitochondrial biogenesis

In relation to the above, it is essential that mtDNA replication and processes of mitochondrial fission/fusion are coordinated; this is achieved with the aid of the transcriptional co-activator PGC1α (PPARγ co-activator 1α), a key regulator of mitochondrial biogenesis. Its role is to interact and co-activate numerous nuclear transcription factors, including Nrf1 (nuclear respiratory factor 1). Nrf1 can activate the expression of mitochondrial target genes, including the mitochondrial transcriptional factor A (TFAM), a factor critical for the initiation of mtDNA transcription and replication. Nrf1 also regulates the transcription of nuclear genes encoding respiratory complex subunits and other mitochondrial proteins. PGC1α is expressed in high levels in mitochondrial-rich cells with high energy demands such as neurons (Andersson and Scarpulla, 2001) and is implicated in the dynamic process of neuroplasticity associated with newly generated neurons in the embryonic and early post-natal brain period (Cowell *et al.*, 2007). A number of signalling molecules, including NO, oestrogen and growth factors [BDNF and EGF and basic fibroblast growth factor (FGFs)], are now known to regulate neural plasticity and mitochondrial biogenesis (Barsoum *et al.*, 2006; Gutsaeva *et al.*, 2008; Hebert *et al.*, 2009; Renton *et al.*, 2010), and hence have the ability to influence processes associated with neurogenesis and related disease states.

Mitochondrial fission, fusion and dynamics

The section on mitochondrial biogenesis indicates a clear relationship between mtDNA and the processes of fission and fusion, while also indicating an important link between neurogenesis, disease onset and the influence of molecules such as growth factors. In axons and dendrites, the functional properties of mitochondria are known to differ due to their modulation by fission, fusion and movement (Mattson *et al.*, 2008). The dynamic nature of mitochondria in relation to their movement, fusion and fission appears to be essential for successful cell division and correct distribution of mitochondria to daughter cells and for the transport of the organelle to the potential sites of action. The dynamics of mitochondria

are mediated by three GTPases known as mitofusins (Mfn1/2), optic atrophy 1 (OPA1) and dynamin-related protein 1 (Drp1). These GTPases are therefore responsible for the processes associated with mitochondrial fusion/fission. The travelling or movement of mitochondria along the cytoskeletal tracks is mediated by kinesin and dynein motors and by the action of the adaptor protein a Milton and the atypical GTPase Micro. The successful interrelationship between these two pathways, which are Ca^{2+} sensitive, ensures that the balance between fusion and fission, which governs the shape, number, distribution and function of mitochondria, is successfully achieved (Liu and Hajnoczky, 2009; MacAskill and Kittler, 2010).

Intact mitochondrial membrane structures are also essential for successful fusion/fission, with the Mfns being an integral component of the outer membrane mitochondrial (OMM) proteins that mediate fusion, together with OPA1, which is relocated in the mitochondrial inner membrane space (IMS) and interacts with the IMM, promoting fusion and cristae remodelling. For successful fusion, a proton gradient is required, hence damaged or metabolically compromised mitochondria are unable to fuse. Drp1 is required for successful mitochondrial fission; this protein eventually reaches the organelle via several post-translational modifications involving phosphorylation and sumoylation. Ca^{2+} plays a key role in controlling Drp1-dependent fission, a complex process that involves calcineurin (a Ca^{2+}- and calmodulin-dependent serine/threonine protein phosphatase that participates in a number of cellular processes and Ca^{2+}-dependent signal transduction pathways; Rusnak and Mertz, 2000) and CaM-kinase 1α (a Ca^{2+}/calmodulin-dependent kinase responsible for phosphorylation of Drp1). Resting levels of Ca^{2+} therefore enhance fission, while high levels of the cation promote fragmentation, confirming a link between motility and fusion/fission. In contrast, Mfns appear not to be linked to Ca^{2+} regulation (Han *et al.*, 2008; Cali *et al.*, 2012b). Studies linking Ca^{2+} homeostasis and changes in fission/fusion resulting in mitochondrial dysfunction provide the potential for the initiation of processes such as apoptosis and the onset of disease states and ageing (Jendrach *et al.*, 2005).

Mitochondrial Ca^{2+} handling

Study after study, including those relating to fission/fusion, confirms Ca^{2+} to be the principal second messenger that contributes to the regulation of both neurotransmission and short- and long-term neuronal plasticity in the brain, with mitochondria and related ATP/ADP ratios playing a major role in the control of Ca^{2+} homeostasis (Gleichmann and Mattson, 2011). The electrochemical gradient produced by the ETC (negative $\Delta\psi_m$) also helps to sustain Ca^{2+} transfer into the mitochondrial matrix, which occurs via a downhill gradient through a low-affinity mitochondrial Ca^{2+} uniport (MCU; low Ca^{2+} affinity and operates at micromolar cytosolic levels) and the leucine-zipper EF-hand-containing transmembrane protein 1 (LETM1). MUC is regulated by mitochondrial Ca^{2+}-uptake 1 (MICU1; a Ca^{2+} sensor that regulates the Ca^{2+}-influx capacity of MUC). In contrast, LETM1 is a high-affinity mitochondrial Ca^{2+}/H^+ exchanger that imports Ca^{2+} at cytosolic concentrations > nanomolar. Ca^{2+} efflux occurs through a Na^+/Ca^{2+} exchanger, molecularly identified as $Na^+/K^+/Ca^{2+}$-exchange protein 6 (NKCX6) and via the H^+/Ca^{2+} exchanger (Palty *et al.*, 2010; Perocchi *et al.*, 2010; Baughman *et al.*, 2011; De Stefani *et al.*, 2011). NKCX6 activity is negatively regulated by stomatin-like protein 2, which is located in the IMM. At high matrix Ca^{2+} levels, the mitochondrial permeability transition pore (mtPTP), a protein complex, opens. Cyclophilin D (CYPD) desensitizes the mtPTP to Ca^{2+} and therefore facilitates mtPTP opening (Patergnani *et al.*, 2011). The MCU is therefore sensitive to microdomains of high concentrations of Ca^{2+}, resulting from the opening of Ca^{2+} channels associated with plasma [voltage-operated channel (VOC)] and/or the endoplasmic reticulum (ER) membranes. The integral OMM protein Mfn2 has been shown to enhance ER-mitochondrial tethering and hence could influence ER-mitochondrial Ca^{2+} transfer through this physical coupling while also being implicated in a relationship with mitochondrial fusion (De Brito and Scorrano, 2008). The concept of tethering between mitochondria and ER has now been extended to include the plasma membrane and the Golgi compartment (De Brito and Scorrano, 2008; Cai *et al.*, 2011; Pizzo *et al.*, 2011). Increases in organelle tethering may therefore have important consequences in relation to overall mitochondrial function and the initiation of processes associated with the development of disease states.

Biochemically, mitochondrial Ca^{2+} handling is a complex and balanced process involving essential components and regulators associated with both the OMM and IMM, which include voltage-dependent anion channel (VDAC; OMM), adenine nucleotide transporter (IMM) and CYPD (Ricchelli *et al.*, 2011). In relation to tethering, VDACs tend to gather at the ER/mitochondrial contact sites and therefore play a major role in the rapid transfer of the high Ca^{2+} microdomain from the surface of mitochondria to the intermembrane space (IMS) to which the MCU is exposed (Szabadkai *et al.*, 2006). The mitochondrial uniporter and antiporters therefore play a significant role in the regulation of intracellular Ca^{2+}, redox signalling and ATP levels (Baydoun *et al.*, 1988; 1990; Mammucari *et al.*, 2011; Cali *et al.*, 2012a). Mitochondrial Ca^{2+} overload can result in excitotoxicity, leading to production of ROS, organelle damage, activation of the mtPTP and the release of pro-apoptotic proteins (e.g. Bax, Bak, Bad; Starkov *et al.*, 2004; Giacomello *et al.*, 2007; Nicholls, 2009). These proteins are associated with a complex network of biochemical pathways and physiological processes leading to apoptosis (Young *et al.*, 2010). Apoptosis can be initiated by Ca^{2+} overload, oxidative stress, overactivation of glutamate receptors, DNA damage and mitochondrial dysfunction (Hroudova and Fisar, 2011).

The role of mitochondria in apoptosis

Mitochondria are significant organelles in terms of apoptosis and are known to contain their own collection of pro- [DIABLO: direct IAP-binding protein with low PI and also known as SMAC: second mitochondria-derived activator of caspases, Omi/HtrA2, apoptosis-inducing factor (AIF) and endonuclease G (EndoG)] and anti- (XIAP, cIAP-1 and cIAP-2) apoptotic proteins, which are in equilibrium, regulating cell death and life of the cell (Pinton and Rizzuto, 2006). The links between the benefits of mitochondrial efficient energy supply

with the ability of mitochondria to kill cells via apoptosis go back to the origins of life (Spedding *et al.*, 1999). The biochemical activation of apoptosis by the intrinsic pathway involves mitochondria and results from high levels of Ca^{2+} and ROS, which are known examples of stimuli that can cause leakage of cytochrome c, AIF, DIABLO/SMAC and EndoG (Shoshan-Barmatz and Ben-Hall, 2012) from mitochondrial MIS into the cytoplasm, resulting in activation of the cascade of cysteine-protease enzymes (caspases) and the onset of apoptosis (Youle and Strasser, 2008).

The extrinsic pathway involves the activation of death receptors (e.g. TNF-α receptor 1) located on the cell surface, which, in turn, triggers caspase-8 activation through protein–protein interactions. Activation of either pathway results in the following reactions: cleavage of BH3-interacting domain death agonist (BID) to truncated BID (tBID), translation of tBID to mitochondria, a combined action of tBID and Bcl-2 family proteins Bax (intrinsic) and Bcl-2 antagonist/killer (Bak; extrinsic) resulting in changes in membrane permeability, leakage of apoptogenic factors and apoptosis. The overall mitochondrial process associated with apoptosis is controlled by the balance between the pro-apoptotic Bax, Bak (i.e. promote OMM permeabilization) and Bcl-X_S and the anti-apoptotic Bcl-2, Bcl-X_L Mcl-1 and Bcl-W (Brunelle and Letai, 2009). There is a third group acting as sentinels for cell death signals: Bim, Bid, Bad, Puma, Noxa, Hrk/DP5, Bik and Bmf (McKernan *et al.*, 2009; Vogel *et al.*, 2009).

Anti-apoptotic proteins including Bcl-2 also have the ability to lower ER Ca^{2+} levels, which, in turn, will influence mitochondrial Ca^{2+} handling. The finding that anti-apoptotic Bcl-2 protein lowers the Ca^{2+} ER content and that Ca^{2+} can sensitize cells to apoptotic challenges, acting on mitochondria, indicates a critical role for Ca^{2+} in apoptosis. Bcl-2 is now known to be located in the cytoplasm, at the nuclear envelope and ER and mitochondrial membranes, a fact that further supports the link between Ca^{2+} homeostasis and anti-apoptotic proteins and mitochondrial function. Mitochondrial responses to pathophysiological events are related to the amount of Ca^{2+} released from the ER, which is critical to the transduction of the signal in mitochondria and the modulation of the IP_3R opening by pro- or anti-apoptotic proteins (Cali *et al.*, 2012b).

In addition to the Ca^{2+} uniporter and antiporters associated with the IMM and OMM, the mtPTP is believed to be significantly involved in the pathophysiological aspects associated with mitochondrial dysfunction following Ca^{2+}-induced swelling and fragmentation, resulting in decreased levels of ATP; this releases essential nucleotides, cytochrome c and caspase co-factors, resulting in the potential for the initiation of synaptic apoptosis (Kroemer and Reed, 2000; Pacher and Hajnoczky, 2001; Cuimsee and Mattson, 2005; Pinton *et al.*, 2008; Ricchelli *et al.*, 2011). During the development of the nervous system many newly generated neurons and adult brains during neurogenesis undergo apoptosis, and pathological conditions associated with neurodegenerative diseases also show evidence of this process (Bredesen *et al.*, 2006; Deng *et al.*, 2010), while up-regulation of the protective Bcl-2 family may aid in the neuroprotective mechanisms especially those associated with mitochondria (Hunsberger *et al.*, 2009).

Neurogenesis, neuroprotection, neurotrophic factors and mitochondrial energetics

The previous sections have attempted to identify the significance of mitochondrial function and related dynamics with respect to maintaining intracellular and cellular integrity especially in relation to structure, location, efficient bioenergetics and cation homeostasis. These sections have also indicated key roles for mitochondria in terms of pathophysiological or biochemical changes that could lead to the onset and development of disease states, including those associated with the CNS. This section therefore takes the significance of mitochondria a step further by linking changes in function to factors such as BDNF.

Brain-derived neurotrophic factor

Discovered in the 1950s, neurotrophins are target-derived factors that support the survival and growth of sensory and motor neurons (Cohen *et al.*, 1954). The prototype for which is the nerve growth factor (NGF), also the first to be discovered (Levi-Montalcini and Hamburger, 1953). Others include BDNF, neurotrophins (NT)-3, 4/5 and 6, insulin-like growth factors, FGFs and VEGF, etc., but the best characterized remains the neurotrophin family comprising NGF, BDNF, NT-3 and NT-4 (Castren *et al.*, 2007). For the purposes of this review, we will focus on BDNF (a basic dimeric polypeptide approximately 13 kDa in size).

Neurotrophins mediate their effects through two kinds of receptors: high-affinity tyrosine kinase (trk) and low-affinity pan-neurotrophin receptor (p75). The trk receptors are neurotrophin specific, but p75 receptors are not, and upon activation, the p75 receptors bind to trk receptors to form a complex and modulate signal transduction (Poo, 2001). Activation of trk receptors results in the activation of signalling cascades such as PLC, PIK3 and RAS-MAPK, which are involved in neurite growth, maintenance and differentiation. In contrast, activation of the p75 receptors can have both pro- and anti-neurotrophic effects (Murray and Holmes, 2011).

BDNF is secreted as its glycosylated precursor, which is 24–30 kDa in size, the pro-domain from which it is proteolytically cleaved to yield its mature 13 kDa form (Matsumoto *et al.*, 2008). Until very recently, mature neurotrophins were considered to be the only functionally active type, but recent evidence has shown pro-neurotrophins to have high affinity for p75 receptors (Hempstead *et al.*, 2001). Upon binding with p75, the proBDNF:p75 complex binds with another structurally unrelated receptor, sortilin, to form a co-receptor complex that induces pro-apoptotic signalling pathways, possibly through the activation of the JNK-BAX signalling cascade (Hempstead *et al.*, 2001; Teng *et al.*, 2005; 2010). There is some evidence to suggest that in the absence of trk receptors, mature BDNF will bind to the p75 receptor and elicit opposing effects to those elicited through trk binding and encourage cell death pathways (Woo *et al.*, 2005).

It is now well established that neurotrophic factors such as NGF, NT-3, NT-4/5 and BDNF promote the growth, differentiation and survival of nerve cells and plasticity of adult neurons. Alterations in the activity of these key

neurotrophins can therefore produce detrimental changes to cortical function and synaptic transmission in the developing and ageing brain, resulting in neuronal dysfunction and the onset of psychiatric and other disorders (e.g. schizophrenia; Favalli *et al.*, 2012). Some of the sections above have already indicated roles for BDNF. BDNF is the main activity-dependent neurotrophin in the CNS, which couples neuronal activity to neurotrophic effects, balanced between both excitatory glutamatergic and inhibitory GABAergic systems via its tyrosine kinase receptor (trkB) (Schinder and Poo, 2000; Kalb, 2005). The effects of BDNF on synaptic transmission vary in terms of whether the exposure is acute or chronic. The former produces increases in presynaptic release of excitatory neurotransmitters (i.e. glutamatergic) and the mean amplitude of evoked EPSCs, causing a decrease in postsynaptic GABA receptors and GABAergic inhibition, while the latter causes an increase in axonal branches and the total length of the axons of GABAergic neurons, increased levels of GAD_{67} mRNA and maturation of GABA neurons (Kohara *et al.*, 2007).

BDNF is also implicated in synaptic plasticity, which is the change in strength in the connectivity between neurons in response to changing environments with the balance between long-term potentiation (LTP, a lasting increase in synaptic strength, following high-frequency stimulation of afferent fibres; Cooke and Bliss, 2006) and long-term depression (LTD, a reduction in synaptic strength resulting from changes in postsynaptic receptor density; Man *et al.*, 2000). LTP depends on the activation of NMDA-type glutamate receptors, which produce a rapid increase in Ca^{2+} in postsynaptic dendritic spines. Data suggest that changes in the release and/or synthesis of BDNF and its receptors can result in the regulation of synaptic plasticity especially in the hippocampus, with exposure to the neurotrophin resulting in enhanced synaptic efficiency and LTP. These data also indicate a potential role for BDNF in the pathology of diseases, including schizophrenia (Figurov *et al.*, 1996; Minichiello *et al.*, 2002; Favalli *et al.*, 2012).

Mitochondrial energetics and BDNF

Using a novel *in vitro* synaptosome-mitochondrial preparation (astrocyte/nerve ending/mitochondrial unit; Markham *et al.*, 2004), BDNF was shown to increase the respiratory control index (RCI) of rat brain (but not liver or heart) mitochondria, resulting in a 64% increase in the efficiency of respiratory coupling, through an MEK-kinase mechanism via complex 1. This approach was specifically designed to mimic the synaptosomal nerve ending but with the oxygen electrode directly in contact with the mitochondria in order to measure oxygen utilization. Electron microscopy confirmed that the reconstituted sonicated synaptosome/mitochondria mixture looked similar to nerve endings. The observed effects of BDNF on this mixture were found not to be due to changes in proton pumping at complex I, Ca^{2+} cycling or via a direct action on ATPase activity (Markham *et al.*, 2004).

BDNF also has marked neuroprotective effects against excitotoxic lesions induced via AMPA and NMDA excitotoxins. These protective effects are mediated via the trkB-MEK-MAPK cascade that has been extensively studied in a newborn mouse model (Gressens *et al.*, 1997; Husson *et al.*, 2002; Dicou *et al.*, 2003; Plaisant *et al.*, 2003). The above studies indicate a very high parallelism between the observed mitochondrial effects in relation to modified energy metabolism and on neuroprotection with respect to neurotrophin activities. The inflammatory cytokine, IL-1β, was assessed, as this cytokine has been shown to switch astrocytic energy metabolism (Gavillet *et al.*, 2008) and also to exacerbate neuronal damage in the newborn mice, which may be the cause of several types of neurodevelopmental deficits in humans (Plaisant *et al.*, 2003); the effects of IL-1β can be blocked by some antidepressants, while other studies have identified it to be essential for the mediation of anti-neurogenic and anhedonic effects associated with stress (Koo and Duman, 2008). Bcl2 has also been postulated to be implicated in the effects of antidepressants (Perera *et al.*, 2007; Pittenger and Duman, 2008) and Bcl2 homology domain 3 (BH3)-mimetics such as ABT 737, which occupy the hydrophobic pocket coupling Bcl2 to accessory proteins, have been reported (Chauhan *et al.*, 2007; Hickman *et al.*, 2008; Tagscherer *et al.*, 2008).

Using the above rodent model, intracerebral injections of ibotenate to mouse pups resulted in the development of grey matter lesions and white matter cysts (Gressens *et al.*, 1997; Spedding and Gressens, 2008); co-administration of BDNF produced a dose-dependent reduction in these lesions (Figure 2A,B). In contrast, co-administration of glial cell line-derived neurotropic factor (GDNF) had no significant effect. The co-administration of NGF or IL-1β resulted in a dose-dependent and significant exacerbation of mouse brain lesions. The neuroprotective effects seen with BDNF were abolished by co-administration of anti-BDNF antibody or MEK inhibitors, or ABT-737, a BH3 mimetic and Bcl2 antagonist (Hetman *et al.*, 1999; Han and Holtzman, 2000; Hickman *et al.*, 2008; Li *et al.*, 2008).

The actions of BDNF, GDNF and NGF were measured in a parallel *in vitro* study on oxidative metabolism of mouse brain mitochondria. BDNF produced a concentration-dependent increase in the respiratory control index (RCI, a measure of respiratory coupling efficiency, ATP synthesis and organelle integrity) of mouse brain mitochondria when co-incubated with synaptosomes containing signal transduction pathways (Markham *et al.*, 2004); BDNF had no effect on pure mitochondria and enhanced oxidation in the presence of complex I substrate (glutamate plus malate). BDNF-induced positive effects on respiratory efficiency associated with complex I were inhibited by anti-BDNF antibody, MEK inhibitors (PD98059 and U0126) or ABT 737 (BH3 mimetic), and also by IL-1β, indicating that the mitochondrial effects were mediated via the same MEK-Bcl2 pathway associated with neuroprotection (Figure 3A,B). The interplay between BDNF and IL-1β in excitotoxicity and in depression has been reported (Plaisant *et al.*, 2003; Perera *et al.*, 2007; Gavillet *et al.*, 2008), but the direct effects on mitochondrial RCI are major and novel. The interplay reflects a deep physiological role whereby inflammatory cytokines block trophic effects in sickness and perhaps depression (Koo and Duman, 2008; Pittenger and Duman, 2008; Spedding and Gressens, 2008; Markham *et al.*, 2012). The ability of BDNF to modify complex I was observed under acute *in vitro* conditions and hence unlike the effects involving cAMP or any associated mtDNA mediation (Leadsham and Gourley, 2010). This finding, that an anti-inflammatory cytokine can block the

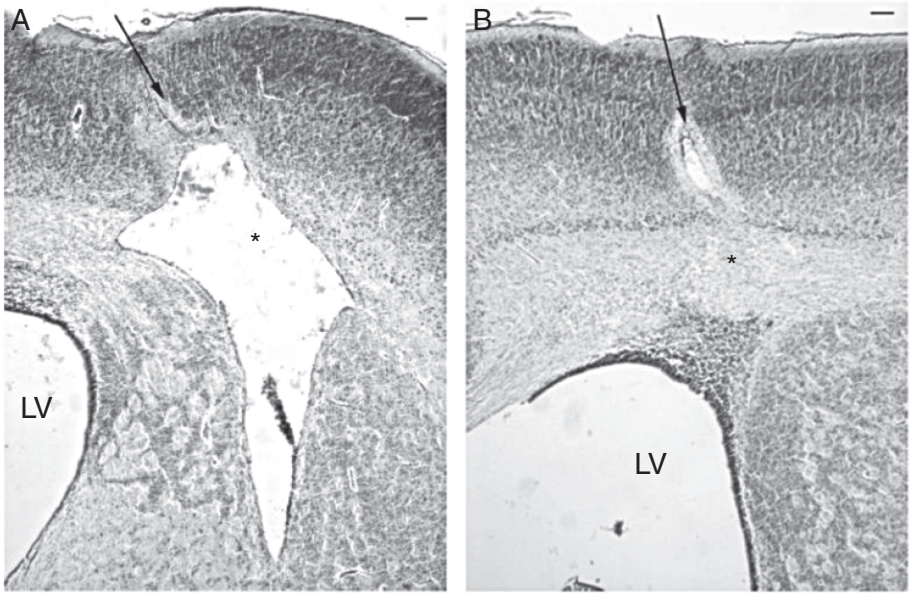

Figure 2

BDNF protects against ibotenate-induced brain lesions. Cresyl violet-stained sections show brain lesions induced by ibotenate injection P5 and studied at P10. (A) Brain from a pup co-treated with intracerebral ibotenate (10 μg) alone, showing the typical neuronal loss in layers II-IV (arrow) and the white matter cystic lesion (*). (B) Brain from pup co-treated with intracerebral ibotenate and BDNF (50 ng). Bar: 40 μm. LV: left ventricle (from Markham *et al.*, 2012).

effects of BDNF on mitochondria, may have profound implications, depending on the pathophysiological conditions (Markham *et al.*, 2012). In contrast, GDNF failed to modify RCI, and NGF had only weak effects on RCI (Markham *et al.*, 2005).

The complex I inhibitor, rotenone, a compound implicated in the aetiology of PD, inhibited both the *in vitro* mitochondrial and the *in vivo* neuroprotective effects of BDNF (Gutman *et al.*, 1970; Sherer *et al.*, 2003). The published data clearly indicate that the neuroprotective effect of BDNF is mediated via the classic trkB-MEK pathway and that Bcl2 is also involved. Evidence confirms that this beneficial effect on mitochondrial function is mediated via the same pathway and was specific to complex I. The experiments involving rotenone, BDNF and ibotenate-induced brain lesions indicate that the mitochondrial effect may be important in the neuroprotective action of the neurotrophin, indicating a key relationship (Shoshan-Barmatz *et al.*, 2008; Spedding and Gressens, 2008; Markham *et al.*, 2012).

Mitochondria, neuroplasticity and neuroprotection

Neuroplasticity. Neuroplasticity describes a range of adaptive changes that occur in the structure and function of cells in the nervous system in response to physiological or pathological events (Cheng *et al.*, 2010b). Sprouting and growth of axons or dendrites, synapse formation and neurogenesis (production of new neurons from stem cells) are all examples of neuroplasticity. The following three classes of intercellular signals are involved in the regulation of the genesis and adaptive plasticity of the nervous system (Loers and Schachner, 2007; Gottmann *et al.*, 2009); neurotransmitters (glutamate; Mattson, 2008), neurotrophic factors (BDNF; Lipsky and Marini, 2007) and cell adhesion molecules (NCAM; Hildebrandt *et al.*, 2007).

In terms of neuroplasticity, mitochondrial distribution and related ATP metabolism plus Ca^{2+} homeostasis are key factors in neuronal morphogenesis synaptogenesis, development and synaptic plasticity, and axogenesis. Mitochondria have been found to be more abundant in regions of growing axons, with their movement being anterograde. Evidence confirms that NGF is one of the signals inducing accumulation of mitochondria in the active growing cone, ensuring that ATP requirements are met for successful axogenesis (Mattson and Partin, 1999; Chada and Hollenberck, 2004). The number of mitochondria per cell increases during neuronal differentiation; however, the velocity which individual mitochondria move decreases as neurite outgrowth slows and synaptogenesis occurs (Chang and Reynolds, 2006). The dynamic movement and location of mitochondrial organelles are essential features of neuronal homeostasis-associated intracellular signalling pathways, with organelle dysfunction and defective trafficking being implicated in diseases of the CNS including the pathogenesis of axonal degeneration (Cai and Sheng, 2009).

It is generally agreed that the event that leads to induction of LTP is the influx of Ca^{2+} into the postsynaptic spine. In most areas of the brain where LTP is manifested, the influx of Ca^{2+} is mediated by the activation of the NMDA receptor (Lynch, 2004), linked to the opening of the mtPTP; this allows the influx of Ca^{2+} across the IMM, which is otherwise impermeable to Ca^{2+} (Miller, 1998; Duchen, 1999). The ability of mitochondria to sequester this influx of Ca^{2+} is a key to

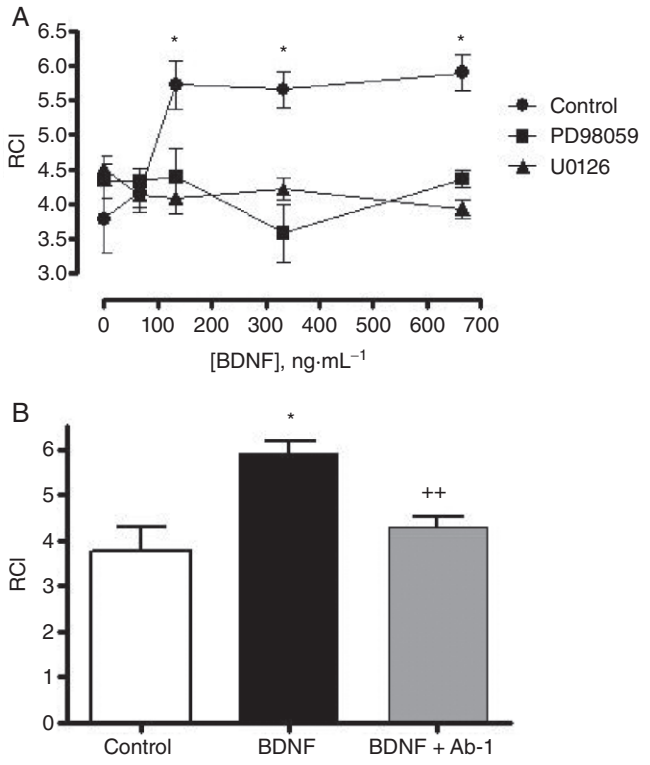

Figure 3

The effect of BDNF (66.6–666 ng·mL^{-1}) on mouse brain mitochondrial RCI with 5 mM glutamate plus 5 mM malate as substrate. (A) Effect of kinase inhibitors. Each point represents mean ± SEM (n = 6). Control, 10 μL of synaptosomes plus BDNF, PD98059 and U0126 were used at 10 μM and 1 μM respectively. *P < 0.01 as compared with the corresponding control. (B) Effect of BDNF-neutralizing antibody (Ab-1). Bars represent mean ± SEM (n = 6). *P < 0.05 as compared with control (10 μL of synaptosomes, which are required for the effects of BDNF); ++P < 0.01 as compared with BDNF alone (from Markham *et al.*, 2012).

maintaining and modulating the tone of synaptic plasticity (Einat *et al.*, 2005). NMDA receptor-induced Ca^{2+} influx is almost exclusively cleared by the mitochondria (Wang and Thayer, 2002).

Also implicated in LTP is the neurotrophin BDNF; this neurotrophin is known to interact closely with the NMDA receptors (Suen *et al.*, 1997). NMDA receptor-induced Ca^{2+} influx activates the CAMKII, which, in turn, activates the MAPK cascade that ultimately results in the cAMP response element-binding protein (CREB)-mediated transcription of BDNF (Platenik *et al.*, 2000; Vaynman *et al.*, 2003). Thus, mitochondrial regulation of Ca^{2+} clearance may be the point of convergence between early stage LTP, resulting from the activation of NMDA receptors and late-stage LTP, resulting from an increase in BDNF that encourages new synapse formation (Figure 4).

Mitochondrial-regulated caspase activation is also involved in the modulation of synaptic plasticity (Figure 4; Manoli *et al.*, 2007). Hippocampal studies confirmed that stimulation of NMDA receptors caused the release of mitochondrial cytochrome c followed by activation of cytosolic caspases 3 and 9. Inhibition of caspases and overexpression of anti-apoptotic protein X-linked inhibitor of apoptosis protein (XLAP) or Bcl-xl blocked the removal of AMPA receptors. This block on the removal of AMPA receptors resulted in a block on NDMA receptor-dependent LTD (Li *et al.*, 2010). Further studies confirmed that caspase-3 activation mediated by the Bcl-2 antagonist of cell death (BAD)-Bax cascade is specifically involved in NMDA receptor-dependent LTD, but not metabotropic glutamate (mGlu) receptor-mediated LTD (Jiao and Li, 2011). The significance of mitochondria in synaptic plasticity is also supported by the findings that both Bcl-2 and Bcl-xl are involved in the facilitation of neurite outgrowth, axonal regeneration and neurogenesis (Jonas, 2006; Creson *et al.*, 2009). A more recent study indicates a role for mitochondria oxidative phosphorylation in the promotion of neuroplasticity in effects mediated by BDNF. BDNF has been shown to enhance mitochondrial ATP production via an increase in respiratory coupling and therefore aid the neuroprotective mechanisms associated with neuroplasticity (Markham *et al.*, 2012).

Neuroprotection. In addition to neuroplasticity, various studies also clearly indicate BDNF to have a major role in neuroprotection in relation to damage resulting from oxidative, metabolic and excitotoxic stress, which can lead to the onset of various diseases [e.g. Huntington's disease (HD)] and ageing (Marini *et al.*, 2007; Jiang *et al.*, 2011). The exposure of hippocampal or cortical neurons to 1–100 ng·mL^{-1} BDNF resulted in protection from the following potential causes of acute and/or chronic neurodegenerative diseases; amyloid-β peptide (Counts and Mufson, 2010), oxidative stressors (e.g. Fe^{2+} and H_2O_2; Harper *et al.*, 2009), glucose and oxygen deprivation (Cheng and Mattson, 1994), glutamate and excitotoxins (Wu *et al.*, 2004a,b), and mitochondria toxins (Markham *et al.*, 2012). Animals exposed to a diet rich in antioxidants showed increased levels of BDNF mRNA and a positive correlated improvement in cognitive performance and reversal of neuronal atrophy (Nagahara *et al.*, 2009; Fahnestock *et al.*, 2012). The invasive procedure of infusing BDNF into the brain of hypoxic mice resulted in the restoration of memory via an action on LTP (an electrophysiological effect essential for long-term memory) of synaptic transmission at the key hippocampal CA1 synapses (Xie *et al.*, 2010). BDNF is able to induce the transformation of early phase to late-phase LTP, while LTP itself is mediated via AMPA and NMDA receptors, which, in turn, can also be controlled by the neurotrophin (Lu *et al.*, 2008; Diogenes *et al.*, 2011).

In addition to the up-regulation of the AMPA receptor subunits GluA1, GluA2 and GluA3 associated with cultured hippocampal neurons, BDNF can also alter the frequency of AMPA receptor-mediated miniature EPSCs (Caldeira *et al.*, 2007a,b). A recent study involving hippocampal slices from Tau transgenic mice confirmed that NMDA receptor dysfunction contributed to impaired BDNF-induced facilitation of hippocampal synaptic transmission, which is likely to be significant in the occurrence of cognitive deficits in patients with Alzheimer's disease (Burnouf *et al.*, 2013). A reduction in BDNF levels or trkB-mediated BDNF signalling has also been shown to reduce neuronal protection and increase amyloidogenic APP activity. Brain damage following transient global ischaemia was also increased when BDNF

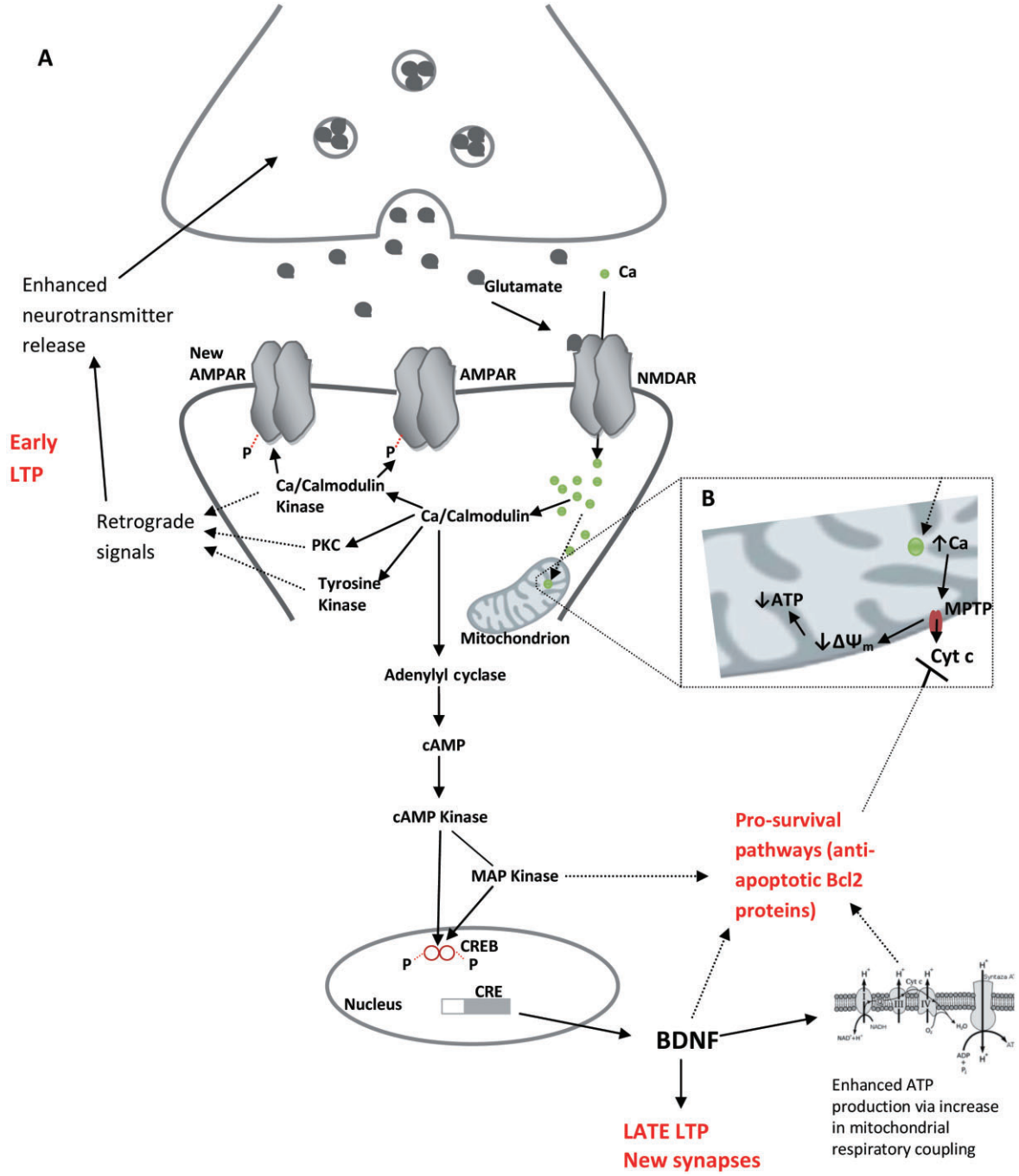

Figure 4

Mitochondrial regulation of calcium clearance: a point of convergence for retrograde and anterograde signalling. (A) The release of glutamate from the presynaptic vesicles opens postsynaptic NMDA receptors (NMDAR) to allow the influx of calcium (Ca) into the postsynaptic spine. This event leads to the induction of LTP. Ca will activate Ca/calmodulin, which, in turn, will activate (1) Ca/calmodulin kinase, which phosphorylates the AMPA receptors; (2) PKC; (3) tyrosine kinase; and (4) AC. The first three are involved in early stage LTP that is maintained by enhanced neurotransmitter release from the presynaptic spine via retrograde signalling. AC activates cAMP, which, in turn, activates cAMPK. cAMPK can either directly activate cAMP response element-binding protein (CREB) for the transcription of BDNF, which is involved in late phase LTP through the formation of new synapses, or it can activate CREB via the MAPK pathway. MAPK and BDNF can activate the transcription of pro-survival pathways. (B) The opening of NMDA receptors allow the influx of Ca into the cell, which is mopped up by mitochondria. As the concentration of Ca increases within the mitochondria, it triggers the opening of mitochondrial permeability transition pore (MPTP). This serves a dual purpose: (1) reducing the mitochondrial membrane potential, which, in turn, reduces ATP production, thus highlighting the areas that need the allocation of glucose for maintenance of LTP, and (2) releasing cytochorome c (Cyt c) and starting the apoptotic cascade. The release of Cyt c can be prevented by the transcription and release of pro-survival proteins like Bcl2; this process, in turn, relies on the concentration of intracellular calcium. Hence, inextricably linking the process of synaptic plasticity to mitochondrial energy production and intracellular calcium movements.

activity was blocked by trkB-Fc fusion protein (Matrone *et al.*, 2008).

Exercise, diet, cognitive challenges, BDNF and mitochondrial function

Exercise and cognitive challenges

Physical exercise or cognitive stimulation causes the up-regulation of neurotrophic factors (BDNF), enhanced synaptic plasticity and stimulation of neurogenesis resulting in the protection of neurons against age-related dysfunction and disease (Spedding and Spedding, 2008; Barrientos *et al.*, 2011; Marlatt *et al.*, 2012; Noakes and Spedding, 2012). Vigorous intermittent exercise, energy restriction and cognitive challenges activate excitatory neuronal circuits that use glutamate in their synapses. Activation of glutamate receptors results in Ca^{2+} influx and Ca^{2+}/calmodulin (CaM)-dependent kinases. The CaM kinases stimulate the local translation of BDNF mRNA in dendrites and activation of the transcription factor for CREB, which induces the expression of the *Bdnf* gene (Lazarov *et al.*, 2010). At the site of production and adjacent neurons, BDNF activates the high-affinity receptors trkB; these activated receptors are able to engage the PI3K-Akt kinase pathway, which, in turn, up-regulates the production of key proteins involved in the processes of synaptic plasticity and neurogenesis (neuroplasticity) resulting in neuroprotection. In the hippocampus, expression of exercise-induced BDNF requires the locus coeruleus projection. Exercise-related increased levels in BDNF in the hippocampus result in the activation of the ERK pathway, which converges on the transcription factor for CREB, which is indicated in enhanced learning and memory (Stranahan and Mattson, 2012).

In addition to the above route of neuroprotection, there are other adaptive stress response signalling pathways that involve neuroprotective proteins, trophic factors, protein chaperones (essential for protein folding and ensure proteostasis; Morimoto, 2008; Hartl *et al.*, 2011), anti-apoptotic proteins, antioxidant enzymes, PGC-1, uncoupling proteins (mitochondrial transporter protein: UCP2, 3 and 4; Manzanero *et al.*, 2011) and DNA repair enzymes (aputinic-apyrimidinic endonuclease 1; APE1). The hippocampus has a high expression of UCP2 (Richard *et al.*, 2001), which is subject to regulation by neuronal and hormonal input, for the coordination of homeostasis (Diano *et al.*, 2003). Exercise increases UCP2 levels in the hippocampus and lowers cellular oxidative stress (Vaynman *et al.*, 2006). Cells that have higher levels of UCP2 have lower ATP production per mitochondrion but a higher ATP production per cell (Harper *et al.*, 2002; Horvath *et al.*, 2003). Through this mechanism, mitochondria are thought to protect themselves from oxidative stress under conditions of high energy demand. UCP2 can also regulate mitochondrial proliferation (Andrews *et al.*, 2005); it is likely that exercise increases the efficiency of mitochondrial energy production by limiting the oxidative stress, and this supports the process of synaptic plasticity mediated by BDNF (Vaynman *et al.*, 2006).

The health of the brain is therefore aided by life-long challenges such as exercise, cognitive stimulation and dietary energy restriction, which results in neurons being exposed to metabolic stress. It has been argued that BDNF is a crucial factor bridging mitochondrial metabolism, and in biochemical terms, this, in turn, results in the production of proteins specifically involved in neurogenesis, neuronal survival, learning and memory, control of oxidative metabolic and proteotoxic stress, and regulation of mitochondrial biogenesis. BDNF signalling mediates the up-regulation of a number of proteins, including antioxidant enzymes, the cell survival protein Bcl-2, DNA repair enzyme APE1 and the protein chaperone GRP-78. Impairment of BDNF production and/or impairment of its related signalling may aid the onset of neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases (Du *et al.*, 2009; Rothman and Mattson, 2013). The above findings clearly indicate the involvement of mitochondria and confirm that BDNF signalling mediates the beneficial effects of exercise and dietary restrictions.

Dietary intake and cognitive changes

Studies on dietary restrictions outlined in the previous section appear to have the ability to influence the rate of onset of cognitive-related diseases. The brain has a very low capacity to store energy; therefore, it is imperative that it controls its energy supply. This is achieved by maintaining the balance between ATP and ADP within a narrow concentration range, known as the set point. The set point is maintained through a special set of ATP-sensitive potassium channels (K_{ATP} channels) that couple energy metabolism to $\Delta\psi$ (Peters *et al.*, 2004).

When an excitatory stimulus is provided to the cell, if the ATP to ADP ratio is high, the K_{ATP} channels remain closed and the cellular membrane will depolarize and allow an influx of Ca^{2+} and propagation of the stimulus through the release of glutamate or BDNF will ensue; however, if the ATP to ADP ratio is low, these channels will open and will not allow the depolarization of the neural membrane, and the stimulus will not be propagated (Peters *et al.*, 2004). This serves a dual purpose; firstly, this is a cytoprotective effect because it conserves the energy within the neuron for structurally important functions (Garcia *et al.*, 1999). Secondly, it highlights the areas of low energy and facilitates the 'allocation' of glucose to these areas through a feedback loop (Fehm *et al.*, 2006). Thus, any displacement in this set point can result in disease states.

Additional studies indicate a bidirectional relationship between energy intake and brain function with excessive intake impairing function with dietary restrictions causing enhancement. These changes in brain function are now thought to involve the relationship between synaptic plasticity and neurogenesis. Diseases such as diabetes and obesity, which are associated with excessive dietary intake, are linked to brain ageing resulting from changes in hippocampal neurogenesis, LTP and hormone levels (Stranahan and Mattson, 2008). Energy restrictions have been shown to improve memory and LTP in mice coupled to enhanced neurogenesis via a BDNF-dependent mechanism (Lee *et al.*, 2002).

Energy restrictions have also been shown to help deficits in learning and memory (mice model for AD), protect dopaminergic neurons and improve motor function (mouse and

monkey models for PD), and protect striatal and cortical neurons (mouse model for HD). Restrictive dietary protection of neurons against ageing and disease is thought to involve pathways that respond to cellular stress and the resultant production of cytoprotective proteins such as protein chaperones, DNA repair enzymes, mitochondrial proteins and neurotrophic factors (Yang *et al.*, 2010). Evidence indicates that restrictions in dietary intake result in the activation of genes encoding for proteins required for cell survival, synaptic plasticity and intracellular energy metabolism. It has also been shown that the evolutionary vitagenes control the hermetic responses of cells to stress via the encoding of proteins essential for the control of cellular redox activities, ion homeostasis, protein metabolism, membrane viability and energy metabolism (Xu *et al.*, 2007; Calabrese *et al.*, 2010).

A dietary intake rich in phytochemicals such as sulforaphane (high levels in broccoli) and flavonoids (high levels in grapes and blueberries) appears to have the ability to influence pathways in neurons involved in the cellular stress response, especially in relation to the up-regulation of the expression of neurotrophic factors, antioxidant enzymes and proteins associated with intracellular energy metabolism, thus providing an additional mechanism of neuroprotection (Son *et al.*, 2008). Sulforaphane causes the activation of nuclear regulatory factor 2 antioxidant response element pathway, resulting in the expression of the antioxidant enzymes haeme oxygenase 1 and NAD(P)H + H^+-quinone oxidoreductase 1 or NAD(P)H + H^+ dehydrogenase [quinone] 1 (Kraft *et al.*, 2004). The effects of flavonoids in relation to enhanced learning and memory is likely to involve sirtuins (a family of NAD^+-dependent protein deacetylases) and CREB (Spencer, 2010). Once again, key individual or interrelated roles are implicated for BDNF and mitochondrial function and the resultant cognitive changes; however, it should be stated that the overall mechanisms involved are also likely to be influenced by the presence of glucocorticoids (Du *et al.*, 2009).

Mitochondrial and BDNF responses to glucocorticoids

Relationship between glucocorticoids and BDNF

In addition to the above challenges, BDNF signalling is also known to be negatively regulated by glucocorticoids, resulting in cognitive impairment, neuronal cell damage, dendritic atrophy, reduced hippocampal neurogenesis, changes in LTP and impairment of synaptic plasticity (Suri and Vaidya, 2013). Chronic stress induces activation of the hypothalamic–pituitary–adrenal axis, which results in the release of the glucocorticoid cortisol in humans and corticosterone in rodents. In the hippocampus, high levels of glucocorticoids can result in a reduction in BDNF protein and its mRNA by a mechanism that is not totally understood but is believed to involve transcriptional control. This direct method of control could involve glucocorticoid response elements that are present in the promoter region of exon IV of the *BDNF* gene, while CREB is implicated in a possible indirect method of BDNF regulation (Alboni *et al.*, 2011; Chen *et al.*, 2012). The gene *mkp-1* is involved in the expression of MAP-1, a phosphatase involved in the feedback control of MAPK duration, which is co-responsive to BDNF and dexamethasone. MAPK activity is central to the control of cytoskeleton dynamics due to its ability to phosphorylate microtubule- and actin-associated proteins. Excess activity of MAP-1 results in destabilization of microtubule filaments, while decreased levels reduce BDNF and neuronal activity associated with the production of new axon branches (Jeanneteau and Chao, 2012).

The ability of the synthetic glucocorticoid dexamethasone to decrease BDNF-induced increases in levels of synaptic proteins via a reduction in the activation of the MAPK/ERK pathway implies that this signalling pathway is important in the control of glucocorticoid-induced reductions in BDNF levels/activity (Kumamaru *et al.*, 2008). A more recent study confirmed the ability of dexamethasone to alter interactions between Src homology-2 domain-containing phosphatase2 (Shp2) and the trkB receptor, which binds BDNF in cortical neurons, suggesting that control of neurotrophin function by glucocorticoids is via Shp2 (Kumamaru *et al.*, 2011). The ability of RU486, an antagonist of glucocorticoid receptors (GRs), to abolish the dexamethasone inhibition of BDNF-induced alterations in synaptic proteins and neuronal function indicates that glucocorticoids mediate BDNF via GRs and not by mineralocorticoid receptors (MRs; Kumamaru *et al.*, 2008). However, a previous study by Hansson *et al.* (2000) found that in adrenalectomized mice, hippocampal BDNF levels were negatively regulated by both GR and MR signalling. The biphasic properties of glucocorticoids are therefore clearly implicated in neural plasticity and spatial memory involving signalling pathways and BDNF.

Relationship between stress, glucocorticoids and mitochondrial function

Du *et al.* (2009) reported the ability of glucocorticoids to regulate mitochondrial function including mitochondrial oxidation, $\Delta\psi_m$ and Ca^{2+} handling. Long-term exposure to corticosterone (CORT) produced an inverted 'U'-shaped effect, with low levels (100 nM) being neuroprotective, while high levels (1 μM) enhanced kainic acid (KA)-induced toxicity/apoptosis of cortical neurons (KA is known to produce apoptosis in a number of neuronal tissues; Lee *et al.*, 2010). Du *et al.* (2009) confirmed the ability of GRs to form a complex with the anti-apoptotic protein Bcl-2 in primary cortical neurons following acute exposure to CORT and translated with Bcl-2 into mitochondria. Prolonged exposure to CORT resulted in decreased GR and Bcl-2 levels in mitochondria. GRs have a lower affinity for endogenous glucocorticoids and are, therefore, thought to be more significant than MRs in terms of the response to, and regulation of, stress when endogenous levels of glucocorticoids are high. A study involving rat C6 glioma cell mitochondria confirmed the ability of GRs to translocate to the organelle (Koufali *et al.*, 2003). All three mitochondrial functions of oxidation, membrane $\Delta\psi_m$ and Ca^{2+} movements exhibited the biphasic effects associated with exposure to CORT. Low levels of CORT resulted in significant increases in mitochondrial oxidation, $\Delta\psi_m$ and Ca^{2+} holding, while higher levels caused reductions in all three parameters after 3 days of exposure to the glucocorticoid. These findings, in conjunction with others, suggest

a number of key interrelationships between glucocorticoids, BDNF, apoptosis proteins and mitochondrial function in relation to neurodegeneration and disease onset.

Using two rat models, one involving chronic unpredictable mild stress (CUMS; Kompagne *et al.*, 2008) and CORT treatment, Liu and Zhou (2012) carried out a simultaneous set of experiments designed to study the effects of exercise preconditioning on behavioural, electrophysiological, biochemical and mitochondrial function in the same animal. CUMS is a 40-day variate-stressor paradigm, with animals being subjected to a variety of mild stressors (e.g. cage tilting for 24 h, swimming in cold in 5°C cold water for 5 min, swimming in 45°C hot water, fasting for 48 h and water deprivation for 24 h; Rezin *et al.*, 2008). The overall findings confirmed that both CUMS and CORT impaired mitochondrial function and increased oxidative stress in the brain of a depressed rat model by altering the intracellular redox state associated with several redox pairs including NAD^+/NADH + H^+, $NADP^+$/NADP + H^+ and GSH/GSSH. These redox pairs are essential in maintaining brain energy supply and function (Wilhelm and Hirrlinger, 2011), with an essential relationship between nucleotide oxidation/reduction, mitochondrial dysfunction and neuronal activation (Galeffi *et al.*, 2011). Increased levels of brain reduced GSH were found to provide neuroprotection against oxidative stress and mitochondrial dysfunction. CORT and CUMS also caused increases in the production of ROS while decreasing membrane potential in isolated mitochondria.

The results from the above study also showed a reduction in enzyme activities associated with complex 1 (NADH + H^+ dehydrogenase), IV (cytochrome oxidase) and citrate synthase in isolated brain mitochondria while also confirming that manganese-dependent SOD (Mn-SOD) activity was reduced by CORT, but not by CUMS. Chronic mild stress produces oxidants and an imbalance between SOD and catalase activities, which combine to aid the development of stress-related depression. In animals exposed to CORT, Mn-SOD activity was altered, GSH/GSSH ratio was reduced and the expressions of SOD1 and SOD2 were down-regulated (Lucca *et al.*, 2009). Manganese superoxide dismutase (Mn-SOD, SOD2) is a key antioxidant enzyme found in the mitochondrial matrix that scavenges ROS (Holley *et al.*, 2010). SOD1 and calcineurin (Rusnak and Mertz, 2000) are co-localized in the cytoplasm and membranes of neurons; the latter is stabilized by Cu–Zn superoxide dismutase (SOD1) and provides protection against superoxide ($O_2^{\bullet-}$). CUMS was found to decrease the expression of SOD2, but not SOD1, with no significant effect on Mn-SOD activity. These *in vitro* and *in vivo* studies suggest an association between gene expression of SOD, mitochondrial function and depression.

The CORT model resulted in a reduction in mtDNA with possible implications for mitochondrial biogenesis and a reduction in organelle and related intracellular bioenergetics. The detrimental changes in mitochondrial function following exposure to the CUMS paradigm appear to be connected to the inhibition of mitochondrial respiration and dissipation of mitochondrial membrane potential in hippocampus, cortex and hypothalamus. The CUMS paradigm was found to damage the ultra-structure of the brain mitochondria, while mitochondrial respiratory complexes I, III and IV associated with cerebral cortex and cerebellum were also inhibited, indicating that oxidative-induced mitochondrial dysfunction is important in the onset of stress and related disorders, with evidence pointing towards the theory that CORT and CUMS may share a similar pathophysiology as depression (Rezin *et al.*, 2009; Gong *et al.*, 2011), involving reduced expression of oxidant enzymes and mitochondrial dysfunction.

The studies involving pre-adaptation to exercise in relation to the following two groups exercise × CUMS and exercise × CORT confirmed a difference in relation to the effects on complex activity, SOD2 expression, mitofusion expression, BDNF and mitochondrial function. The overall findings of the above studies involving both exercise groups indicated that CORT's ability to impair mitochondrial function and to reduce expression of mitofusin, SOD2 and BDNF mRNA was independent of exercise, suggesting that unlike CUMS, CORT-induced depression cannot be prevented by exercise and, therefore, indicates different molecular mechanisms underlying the pathophysiology of depression and responses to exercise. Studies involving the CORT and CUMS groups were able to show that CORT reduced the brain mRNA of Mfn1 and Mfn2, reducing the potential for normal fusion to take place, and in agreement with previous studies, this effect was independent of exercise (Del *et al.*, 2008; Liu and Zhou, 2012). These findings indicate different mechanistic responses to exercise involving complex interrelationships between stress, glucocorticoids, BDNF and mitochondria, which, in turn, may influence the development of neurodegenerative diseases.

Mitochondria and therapeutic conditions associated with the CNS

Depression

Neurotrophin hypothesis. It has been clearly demonstrated that BDNF, the small dimeric neuroprotective protein, is critical for the development as well as maintenance of both peripheral and CNS. In addition, it promotes neuronal survival and proliferation (Yulug *et al.*, 2009). Since it performs functions that are critical to the survival of neurons, its deficiency or loss has profound consequences. The absence of neurotrophins triggers the intrinsic death programme (ontogenetic) in neurons, and this forms the basis for the neurotrophic hypothesis of depression (Yu *et al.*, 2008). According to this hypothesis, a deficiency in the neurotrophic support during the development of depression may contribute to the pathology in the hippocampus and its reversal through antidepressant treatment may help to alleviate depressive symptoms (Nestler *et al.*, 2002; Castren *et al.*, 2007).

There is now considerable evidence suggesting that the neurotrophin that is most likely to be involved in this is BDNF, as it is the most prevalent neurotrophin in the brain (Smith *et al.*, 1995), with both acute and chronic stress producing decreased levels of BDNF in the dentate gyrus and the pyramidal cell layer of the hippocampus in various animal models followed by increased levels after chronic antidepressant treatment (Smith *et al.*, 1995; Yulug *et al.*, 2009). The infralimbic prefrontal cortex of rats is equivalent to the area

that is at risk of depression in humans; acute stress, increasing corticosterone, reduced BDNF levels and the neurotrophic cascade eventually lead to a reduction in dendritic arborization in this area (Qi *et al.*, 2009). The levels of BDNF in *post-mortem* brains of patients suffering from depression are also reduced, while antidepressant treatment was found to restore these levels to the normal range (Chen *et al.*, 2001; Qi *et al.*, 2009). The serum concentration of BDNF in depressed patients was seen to be normalized after antidepressant treatment (Shimizu *et al.*, 2003).

Understanding the effect that antidepressants have on the BDNF receptor trkB in activating PLCγ signalling (which, in turn, activates CREB, causing transcriptional changes in genes responsible for plasticity-related molecules; Rantamaki *et al.*, 2004), has led to the modified neurotrophic hypothesis, which rather than state the lack of BDNF as the predisposing factor for depression, emphasizes its role as a 'tool' in the activity-dependent modification of neuronal networks, which regulate aspects that influence mood (Nagappan & Lu, 2005; Castren *et al.*, 2007; McKernan *et al.*, 2009). However, stress has different effects on the different brain circuits, with hippocampus to prefrontal cortex showing atrophy and reduced plasticity, whereas the amygdala–frontal cortex circuit, fear and emotion, is reinforced, a core feature of psychiatric disease, dependent on glucocorticoids and BDNF (reviewed by Godsil *et al.*, 2013).

Role of mitochondria in neurotrophin hypothesis. Prolonged stress leads to atrophy and cell loss in the limbic regions of the brain, and the mechanism for this is mediated by mineralocorticoid, glucocorticoid and NMDA receptors (Czeh and Lucassen, 2007; Yulug *et al.*, 2009). The release of cortisol and other excitatory neurotransmitters like glutamate as a result of stress can lead to the activation of cascades downstream from the receptors. Ultimately, the decision as to which cascade to activate, that is, apoptotic or necrotic or both, lies with the mitochondria. The mitochondrial membrane houses a number of important pro- and anti-apoptotic proteins, and it is the delicate, yet critical balance between these proteins that may determine the fate of the hippocampal neurons (McKernan *et al.*, 2009; Yulug *et al.*, 2009).

The proteins that determine the outcome belong to the Bcl-2 family of proteins that can be classified into three groups depending on their activity and structure (i.e. anti- and pro-apoptotic groups and the sentinels for cell death signals group). The third group or sentinels act by binding to the anti-apoptotic Bcl-2 family members, forming heterodimers and activating pro-apoptotic Bax/Bak, resulting in the release of mitochondrial factors that mediate cell death (McKernan *et al.*, 2009; Chipuk *et al.*, 2010).

One of the factors that increases the synthesis of pro-survival Bcl-2 is CREB; the transcriptional regulation of CREB, in turn, relies on the activation of the MAPK/ERK cascade, which is activated through BDNF-stimulated trkB receptors (Yulug *et al.*, 2009). This brings us full circle confirming the significant roles for BDNF and mitochondria in the onset of diseases associated with the CNS.

Neurodegenerative diseases

The three most common neurodegenerative diseases Parkinson's, Huntingdon's and Alzheimer's, all have distinct pathological aetiologies, which have components that are associated with mitochondrial dysfunction. From the current review, it can be seen that mitochondrial dysfunction resulting from loss of ATP production, increased Ca^{2+} uptake, increased ROS production, altered fission, fusion and apoptosis can affect neuronal function in terms of synaptic plasticity, energy metabolism, axonal transport and neurotransmitter release resulting in psychiatric changes and neuronal loss. In addition to the above effects, there is also clear evidence of organelle dysfunction resulting from changes to genetic material, especially genes coding key mitochondrial proteins, which can lead to disease initiation and development (Cali *et al.*, 2012b).

Parkinson's disease

PD is characterized by the progressive degeneration of dopaminergic and noradrenergic neurons that control motor and autonomic nervous function respectively. Studies since the early 1990s have proven that mitochondrial dysfunction is pivotal to the onset and development of the disease due to changes in energy production, selective inhibition of complex I by toxins or inherited mutations of genes encoding for proteins involved in organelle physiology (Schulz and Beal, 1994; Greenamyre *et al.*, 1999; Nuytemans *et al.*, 2010). Mutations in terms of loss of function to the genes *Parkin*, *DJ-1* and *Pink 1* result in alterations to mitochondrial structure via altered fusion, biogenesis via reduced complex I activity and synaptic plasticity via suppressed neurotransmitter release. Leucine-rich repeat kinase 2 is associated with the OMM and can interact with *Parkin* to produce cells that are more vulnerable to mitochondrial dysfunction via a mechanism involving autosomal dominantly inherited mutation (Saha *et al.*, 2009).

It therefore appears that the development of PD is dependent, in a number of ways, on changes of cytosolic Ca^{2+} levels, which, in turn, can initiate mitochondrial dysfunction. The multifunctional protein DJ-1, whose predominant role is as an antioxidant, also plays a major part in controlling basal cytosolic levels of Ca^{2+} and the interrelationship between mitochondrial Ca^{2+} handling and the properties of L-type VOCs of dopaminergic neurons of the substantia nigra. Experiments using knockout models confirmed an essential role for DJ-1 in protecting dopaminergic neurons from Ca^{2+}-induced mitochondrial uncoupling and ROS production, resulting from increased Ca^{2+} entry and resultant oxidative stress during physiological pace-making (Guzman *et al.*, 2010). Studies involving mitochondrial kinase PINK1 have also provided evidence, sometimes of a controversial nature, for a link between Ca^{2+} homeostasis and mitochondrial dysfunction and PD. The loss of $\Delta\psi_m$, increased mitochondrial size with loss of cristae and reduced ATP levels were observed in a study involving the mutant expression; these changes were totally reversed by the presence of the MUC inhibitor, ruthenium red, indicating mitochondrial Ca^{2+} uptake was involved (Marongiu *et al.*, 2009).

Parain *et al.* (1999) showed that the substantia nigra of PD patients expressed lower levels of BDNF. As BDNF is the neurotrophic factor providing trophic support for the dopaminergic neurons of the subtantia nigra (Hyman *et al.*, 1991), this presents a tantalizing possibility that the above-mentioned mutations arise as a result of inadequate trophic support,

which may itself be a result of inadequate anterograde BDNF signalling that translates as postsynaptic changes.

Alzheimer's disease: a metabolic catastrophe?

AD can also be inherited in an autosomal dominant manner resulting from mutations to amyloid precursor protein (APP) or presenilin-1 and -2 genes (*PSEN-1* and *PSEN-2*) causing problems with neurogenesis and synaptic plasticity and the onset of dementia at ~49 years of age. Both sporadic and familial AD are characterized by the presence of extracellular amyloid plaques [i.e. aggregates of amyloid-β (Aβ) peptides derived from the APP following cleavage by the β- and γ-secretase, and intracellular neurofibrillary tangles, formed by hyper-phosphorylated tau protein; LaFerla *et al*., 2007]. Aβ oligomers have been found to induce massive Ca^{2+} transfer between ER and mitochondria, causing organelle Ca^{2+} overload thus providing the conditions suitable for ROS production, opening of the mtPTP and the release of cytochrome c (Ferreiro *et al*., 2008). mtPTP opening is also promoted by the interaction of Aβ with CYPD, causing neuronal injury and a decline in cognitive functions (Du *et al*., 2008). These studies indicate important links between excessive Ca^{2+} levels, organelle tethering/dynamics and mitochondrial dysfunction and AD.

Indeed, the decline in oxidative metabolism as assessed by the uptake of [^{18}F]-fludeoxyglucose (FDG) measured by positron-emission tomography (FDG-PET) in key brain areas, such as the precuneus, is the most linear decline of any parameter in AD, and there are >170 studies listed in clintrial.gov on FDG-PET in AD. The availability of large cohorts of patients with familial AD has allowed precise analysis of the long-lived (up to 30 years) biomarker changes prior to dementia. There are early and major changes in oxidative metabolism (Figure 5; Bateman *et al*., 2012). Dragicevic *et al*. (2010) have shown that mitochondrial amyloid-β levels are associated with the extent of mitochondrial dysfunction in different brain regions and the degree of cognitive impairment in 12-month-old AβPPsw and AβPP + PS1 mouse models of AD, with hippocampal and cortical neurons being most affected. Wang *et al*., (2009a,b) showed an impaired balance of mitochondrial fission and fusion in AD.

Trushina *et al*. (2012) identified early mitochondrial dysfunction and the resulting metabolic signature, first, in three commonly used transgenic mouse models of FAD, mice expressing mutant human presenilin 1, PS1(M146L) and the double mutation of human amyloid precursor protein APP(Tg2576) and PS1(M146L). Significant changes in mitochondrial morphology were detected in APP and APP/PS1 mice, and there was a loss of the integrity of synaptic mitochondria and energy production in all three models. They also revealed altered energy metabolism and mitochondrial dysfunction in the brains of FAD mice, dependent on the individual mutations. ADP, the Krebs cycle, energy transfer, carbohydrate, neurotransmitter and amino acid metabolic pathways were perturbed with a particular lesion in sphingolipids and ceramides.

Using brain slices from APP, PS1 and APP/PS1 animals, the decrease was found to be most prominent in the brains of APP and APP/PS1 mice (loss of 50%). The decrease in the oxidative activity of PS1 mice was about 35%. The changes in mitochondrial ultra-structure observed in FAD mice correlate

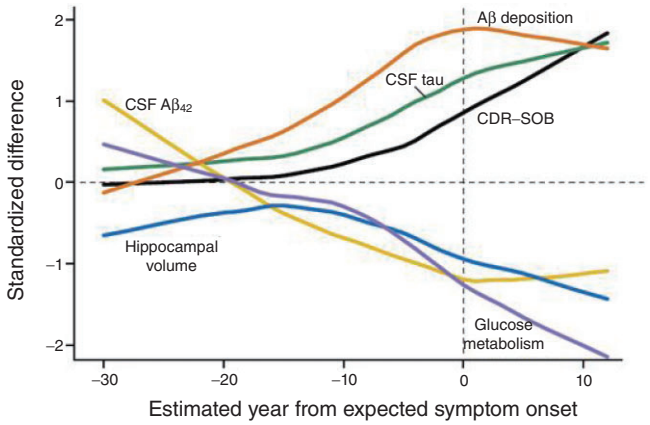

Figure 5

The insidious onset of familial Alzheimer's disease. The normalized differences between mutation carriers and non-carriers are shown with the estimated years from expected symptom onset (~49 years old.) Decreasing Aβ42 levels in the CSF (CSF Aβ42) is concomitant with increasing fibrillar Aβ deposition. Slightly later, the levels of CSF tau increase and hippocampal atrophy (volume) and hypometabolism (glucose metabolism) in the precuneus start to manifest (5–10 years before symptom onset), and cognitive and clinical changes (as measured by the Clinical Dementia Rating–Sum of Boxes [CDR-SOB]) begin. Mild dementia (CDR 1) occurred ~3.3 years before the expected symptom onset. Note that the change in metabolism (arrows) measured by FDG-PET) is the only change that is monotonic over the disease course with >2 standardized differences (from Bateman *et al*., 2012).

with the loss of mitochondrial function, implying major effects on metabolism. APP/PS1 mice display marked gender differences, with female mice having greater metabolic disturbances, similar to those observed in human AD patients. Then, Trushina *et al*. (2013) showed that many of these changes in the CSF and plasma of AD patients were translatable between mice and men.

Laske *et al*. (2006) for the first time presented evidence from human serum and CSF of stage-dependent changes in BDNF levels of AD patients. They showed that in the early stages, an increase in the BDNF levels was observed, probably a compensatory mechanism. As the disease progressed, a decline in the trophic factor levels was observed, which coincided with the severity of the disease.

Chen and Zhong (2013) showed impaired cerebral glucose hypometabolism possibly due to impairments of insulin signalling and altered thiamine metabolism, leading to well-characterized anomalies in the Krebs cycle. Markham *et al*. (2012) showed that BDNF could increase the respiratory efficiency of the brain mitochondria, and inflammatory cytokines blocked this increase – which may account for at least some of the changes in metabolism, as BDNF is reduced and inflammatory cytokines increased at the time of AD 'conversion'. Golenbock's group has shown that Aβ activates the inflammasome, NLRP3, to produce IL-1β (Halle *et al*., 2008) and this effect is a major factor contributing to pathology of APP/PS1 mice (Heneka *et al*., 2013). It could be that as the disease progresses and levels of BDNF decline, the lack of trophic support coupled with increased inflammation con-

tributes to the progression of metabolic failure and neuronal atrophy (Markham *et al.*, 2012). Thus, there are real reasons to think that disrupted brain metabolism is a core feature of AD and therapies should be aimed at it directly.

Huntington's disease

Mitochondrial dysfunction is also implicated in impaired synaptic plasticity, and motor and cognitive deficits associated with HD. It is known that polyglutamine repeat expansions in the huntingtin protein cause the disease and that the mutated form of Huntingtin causes a decrease in cortical BDNF gene transcription (Zuccato *et al.*, 2001). Therefore, mutant huntingtin proteins can aid in the development of neurodegenerative changes in the CNS. An early target for these mutant proteins appears to be mitochondria, causing defective ATP production, Ca^{2+} transport, opening of the mtPTP and trafficking, which, in turn, induces impaired neural plasticity. Huntingtin was also shown to influence intracellular Ca^{2+} signalling via IP_3R activity and expression causing increases in ER Ca^{2+} levels in precursors of Huntingdon's disease neurons, therefore providing an environment to produce an imbalance between ER and mitochondria. In other studies involving mutant huntingtin models, enhanced calcineurin activity and related movement of calcineurin-dependent Drp1 to mitochondria was found to alter the balance between fission and fusion, therefore providing the trigger for Ca^{2+} dysregulation in the death of striatal neurons via increased mitochondrial fragmentation and apoptotic activity (Costa *et al.*, 2010). In a recent study on glutamate toxicity, Suwanjang *et al*. (2013) showed that glucocorticoids such as CORT can protect against Ca^{2+} overload, detrimental Ca^{2+} signalling and cell death by activating the plasmalemmal Ca^{2+} ATPase, which then modulates the delayed Ca^{2+} deregulation. Once again these findings indicate strong interrelationships between Ca^{2+} handling/homeostasis, mitochondrial dysfunction, trophic support and disease states. At the nuclear level, huntingtin was found to impair the transcription of nuclear genome-encoded mitochondrial proteins associated with biogenesis and subcellular trafficking of mitochondria, resulting in organelle dysfunction and disease onset. However, the role of BDNF is less clear and may involve an indirect mechanism (Oliveira, 2010).

Mood disorders

This is a family of diseases that relate to rare aspects of mitochondrial dysfunction. Usually the prime pathological defect is characterized by genetic impairment of one or more of the biochemical aspects of mitochondrial metabolism resulting in psychiatric symptoms such as depression, psychosis, bipolar disorder (BD) and personality change (Kato, 2001; Orth and Schapira, 2001; Niciu *et al.*, 2013).

BD is a complex, highly heritable major mood disorder characterized by episodes of hypomania and depression. Like other major mood disorders and major depressive disorders, initial pathophysiological and psychopharmacological research centred around monoamine (5-HT, noradrenaline and dopamine)- and amino acid (GABA and glutamate)-based neurotransmission. In relation to mitochondrial function and cell survival, more recent studies have shown that the pathophysiological impairments of second messenger/signal transduction cascades affected by BP include increased pro-apoptotic gene expression, decreased anti-apoptotic/antioxidant gene expression, decreased Bcl-2 expression, increased IP3-mediated intracellular Ca^{2+} levels and increased anterior cingulate cortex glutamate. In terms of the second messenger/cascades associated with cAMP/PKA/CREB, these were found to show increases in AC and PK levels/activity and decreased CREBP1 expression, while potential alterations to ERK/MAPK have yet to be determined (Niciu *et al.*, 2013). BD is therefore associated with increased intracellular Ca^{2+}; this could involve its release from the ER and mitochondria, and/or via influx through the stimulation of plasma membrane receptors, decreased expression of anti-apoptotic proteins (Bcl-2), increased expression of pro-apoptotic proteins (Bax-1), decreased expression of CREBP1 and increased IP3-mediated Ca^{2+} release. Therefore, the development of BD is likely in part to be related to eventual mitochondrial dysfunction and associated apoptotic events (Kim *et al.*, 2010). The intracellular events outlined here share a degree of commonality with other neurodegenerative diseases, especially in terms of pivotal roles for Ca^{2+} and mitochondria, and are possibly closely linked to BDNF transcription.

Schizophrenia is a major mental illness and affects 1% of the world's population, manifesting itself in high suicide rates and disruption of social functioning including aggressive behaviour. Studies involving animal models indicate that mutation of the *BDNF* gene may be involved in aggressive behaviour. These studies indicated that changes in behaviour were related to abnormal levels of forebrain 5-HT. An association with the polymorphins of the *BDNF* gene especially $Val^{66}Met$ (G196A) has also been studied extensively. This is a single nucleotide polymorphism in the *BDNF* gene involving a valine (Val) and methionine (Met) substitution at codon 66 in the pro-domain (BDNFMet). Studies have shown that the Met (A) allele of $Val^{66}Met$ is associated with an abnormal pattern of increased bilateral hippocampal activation and impaired episodic memory in humans (Spalletta *et al.*, 2010). Transcranial magnetic and transcranial direct current stimulation studies designed to study synaptic plasticity in the motor cortex showed alterations in subjects with the $Val^{66}Met$ polymorphism, indicating once again a key role for BDNF in neural plasticity and that changes in its activity and associated pathways may contribute to the pathology of schizophrenia (Favalli *et al.*, 2012). Patients with schizophrenia also show altered energy metabolism in various areas of the brain including the prefrontal cortex, temporal and parietal cortices, thalamus, basal ganglia and cerebellum. Observed changes in complex I activity relating to two single nucleotide polymorphisms in a nuclear encoded subunit of the complex, NADH + H^+ dehydrogenase (uniquone) flavoprotein 2, were found to be indicators of the disease, suggesting a role for mitochondria in the onset of the disease (Hroudova and Fisar, 2011). With respect to these conditions, findings from various studies have demonstrated the important involvement of both BDNF and changes in mitochondrial function and disease onset.

Ageing

In scientific terms, ageing is associated with numerous physiological alterations across multiple organ systems, including the CNS and can lead to an increase in the variability

associated with cognitive and motor capabilities (Gallagher *et al.*, 1993; Albert, 1997). Age-related pathologies may arise from a combination of genetic and environmental factors. Changes in cognitive performance are also known to be influenced by biochemical events, such as oxidative stress, impaired cellular energy metabolism, perturbed cellular Ca^{2+} signalling or the abnormal accumulation of damaged proteins and organelles (Mattson and Magnus, 2006; Wong and Cuervo, 2010). Free radical production, including ROS and peroxynitrite, is known to increase and accumulate during the ageing process, resulting in an increase in the oxidation of key proteins and lipid peroxidation (Manoli *et al.*, 2007). Biochemical changes relating to membrane-associated oxidative stress are clearly indicated in neuronal dysfunction, which results in neurodegeneration and the onset of diseases such as Alzheimer's (Floyd and Hensley, 2002; Mattson, 2009; Kapogiannis and Mattson, 2011). Changes in intracellular energy metabolism in relation to impaired mitochondrial function resulting in reduced levels of ATP and NAD^+ provide the potential to influence both neuronal plasticity and dysfunction (Markham *et al.*, 2012). Mitochondrial dysfunction may result from one or a combination of effects including oxidative membrane damage, changes to respiratory chain proteins or alterations to mtDNA (Gibson *et al.*, 2010). Amyloid-β (Aβ) in AD, α-synuclein in PD and huntingtin in HD are disease-specific factors capable of compromising intracellular energy metabolism (Stranahan and Mattson, 2012).

A number of studies have also demonstrated a link between mitochondrial movements and fusion/fission and apoptosis (cell death). Mitochondrial fragmentation resulting from loss of mitofusins and OPA1 results in increased sensitivity to cell death stimuli, while their overexpression results in increased survival in neurons (Barsoum *et al.*, 2006; Jahani-Asl *et al.*, 2007). The pro-apoptotic proteins Bax and Bak have also been linked to components of the fusion/fission process (Jahani-Asl *et al.*, 2010). In relation to fission of the OMM, it has already been confirmed that the process requires Drp1 and Fis1, while fusion is controlled by two mitofusins: Mfn 1 and Mfn 2. Studies have confirmed that mitochondrial bioenergetics in Drp1-depleted cells are impaired, while conversely, inhibition of respiratory complex

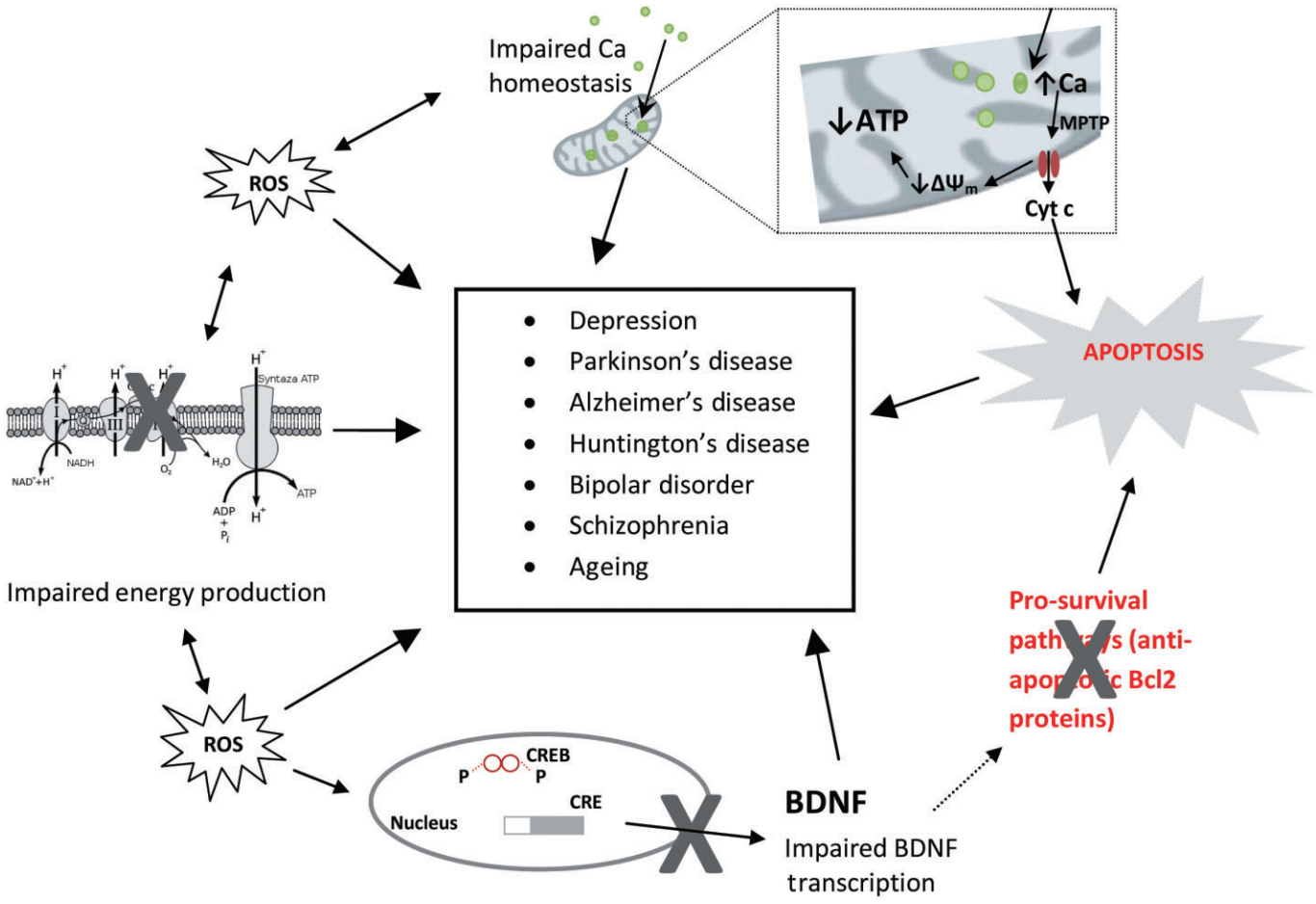

Figure 6

An imbalance in anterograde and retrograde signalling causes disruption of cellular homeostasis and results in a disease state. Impaired calcium homeostasis can result in impaired metabolism, which can disrupt the transcription of trophic factors, all of these have been implicated in disease. Conversely, a lack of trophic support may result in impaired calcium homeostasis and the cycle feeds back into itself, making the condition worse and leading to apoptosis, which is central to neurodegeneration.

I altered the organization of the mitochondrial network (Benard *et al.*, 2007). Imbalance in fission and fusion may result in changes in mitochondrial function, causing the accumulation of essential metabolites in the intercisternal space and INS, resulting in inhibition of the ETC, increased ROS production and ensuing oxidative stress, a potential cause of aging (Jendrach *et al.*, 2005).

Mitochondrial respiration is therefore known to be the major source of cellular ROS, indicating that mitochondria are a prime target for intracellular oxidative damage, which could result in diseases and disorders, including neurodegenerative diseases, schizophrenia and ageing (Cadenas and Davies, 2000; Jendrach *et al.*, 2005; Wallace, 2005; Halliwell, 2006). Neurodegeneration may also be a consequence of oxidative stress induced by the production of H_2O_2 resulting from the oxidation of monoamines by MAO A and B, which are located within the OMM (Naoi *et al.*, 2006). Glutamate and other excitatory amino acids are implicated in the production of ROS and resultant oxidative stress leading to neuronal damage, including changes in synaptic plasticity and learning and memory (Mattson *et al.*, 2008) and impaired Ca^{2+} homeostasis (Nicholls, 2009).

Conclusion

Cellular homeostasis is maintained through a two-way system of communication; the form of adjustment that a cell makes to the changes in homeostatic states is known as retrograde signalling, the most extreme example of which is apoptosis. Opposite to this is the anterograde signalling, where communication flows from the nucleus to the organelles through transcription and expression of proteins such as trophic factors. These responses are affected by an array of 'cues' such as stress-related metabolic changes, ROS accumulation and changes in Ca^{2+} dynamics of the mitochondria. Any perturbation that may cause this delicate system of communication to fail may tip the balance in favour of a disease state. As seen in the later sections of this review (Figures 4 and 6), where a lack of anterograde signalling by BDNF can lead to changes in the postsynaptic neurons or even apoptosis, which manifests behaviourally as depression or neurodegenerative conditions such as Parkinson's, Alzheimer's and Huntington's disease. These conditions are often also accompanied by an element of retrograde signalling failure such as imbalance in Ca^{2+} homeostasis, compromised energy metabolism and accumulation of ROS. Although which happens first is a matter of some discussion, these events are linked and contribute significantly to the progression and manifestation of the disease. Evidence presented in this review strongly indicates that the control of BDNF activity is key to the modulation of synaptic plasticity and that the role played by mitochondria is pivotal in processes involved in neuroprotection and those responsible for the onset and development of neurodegenerative diseases.

Conflict of interest

There no conflict of interest.

References

Albert MS (1997). The ageing brain: normal and abnormal memory. Philos Trans R Soc Lond B Biol Sci 352: 1703–1709.

Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P (2002). BDNF activates CREB via activated protein kinase eliciting a gene transcription response. Available at: http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=m (accessed 7/5/2013).

Alboni S, Tascedda F, Corsini D, Benatti C, Caggia F, Capone G *et al.* (2011). Stress induces altered CRE/CREB pathway activity and BDNF expression in the hippocampus of glucocorticoid receptor-impaired mice. Neuropharmacology 60: 1337–1346.

Andersson U, Scarpulla RC (2001). Pgc-1-related co-activator, a novel serum inducible co-activator of nuclear respiratory factor 1-dependent transcription in mammalian cells. Mol Cell Biol 21: 3738–3749.

Andrews ZB, Diano S, Horvath TL (2005). Mitochondrial uncoupling proteins in the CNS: in support of function and survival. Nat Rev Neurosci 6: 829–840.

Barrientos RM, Frank MG, Crysdale NY, Chapman TR, Ahrendsen JT, Day HEW *et al.* (2011). Little exercise, big effects reversing ageing and infection-induced memory deficits, and underlying processes. J Neurosci 31: 11578–11586.

Barsoum MJ, Yuan H, Gerencser AA, Liot G, Kushnareva Y, Graber S *et al.* (2006). Nitric oxide-induced mitochondrial fission is regulated by dynamin-related GTPases in neurons. EMBO J 25: 3900–3911.

Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC *et al.* (2012). Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 367: 795–804.

Baughman JM, Perocchi F, Girgis HS, Plovanich M, Beicher-Timme C, Sonacki Y *et al.* (2011). Integrative genomics identifies MCU as an essential component of the mitochondrial calcium uniporter. Nature 476: 341–345.

Baydoun AR, Markham A, Morgan RM, Sweetman AJ (1988). Palmitoyl carnitine: an endogenous promoter of calcium efflux from rat heart mitochondria. Biochem Pharmacol 37: 3103–3107.

Baydoun AR, Markham A, Morgan RM, Sweetman AJ (1990). Bay K8644 modifier of calcium transport and energy metabolism in rat mitochondria: a new intracellular site of action. Br J Pharmacol 101: 15–20.

Benard G, Bellance N, James D, Parrone P, Fernandez H, Letellier T *et al.* (2007). Mitochondrial bioenergetics and structural network organisation. J Cell Sci 120: 838–848.

Ben-Shachar D, Karry R (2008). Neuroanatomical pattern of mitochondrial complex I pathology varies between schizophrenia, bipolar, disorder and major depression. PLoS ONE 3: e3676.

Bingwei L (2009). Mitochondrial dynamics and neurodegeneration. Curr Neurol Neurosci Rep 9: 212–219.

Bredesen DE, Rao V, Mehlen P (2006). Cell death in the nervous system. Nature 443: 706–766.

Brunelle JK, Letai A (2009). Control of mitochondrial apoptosis by the Bcl-2. J Cell Sci 122: 437–441.

Burnouf S, Martire A, Derisbourg M, Laurent C, Belarbi K, Leboucher A *et al.* (2013). NMDA receptor dysfunction contributes to impaired brain-derived neurotrophic factor-induced facilitation of hippocampal synaptic transmission in a Tau transgenic model. Aging Cell 12: 11–23.

Butow RA, Avadhani NG (2004). Mitochondrial signaling: the retrograde response. Mol Cell 14: 1–15.

Cadenas E, Davies KJ (2000). Mitochondrial free radical generation, oxidative stress, and aging. Free Radic Biol Med 29: 222–230.

Cai Q, Sheng ZH (2009). Mitochondrial transport and docking in axons. Exp Neurol 218: 257–267.

Cai Q, Davis ML, Sheng ZH (2011). Regulation of axonal mitochondrial transport and its impact on synaptic transmission. Neurosci Res 70: 1–15.

Calabrese V, Cornellus C, Dinkova-Kostova AT, Calabrese EJ, Mattson MP (2010). Cellular stress response, the hormesis paradigm, and vitagenes: novel targets for therapeutic intervention in neurodegenerative disorders. Antioxid Redox Signal 13: 1763–1811.

Caldeira MV, Melo CV, Pereira DB, Carvaiho RF, Corvalho AL, Duarte CB (2007a). BDNF regulates the expression and traffic of NMDA receptors in cultured hippocampal neurons. Mol Cell Neurosci 35: 208–219.

Caldeira MV, Melo CV, Pereira DB, Carvalho R, Correia SS, Beckos DS *et al.* (2007b). Brain-derived neurotrophic factor regulates the expression and synaptic delivery of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor subunits in hippocampal neurons. J Biol Chem 282: 12619–12628.

Cali T, Ottolini D, Brini M (2012a). Mitochondrial Ca^{2+} as key regulator of mitochondrial activities. Advances in mitochondrial medicine. Adv Exp Med Biol Ser 942: 53–73.

Cali T, Ottolini D, Brini M (2012b). Mitochondrial Ca^{2+} and neurogeneration. Cell Calcium 52: 73–85.

Cassarino DS, Bennett JP Jr (1999). An evaluation of the role of mitochondria in neurodegenerative diseases: mitochondrial mutations and oxidative pathology, protective nuclear responses, and cell death in neurodegeneration. Brain Res Rev Res Rev 29: 1–25.

Castren E, Voikar V, Rantamaki T (2007). Role of neurotrophic factors in depression. Curr Opin Pharmacol 7: 18–21.

Chada SR, Hollenberck PJ (2004). Nerve growth factor signalling regulates motility and docking of axonal mitochondria. Curr Biol 14: 1272–1276.

Chang DT, Reynolds IJ (2006). Differences in mitochondrial movement and morphology in young and mature primary cortical neurons in culture. Neuroscience 141: 727–736.

Chauhan D, Velankar M, Brahmandam M, Hideshima T, Podar K, Richardson P *et al.* (2007). A novel Bcl-2/Bcl-X(L)/Bcl-w inhibitor ABT-737 as therapy in multiple myeloma. Oncogene 26: 2374–2380.

Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT (2001). Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biol Psychiatry 50: 260–265.

Chen DY, Bambah-Mukku D, Pollonini G, Alberini CM (2012). Glucocorticoid receptors recruit the CaMKIIα-BDNF-CREB pathways to mediate memory consolidation. Nat Neurosci 15: 1707–1714.

Chen Z, Zhong C (2013). Decoding Alzheimer's disease from perturbed cerebral glucose metabolism: implications for diagnostic and therapeutic strategies. Prog Neurobiol 108: 21–43.

Cheng A, Hou Y, Mattson MP (2010a). Mitochondria and neuroplasticity. ASN Neuro 2: 243–256.

Cheng B, Mattson MP (1994). NT-3 and BDNF protect CNS neurons against metabolic/excitotoxic insults. Brain Res 640: 56–67.

Cheng G, Henter ID, Manji HK (2010b). Translational research in bipolar disorder: emerging insights from genetically based models. Mol Psychiatry 15: 883–895.

Chipuk JE, Moldoveanu T, Llambi F, Parsons MJ, Green DR (2010). The BCL-2 family reunion. Mol Cell 37: 299–310.

Cohen BH, Gold DR (2001). Mitochondrial cytopathy in adults: what we know so far. Cleve Clin J Med 68: 625–626.

Cohen S, Levi-Montalcini R, Hamburger V (1954). A nerve growth-stimulating factor isolated from sarcom as 37 and 180. Proc Natl Acad Sci U S A 40: 1014–1018.

Cooke SF, Bliss TV (2006). Plasticity in the human central nervous system. Brain 129: 1659–1673.

Costa V, Giacomello M, Hudec R, Lopreiato G, Ermal G *et al.* (2010). Mitochondrial fission and cristae disruption increase the response of cell models of Huntington's disease to apoptotic stimuli. EMBO Mol Med 2: 490–503.

Counts SE, Mufson EJ (2010). Noraderenaline activation of neurotrophic pathways protects against neuronal amyloid toxicity. J Neurochem 113: 649–660.

Cowell RM, Blake KR, Russell JW (2007). Localization of the transcriptional coactivator PGC-1alpha to GABAergic neurons during maturation of the rat brain. J Comp Neurol 502: 1–18.

Creson TK, Yuan P, Manji HK, Chen G (2009). Evidence for involvement of ERK, Pl3K, and RSK in induction of Bcl-2 by valproate. J Mol Sci 37: 123–134.

Cuimsee C, Mattson MP (2005). p53 in neuronal apoptosis. Biochem Biophys Res Commun 331: 761–777.

Czeh B, Lucassen PJ (2007). What causes the hippocampal volume decrease in depression? Are neurogenesis, glial changes and apoptosis implicated? Eur Arch Psychiatry Clin Neurosci 257: 250–260.

De Brito OM, Scorrano L (2008). Mitofusin 2 tethers endoplasmic reticulum to mitochondria. Nature 456: 605–610.

De Stefani D, Raffaello A, Teardo E, Szabo I, Rizzuto R (2011). A forty-kilodalton protein of the inner membrane is the mitochondrial calcium uniporter. Nature 476: 336–340.

Del BR, Moggio M, Rango M, D'Angelo MG, Ghezzi S *et al.* (2008). Mutated mitofusion 2 presents with intrafamilial variability and brain mitochondrial dysfunction. Neurology 71: 1959–1966.

Deng W, Aimone JB, Gage FH (2010). New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? Nat Rev Neurosci 11: 339–350.

Diano S, Matthews RT, Patrylo P, Yang L, Beal MF, Barnstable CJ *et al.* (2003). Uncoupling protein 2 prevents neuronal death including that occurring during seizures: a mechanism for preconditioning. Endocrinology 144: 5014–5021.

Dicou E, Rangon CM, Guimiot F, Spedding M, Gressens P (2003). Positive allosteric modulators of AMPA receptors are neuroprotective against lesions induced by an NMDA agonist in neonatal mouse brain. Brain Res 970: 221–225.

Diogenes MJ, Costenia AR, Lopes LV, Jeronimo-Santos A, Sousa VC, Fontinha BM *et al.* (2011). Enhancement of LTP in aged rats is dependent on endogenous BDNF. Neuropsychopharmacology 36: 1823–1836.

Dragicevic N, Mamcarz M, Zhu Y, Buzzeo R, Tan J, Arendash GW *et al.* (2010). Mitochondrial amyloid-beta levels are associated with the extent of mitochondrial dysfunction in different brain regions

and the degree of cognitive impairment in Alzheimer's transgenic mice. J Alzheimers Dis 20: S535–S550.

Du H, Guo L, Fang F, Chen D, Sosunvo AA, Mckhann GM *et al.* (2008). Cyclophilin D deficiency attenuates mitochondrial and neuronal perturbation and ameliorates learning and memort in Alzheimer's disease. Nat Med 14: 1097–1105.

Du J, Wang Y, Hunter R, Wei Y, Blumenthal R, Falke C *et al.* (2009). Dynamic regulation of mitochondrial function by glucocorticoids. Proc Natl Acad Sci U S A 106: 3543–3548.

Duchen MR (1999). Contributions of mitochondria to animal physiology: from homeostatic sensor to calcium signalling and cell death. J Physiol 516: 1–17.

Einat H, Yuan P, Manji HK (2005). Increased anxiety-like behaviors and mitochondrial dysfunction in mice with targeted mutation of the Bcl-2 gene: further support for the involvement of mitochondrial function in anxiety disorders. Behav Brain Res 165: 172–180.

Fahnestock M, Marchese M, Head E, Pop V, Michaiski B, Milgram WN *et al.* (2012). BDNF increases with behavioural enrichment and an antioxidant diet in the aged dog. Neurobiol Aging 33: 546–554.

Favalli G, Li J, Belmonte-de-Abreu P, Wong AHC, Daskalakis ZJ (2012). The role of BDNF in the pathophysiology and treatment of schizophrenia. J Psychiatr Res 46: 1–11.

Fehm HL, Kern W, Peters A (2006). The selfish brain: competition for energy resources. Prog Brain Res 153: 129–140.

Ferreiro E, Oliveira CR, Pereira CM (2008). The release of calcium from the endoplasmic reticulum induced by amyloid-beta and prion peptides activates the mitochondrial apoptotic pathway. Neurobiol Dis 30: 331–342.

Figurov A, Pozzo-Miller LD, Olafsson P, Wang T, Lu B (1996). Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. Nature 381: 706–709.

Floyd RA, Hensley K (2002). Oxidative stress in brain ageing. Implications for therapeutics of neurodegenerative diseases. Neurobiol Aging 23: 795–807.

Fox RM, Markham A, Morgan RM (1993). Calcium antagonists and Bay K8644 promote depolarization of rat heart mitochondrial membrane potential. Further evidence for a role in alteration of oxidative metabolism. Biochem Pharmacol 45: 1995–2001.

Galeffi F, Somjen GG, Foster KA, Turner DA (2011). Simultaneous monitoring of tissue PO2 and NADH fluorescence during synaptic stimulation and spreading depression reveals a transient dissociation between oxygen ulitization and mitochondrial redox state in rat hippocampal slices. J Cereb Blood Flow Metab 31: 626–639.

Gallagher M, Burwell R, Burchinal M (1993). Severity of spatial learning impairment in ageing: development of a learning index for performance in the Morris water maze. Behav Neurosci 28: 8945–8954.

Garcia DA, Franke H, Pissarek M, Nieber K, Illes P (1999). Neuroprotection by ATP-dependent potassium channels in rat neocortical brain slices during hypoxia. Neurosci Lett 273: 13–16.

Gavillet M, Allaman I, Magistretti PJ (2008). Modulation of astrocytic metabolic phenotype by proinflammatory cytokines. Glia 56: 975–989.

Giacomello M, Drago I, Pizzo P, Pozzan T (2007). Mitochondrial Ca^{2+} as a key regulator of cell life and death. Cell Death Differ 14: 1267–1274.

Gibson GE, Starkvo A, Biass JP, Ratan RR, Beal MF (2010). Cause and consequence: mitochondrial dysfunction initiates and propagates neuronal dysfunction, neuronal death and behavioural abnormalities in age-associated neurodegenerative diseases. Biochim Biophys Acta 1802: 122–134.

Gleichmann M, Mattson MP (2011). Neuronal calcium homeostasis and dysregulation. Antioxid Redox Signal 14: 1261–1273.

Godsil BP, Kiss JP, Spedding M, Jay TM (2013). The hippocampal-prefrontal pathway: the weak link in psychiatric disorders? Eur Neuropsychopharmacol 23: 1165–1181.

Gong Y, Chai Y, Ding JH, Sun XL, Hu G (2011). Chronic mild stress damages mitochondrial ultrastructure and function in mouse brain. Neurosci Lett 488: 76–80.

Gottmann K, Mittmann T, Lessmann V (2009). BDNF signalling in the formation, maturation and plasticity of glutamatergic and GABAergic synapses. Exp Brain Res 199: 203–234.

Greenamyre JT, MacKenzie G, Peng TI, Stephans SE (1999). Mitochondrial dysfunction in Parkinson's disease. Biochem Soc Symp 66: 85–97.

Gressens P, Marret S, Hill JM, Brenneman DE, Gozes I, Fridkin M *et al.* (1997). Vasoactive intestinal peptide prevents excitotoxic cell death in the murine developing brain. J Clin Invest 100: 390–397.

Gutman M, Singer TP, Casida JE (1970). Studies on the respiratory chain-linked reduced nicotinamide adenine dinucleotide dehydrogenase: XVII. Reaction sites of piericidin A and rotenone. J Biol Chem 245: 1992–1997.

Gutsaeva DR, Carraway MS, Suliman HB, Demchenko IT, Shitara H, Yonekawa H *et al.* (2008). Transient hypoxia stimulates mitochondrial biogenesis in brain subcortex by a neuronal nitric oxide synthase-dependent mechanism. J Neurosci 28: 2015–2024.

Guzman JN, Sanchez-Padilla J, Wokosin D, Kondapalli J, Llijic E, Shumacker PT *et al.* (2010). Oxidative stress evoked by pace-making in dopaminergic neurons is attenuated by DJ-1. Nature 468: 696–700.

Halle A, Hornung V, Petzold GC, Stewart CR, Monks BG, Reinheckel T *et al.* (2008). The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. Nat Immunol 9: 857–865.

Halliwell B (2006). Oxidative stress and neurodegeneration: where are we now? J Neurochem 97: 1634–1658.

Han BH, Holtzman DM (2000). BDNF protects the neonatal brain from hypoxia-ischemic injury *in vivo* via ERK pathway. J Neurosci 20: 5775–5781.

Han XJ, Lu YF, Li SA, Kaitsuka T, Sato Y, Tomizawa K *et al.* (2008). CaM kinase 1α-induced phosphorylation of Drp1 regulates mitochondrial morthology. J Cell Biol 182: 573–585.

Hansson AC, Cintra A, Belluardo N, Sommer W, Bhatnagar M, Bader M *et al.* (2000). Gluco- and mineralocorticoid receptor-mediated regulation of neurotrophic factor gene expression in the dorsal hippocampus and the neocortex of the rat. Eur J Neurosci 12: 2918–2934.

Harper ME, Antoniou A, Villalobos-Menuey E, Russo A, Trauger R, Vendemelio M *et al.* (2002). Characterization of a novel metabolic strategy used by drug-resistant tumor cells. FASEB J 16: 1550–1557.

Harper MM, Adamson L, Blits B, Bunge MB, Grozdanic SD, Sakaguchi DS (2009). Brain-derived neurotrophic factor released from engineered mesenchymal stem cells attenuates glutamate- and hydrogen peroxide-mediated death of staurosporine-differentiated RGC-5 cells. Exp Eye Res 89: 538–548.

Hartl FU, Bracher A, Hayer-Hartl M (2011). Molecular chaperones in protein folding and proteostasis. Nature 475: 324–332.

Hebert TL, Wu X, Yu G, Goh BC, Halvorsen YD, Wang Z *et al.* (2009). Culture effects of epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF) on cryopreserved human adipose-derived stromal/stem cell proliferation and adipogenesis. J Tissue Eng Regen Med 3: 553–561.

Hempstead BL, Lee R, Kermani P, Teng KK (2001). Regulation of cell survival by secreted proneurotrophins. Science 294: 1945–1948.

Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A *et al.* (2013). NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature 493: 674–678.

Hetman M, Kanning K, Cavanaugh JE, Xia Z (1999). Neuroprotection by brain-derived neurotrophic factor is mediated by extracellular signal-regulated kinase and phosphatidylinositol 3-kinase. J Biol Chem 274: 22569–22580.

Hickman JA, Hardwick JM, Kaczmarek LK, Jonas EA (2008). Bcl-xL inhibitor ABT-737 reveals a dual role for Bcl-xL in synaptic transmission. J Neurophysiol 99: 1515–1522.

Hildebrandt H, Muhienhoff M, Weinhold B, Gerardy-Schahn R (2007). Dissecting polysialic acid and NCAM function in brain development. J Neurochem 103: 56–64.

Holley AK, Dhar SK, St Clair DK (2010). Manganese superoxide dismutase versus p53: the mitochondrial centre. Ann N Y Acad Sci 1201: 72–78.

Holt IJ, Harding AE, Morgan-Hughes JA (1988). Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies. Nature 331: 717–719.

Horvath TL, Diano S, Barnstable C (2003). Mitochondrial uncoupling protein 2 in the central nervous system: neuromodulator and neuroprotector. Biochem Pharmacol 65: 1917–1921.

Hroudova J, Fisar Z (2011). Connectivity between mitochondrial functions and psychiatric disorders. Psychiatry Clin Neurosci 65: 130–141.

Hunsberger J, Austin DR, Henter ID, Chen G (2009). The neurotrophic and neuroprotective effects of psychotropic agents. Dialogues Clin Neurosci 11: 333–348.

Husson I, Mesples B, Bac P, Vamecq J, Evrard P, Gressens P (2002). Melatoninergic neuroprotection of the murine periventricular white matter against neonatal excitotoxic challenge. Ann Neurol 51: 82–92.

Hyman C, Hofer M, Barde Y, Juhasz M, Yancopoulos GD, Squinto SP *et al.* (1991). BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra. Nature 350: 230–232.

Jahani-Asl A, Cheung EC, Neuspiel M, Maclaurin JG, Fortin A *et al.* (2007). Mitofusin 2 protects cerebellar granule neurons against injury-induced cell death. J Biol Chem 282: 23788–23798.

Jahani-Asl A, Germain M, Slack RS (2010). Mitochondria: joining forces to thwart cell death. Biochim Biophys Acta 1802: 162–166.

Jeanneteau F, Chao AV (2012). Are BDNF and glucocorticoid activities calibrated? Neuroscience 239: 173–195.

Jendrach M, Pohl S, Voth M *et al.* (2005). Morphology-dynamic changes of mitochondria during ageing of human endothelial cells. Mech Ageing Dev 126: 813–821.

Jiang M, Wang J, Fu J, Du L, Jeong H, West T *et al.* (2011). Neuroprotective role of Sirt1 in mammalian models of Huntingdon's disease through activation of multiple Sirt1 targets. Nat Med 18: 153–158.

Jiao S, Li Z (2011). Nonapoptotic function of BAD and BAX in long-term depression of synaptic transmission. Neuron 70: 758–772.

Jonas E (2006). BCL-xL regulates synaptic plasticity. Mol Interv 6: 208–222.

Kalb R (2005). The protean actions of neurotrophins and their receptors on the life and death of neurons. Trends Neurosci 28: 5–11.

Kapogiannis D, Mattson MP (2011). Disrupted energy metabolism and neuronal circuit dysfunction in cognitive impairment and Alzheimer's disease. Lancet Neurol 10: 187–198.

Kato T (2001). The other, forgotten genome: mitochondrial DNA and metal disorders. Mol Psychiatry 6: 625–633.

Kim HW, Rapoport SI, Rao JS (2010). Altered expression of apoptotic factors and synaptic markers in postmortembrain from bipolar disorder patients. Neurobiol Dis 37: 596–603.

Kohara K, Yasuda H, Huang Y, Adachi N, Sohya K, Tsumoto TA (2007). A local reduction in cortical GABAergic synapses after loss of endogenous brain-derived neurotrophic factor, as revealed by single-cell gene knock-out method. J Neurosci 27: 7234–7244.

Kompagne H, Bardos G, Szenasi G, Gacsalyi I, Harsing LG, Levay G (2008). Chronic mild stress generates clear depressive but ambiguous anxiety-like behaviour in rats. Behav Brain Res 193: 311–314.

Koo JW, Duman RS (2008). IL-1beta is an essential mediator of antineurogenic and anhedonic effects of stress. Proc Natl Acad Sci U S A 105: 751–756.

Koufali MM, Moutsatsou P, Sekeris CE, Breen BC (2003). The dynamic localisation of the glucocorticoid receptor in rat C6 glioma cell mitochondria. Mol Cell Endocrinol 209: 51–60.

Kraft AD, Johnson DA, Johnson JA (2004). Nuclear factor E2-related factor 2-dependent antioxidant response element activation by tert-butylhydroquinone and sulforaphane occurring preferentially in astrocytes conditions neurons against oxidative insult. J Neurosci 24: 1101–1112.

Kroemer G, Reed JC (2000). Mitochondrial control of cell death. Nat Med 6: 513–519.

Kumamaru E, Numakawa T, Adachi N, Yagasaki Y, Izuni A, Niyaz M *et al.* (2008). Glucocorticoids prevents brain-derived neurotrophic factor-mediated maturation of synaptic function in developing hippocampal neurons through reduction in the activity of mitogen-activated protein kinase. Mol Endocrinol 22: 546–558.

Kumamaru E, Numakawa T, Adachi N, Kunugi H (2011). Glucocorticoid suppresses BDNF-stimulated MAPK/ERK pathway via inhibiting interaction of Shp2 with TrkB. FEBS Lett 585: 3224–3228.

LaFerla FM, Green KN, Oddo S (2007). Intracellular amyloid-beta in Alzheimer's disease. Nat Rev Neurosci 8: 499–509.

Laske C, Stransky E, Leyhe T, Eschweiler GW, Wittorf A, Richartz E (2006). Stage-dependent BDNF serum concentrations in Alzheimer's disease. J Neural Transm 113: 1217–1224.

Lazarov O, Mattson MP, Peterson DA, Pimplikar SW, van Praag H (2010). When neurogenesis encounters ageing and disease. Trends Neurosci 33: 569–579.

Leadsham JE, Gourley CW (2010). cAMP/PKA signalling balances respiratory activity with mitochondria dependent apoptosis via transcriptional regulation. BMC Cell Biol 11: 92–105.

Lee J, Duan W, Mattson MP (2002). Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates,

in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. J Neurochem 82: 1367–1375.

Lee J, Lim E, Kim Y, Li E, Park S (2010). Ghrelin attenuates kainic acid-induced neuronal cell death in the mouse hippocampus. J Endocrinol 205: 263–270.

Levi-Montalcini R, Hamburger V (1953). A diffusible agent of mouse sarcoma producing hyperplasia of sympathetic ganglia and hyperneurotization of viscera in the chick embryo. J Exp Zool 123: 233–278.

Li H, Chen Y, Jones AF, Sanger RH, Collis LP, Flannery R *et al.* (2008). Bcl-xL induces Drp1-dependent synapse formation in cultured hippocampal neurons. Proc Natl Acad Sci U S A 105: 2169–2174.

Li Z, Jo J, Jia JM, Lo SC, Whitcomb DJ, Jiao S *et al.* (2010). Caspase-3 activation via mitochondria is required for long-term depression and AMPA receptor internalization. Cell 141: 859–871.

Lipsky RH, Marini AM (2007). Brain-derived neurotrophic factor in neuronal survival and behaviour-related plasticity. Ann N Y Acad Sci 1122: 130–143.

Liu W, Zhou C (2012). Corticosterone reduces brain mitochondrial function and expression of mitofusin, BDNF in depression-like rodents regardless of exercise preconditioning. Psychoneuroendocrinology 37: 1057–1070.

Liu X, Hajnoczky G (2009). Ca^{2+}-dependent regulation of mitochondrial dynamics by Miro-Milton complex. Int J Biochem Cell Biol 41: 1972–1976.

Loers G, Schachner M (2007). Recognition molecules and neural repair. J Neurochem 101: 865–882.

Lu Y, Christian K, Lu B (2008). BDNF: a key regulator for protein synthesis-dependent LTP and long-term memory? Neurobiol Learn Mem 89: 312–323.

Lucca G, Comim CM, Valvassori SS, Reus GZ, Vuolo F, Petronillho F *et al.* (2009). Effects of chronic mild stress on the oxidative parameters in rat brain mitochondria. Neurochem Int 54: 358–362.

Lynch MA (2004). Long-term potentiation and memory. Physiol Rev 84: 87–136.

MacAskill AF, Kittler JT (2010). Control of mitochondrial transport and localization in neurons. Trends Cell Biol 20: 102–112.

McCormack JG, Denton RM (1990). The role of mitochondrial Ca^{2+} transport and matrix Ca^{2+} in signal transduction in mammalian tissues. Biochim Biophys Acta 1018: 287–291.

McKernan DP, Dinan TG, Cryan JF (2009). 'Killing the Blues': a role for cellular suicide (apoptosis) in depression and the antidepressant response? Prog Neurobiol 88: 246–263.

Mammucari C, Patron M, Granatiero V, Rizzuto R (2011). Molecules and roles of mitochondrial calcium signaling. Biofactors 37: 219–227.

Man HY, Lin JW, Ahmadian G, Liu L, Becker LE *et al.* (2000). Regulation of AMPA receptor-mediated synaptic transmission by clathrin-dependent receptor internalization. Neuron 25: 649–662.

Manji H, Kato T, DiProspero NA, Ness S, Beal MF, Krams M *et al.* (2012). Impaired mitochondrial function in psychiatric disorders. Nat Rev Neurosci 13: 293–307.

Manoli I, Salvatore A, Blackman MR, Su YA, Rennert OM, Chrousos GP (2007). Mitochondria as key components of the stress response. Trends Endocrinol Metab 18: 190–198.

Manzanero S, Gelderblom M, Magnus T, Arumugan TV (2011). Calorie restriction and stroke. Exp Transl Stroke Med 3: 8–21.

Marini AM, Jiang X, Wu X, Pan H, Guo Z, Mattson MP *et al.* (2007). Preconditioning and neurotrophins: a model for brain adaptation to seizures, ischemia and other stressful stimuli. Amino Acids 32: 299–304.

Markham A, Cameron I, Franklin P, Spedding M (2004). BDNF increases brain mitochondrial respiratory coupling, and glutamate metabolism, at complex I, but not complex II. Eur J Neurosci 20: 1189–1196.

Markham A, Cameron I, Franklin P, Spedding M (2005). BDNF, but not GDNF, increases mouse brain mitochondrial respiratory coupling at complex I, but not complex II. Proceedings of British Pharmacological Society. Available at: http://www.pA2online.org/abstracts/Vol2Issue4abst105P.pdf (accessed 11/3/2013).

Markham A, Cameron I, Bains R, Franklin P, Kiss JP, Schwendenimann L *et al.* (2012). Brain-derived neurotrophic factor-mediated effects on mitochondrial coupling and neuroprotection share the same molecular signalling pathways. Eur J Neurosci 35: 366–374.

Marlatt MW, Potter MC, Lucassen PJ, van Praag H (2012). Running throughout middle-age improves memory function, hippocampal neurogenesis, and BDNF levels in female C57BL/6J mice. Dev Neurobiol 72: 943–952.

Marongiu R, Spencer B, Crews L, Adame A, Patrick C *et al.* (2009). Mutant PINK1 induces mitochondrial dysfunction in neuronal cell model of Parkinson's disease by disturbing calcium flux. J Neurochem 108: 1561–1574.

Matrone C, Ciotti MT, Mercanti D, Marolda R, Calissano P (2008). NGF and BDNF signalling control amyloidogenic route and Abeta production in hippocampal neurons. Proc Natl Acad Sci U S A 105: 13139–13144.

Matsumoto T, Rauskolb S, Polack M, Klose J, Kolbeck R, Korte M *et al.* (2008). Biosynthesis and processing of endogenous BDNF: CNS neurons store and secrete BDNF, not pro-BDNF. Nat Neurosci 11: 131–133.

Mattson MP (2008). Glutamate and neurotrophic factors in neuronal plasticity and disease. Ann N Y Acad Sci 1144: 97–112.

Mattson MP (2009). Roles of the lipid peroxidation product 4-hydroxynonenalin obesity, the metabolic syndrome and associated vascular and neurodegenerative disorders. Exp Gerontol 44: 625–633.

Mattson MP, Magnus T (2006). Aging and neuronal vulnerability. Nat Rev Neurosci 7: 278–294.

Mattson MP, Partin J (1999). Evidence for mitochondria control of neuronal polarity. J Neurosci Res 56: 8–20.

Mattson MP, Gleichmann M, Cheng A (2008). Mitochondria in neuroplasticity and neurological disorders. Neuron 60: 748–766.

Miller RJ (1998). Mitochondria – the Kraken wakes! Trends Neurosci 21: 95–97.

Minichiello L, Calella AM, Medina DL, Bonhoeffer T, Klein R, Korte M (2002). Mecahanism of TrkB-mediated long-term potentiation. Neuron 36: 121–137.

Morimoto RI (2008). Proteotoxic stess and inducible chaperone networks in neurodegenerative disease and ageing. Genes Dev 22: 1427–1437.

Murray PS, Holmes PV (2011). An overview of brain-derived neurotrophic factor and implications for excitotoxic vulnerability in the hippocampus. Int J Pept 2011: Article ID 654085.

Nagahara AH, Merrill DA, Coppola G, Tsukada S, Schroeder BE, Shaked GM *et al.* (2009). Neuroprotective effects of brain-derived neurotrophic factorin rodent and primate models of Alzheimer's disease. Nat Med 15: 331–337.

Nagappan G, Lu B (2005). Activity-dependent modulation of the BDNF receptor TrkB: mechanisms and implications. Trends Neurosci 28: 464–471.

Naoi M, Maruyama W, Akao Y, Yi H, Yamaoka Y (2006). Involvement of type A monoamine oxidase in neurodegeneration of mitochondrial signalling leading to cell death or neuroprotection. J Neural Transm Suppl 71: 67–77.

Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM (2002). Neurobiology of depression. Neuron 34: 13–25.

Nicholls DG (2009). Mitochondrial calcium function and dysfunction in the central nervous system. Biochim Biophys Acta 1787: 1416–1424.

Niciu MJ, Ionescu DF, Mathews DC, Richards EM, Zarate CA Jr (2013). Second messenger/signal transduction pathways in major mood disorders: moving from membrane to mechamism of action, part II: bipolar disorder. CNS Spectr 18: 242–251.

Noakes T, Spedding M (2012). Run for your life. Nature 487: 295–296.

Nuytemans K, Theuns J, Cruts M, Van Broeckhoven C (2010). Genetic etiology of Parkinson's disease associated with mutations in the SNCA, PARK2, PINK1, PARK7, and LRRK2 genes: a mutation update. Hum Mutat 31: 763–780.

Oliveira JM (2010). Nature and cause of mitochondrial dysfunction in Huntington's disease: focusing on huntingtin and the striatum. J Neurochem 114: 1–12.

Orth M, Schapira AH (2001). Mitochondria degenerative disorders. Am J Med Genet 106: 27–36.

Pacher P, Hajnoczky G (2001). Propagation of the apoptotic signal by mitochondrial waves. EMBO J 20: 4107–4121.

Palty R, Silverman WF, Hershfinkel M, Caporale T, Sensi SL, Parnis J *et al.* (2010). NCLX is an essential component of mitochondrial Na^+/Ca^{2+} exchange. Proc Natl Acad Sci U S A 107: 436–441.

Parain K, Murer MG, Yan Q, Faucheux B, Agid Y, Hirsch E *et al.* (1999). Reduced expression of BDNF protein in Parkinson's disease substantia nigra. Neuroreport 10: 557–561.

Patergnani S, Suski JM, Agnoletto C, Bononi A, Bonora M, De Marchi1 E *et al.* (2011). Calcium signalling around mitochondria associated membranes (MAMs). Cell Commun Signal 9: 19.

Perera TD, Coplan JD, Lisanby SH, Lipira CM, Arif M, Carpio C *et al.* (2007). Antidepressant-induced neurogenesis in the hippocampus of adult nonhuman primates. J Neurosci 27: 4894–4901.

Perocchi F, Gohil VM, Girgis HS, Bao XR, McCombs JE, Palmer AE *et al.* (2010). MICU1 encodes a mitochondrial EF hand protein required for Ca^{2+} uptake. Nature 467: 291–296.

Peters A, Schweigerb U, Pellerine L, Hubolda C, Oltmannsb KM *et al.* (2004). The selfish brain: competition for energy resources. Neurosci Biobehav Rev 28: 143–180.

Pieczenik SR, Neustadt J (2007). Mitochondrial dysfunction and molecular pathways of disease. Exp Mol Pathol 83: 84–92.

Pinton P, Rizzuto R (2006). Bcl-2 and Ca^{2+} homeostasis in the endoplasmic reticulum. Cell Death Differ 13: 1409–1418.

Pinton P, Giorgi C, Siviero R, Zecchini E, Rizzuto R (2008). Calcium and apoptosis: ER-mitochondria Ca^{2+} transfer in the control of apoptosis. Oncogene 27: 6407–6418.

Pittenger C, Duman RS (2008). Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology 33: 88–109.

Pizzo P, Lissandron V, Capitanio P, Pozzan T (2011). Ca^{2+} signalling in the Golgi apparatus. Cell Calcium 50: 184–192.

Plaisant F, Clippe A, Vander SD, Knoops B, Gressens P (2003). Recombinant peroxiredoxin 5 protects against excitotoxic brain lesions in newborn mice. Free Radic Biol Med 34: 862–872.

Platenik J, Kuramoto N, Yoneda Y (2000). Molecular mechanisms associated with long-term consolidation of the NMDA signals. Life Sci 67: 335–364.

Poo MM (2001). Neurotrophins as synaptic modulators. Nat Rev Neurosci 2: 24–32.

Qi H, Mailliet F, Spedding M, Rocher C, Zhang X, Delagrange P *et al.* (2009). Antidepressants reverse the attenuation of the neurotrophic MEK/MAPK cascade in frontal cortex by elevated platform stress; reversal of effects on LTP is associated with GluA1 phosphorylation. Neuropharmacology 56: 37–46.

Quiroz JA, Gray NA, Kato T, Manji HK (2008). Mitochondrially mediated plasticity in the pathophysiology and treatment of bipolar disorder. Neuropsychopharmacology 33: 2551–2565.

Rantamaki T, Hendolin P, Kankaanpaa A, Mijatovic J, Piepponen P, Domenici E *et al.* (2004). Pharmacologically diverse antidepressants rapidly activate BDNF receptor TrkB and induce phospholipase-Cγ signaling pathways in mouse brain. Neuropsychopharmacology 32: 2152–2162.

Renton JP, Xu N, Clark JJ, Hansen MR (2010). Interaction of neurotrophin signalling with Bcl-2 localized to the mitochondria and the endoplasmic reticulum on spiral ganglion neuron survival and neurite growth. J Neurosci Res 88: 2239–2251.

Rezin GT, Amboni G, Zugno AI, Quevedo J, Streck EL (2009). Mitochondrial dysfunction and psychiatric disorders. Neurochem Res 34: 1021–1029.

Rezin GT, Cardoso MR, Goncalves CL, Scaini G, Fraga DB, Riegel RE *et al.* (2008). Inhibition of mitochondrial respiratory chain in brain of rats subjected to an experimental model of depression. Neurochem Int 53: 395–400.

Ricchelli F, Sileikyte J, Bernardi P (2011). Shedding light on the mitochondrial permeability transition. Biochim Biophys Acta 1807: 482–490.

Richard D, Clavel S, Huang Q, Sanchis D, Ricquier D (2001). Uncoupling protein 2 in the brain: distribution and function. Biochem Soc Trans 29: 812–817.

Rothman SM, Mattson MP (2013). Activity-dependent, stress-responsive BDNF signalling and quest for optimal brain health and resilience throughout the lifespan. Neuroscience 239: 228–240.

Rusnak R, Mertz P (2000). Calcineurin: form and function. Physiol Rev 80: 1483–1521.

Saha JB, Guilllily MD, Ferree A, Lanceta J, Chan D, Ghosh J *et al.* (2009). LRRK2 modulates vulnerability to mitochondrial dysfunction in *Caenorhabditis elegans*. J Neurosci 29: 9210–9218.

Schinder AF, Poo M (2000). The neurotrophin hypothesis for synaptic plasticity. Trends Neurosci 23: 639–645.

Schulz JB, Beal MF (1994). Mitochondrial dysfunction in movement disorders. Curr Opin Neurol 7: 333–339.

Sherer TB, Betarbet R, Testa CM, Seo BB, Richardson JR, Kim JH *et al.* (2003). Mechanisms of toxicity in rotentone models of Parkinson's disease. J Neurosci 23: 10756–10764.

Shimizu E, Hashimoto K, Okanawa N, Kioke K, Komatsu N, Kumakiri C *et al.* (2003). Alterations of serum levels of brain

derived neurotrophic factor (BDNF) in depressed patients with or without antidepressant. Biol Psychiatry 54: 70–75.

Shoshan-Barmatz V, Ben-Hall D (2012). VDAC, a multi-functional mitochondrial protein as a pharmacological target. Mitochondrion 12: 24–34.

Shoshan-Barmatz V, Keinan N, Zaid H (2008). Uncovering the role of VDAC in the regulation of cell life and death. J Bioenerg Biomembr 40: 183–191.

Smith MA, Makino S, Kim SY, Kventnansky R (1995). Stress increases BDNF messenger riboneucleic acid in the hypothalamus and pituitary. Endocrinology 136: 3743–3750.

Son TG, Camandola S, Mattson MP (2008). Hormetic dietary phytochemicals. Neuromolecular Med 10: 236–246.

Spalletta G, Morris DW, Angelucci F, Rubino IA, Spoletini I, Bria P *et al*. (2010). BDNF Val66Met polymorphism is associated with aggressive behaviour in schizophrenia. Eur Psychiatry 25: 311–313.

Spedding M, Gressens P (2008). Neurotrophins and cytokines in neuronal plasticity. Novartis Found Symp 289: 222–233.

Spedding M, Spedding C (2008). Drugs in sport: a scientist-athlete's perspective: from ambition to neurochemistry. Br J Pharmacol 154: 496–501.

Spedding M, Tillement JP, Morin D, Le Ridant A (1999). Medicines interacting with mitochondria: anti-ischemic effects of trimetazidine. Therapie 54: 627–635.

Spencer JP (2010). The impact of the fruit flavoniods on memory and cognition. Br J Nutr 104: 40–47.

Starkov AA, Fiskum G, Chinopoulos C, Lorenzo BJ, Browne SE, Patel MS *et al*. (2004). Mitochondrial alpha-ketoglutarate dehydrogenase complex generates reactive oxygen species. J Neurosci 24: 7779–7788.

Stranahan AM, Mattson MP (2008). Impact of energy intake and expenditure on neuronal plasticity. Neuromolecular Med 10: 209–218.

Stranahan AM, Mattson MP (2012). Recruiting adaptive cellular stress responses for successful brain ageing. Nat Rev Neurosci 13: 209–216.

Suen P, Wu K, Levine ES, Mount HT, Xu JL, Lin SY *et al*. (1997). Brain-derived neurotrophic factor rapidly enhances phosphorylation of the postsynaptic N-methyl-D-aspartate receptor subunit 1. Proc Natl Acad Sci U S A 94: 8191–8195.

Suri D, Vaidya VA (2013). Glucocorticoids regulation of brain-derived neurotrophic factor: relevance to hippocampal structural and functional plasticity. Neuroscience 239: 196–213.

Suwanjang W, Holmstrom KM, Chetsawng B, Abramov AY (2013). Glucocorticoids reduce intracellular calcium contration and protects neurons against glutamate toxicity. Cell Calcium 53: 256–263.

Szabadkai G, Bianchi K, Varnai P, De Stefani D, Wieckowski MR *et al*. (2006). Chaperone-mediated coupling of endoplasmic reticulum and mitochondrial Ca^{2+} channels. J Cell Biol 175: 901–911.

Tagscherer KE, Fassl A, Campos B, Farhadi M, Kraemer A, Bock BC *et al*. (2008). Apoptosis-based treatment of glioblastomas with ABT-737, a novel small molecule inhibitor of Bcl-2 family proteins. Oncogene 27: 6646–6656.

Teng HK, Teng KK, Lee R, Wright S, Tevar S, Almeida RD *et al*. (2005). ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin. J Neurosci 25: 5455–5463.

Teng KK, Felice S, Kim T, Hempstead BL (2010). Understanding proneurotrophin actions: recent advances and challenges. Dev Neurobiol 70: 350–359.

Trushina E, Nemutlu E, Zhang S, Christensen T, Camp J, Mesa J *et al*. (2012). Defects in mitochondrial dynamics and metabolomic signatures of evolving energetic stress in mouse models of familial Alzheimer's disease. PLoS ONE 7: e32737.

Trushina E, Dutta T, Persson XM, Mielke MM, Petersen RC (2013). Identification of altered metabolic pathways in plasma and CSF in mild cognitive impairment and Alzheimer's disease using metabolomics. PLoS ONE 8: e63644.

Vaynman S, Ying Z, Gomez-Pinilla F (2003). Interplay between BDNF and signal transduction modulators in the regulation of the effects of exercise on synaptic-plasticity. Neuroscience 122: 647–657.

Vaynman S, Ying Z, Wu A, Gomez-Pinilla F (2006). Coupling energy metabolism with a mechanism to support brain-derived neurotrophic factor-mediated synaptic plasticity. Neuroscience 139: 1221–1234.

Vogel S, Keifer T, Raulf N, Sterz K, Manoharan A, Borner C (2009). Mechanisms of Bax/Bak activation: is there any light at the end of the tunnel? Gastroenterol Hepatol 2: S11–S18.

Wallace DC (2005). A mitochondrial paradigm of metabolic and degenerative diseases, aging and cancer: a dawn for evolutionary medicine. Annu Rev Genet 39: 359–407.

Wallace DC, Shoffner JM, Trounce I, Brown MD, Ballinger SW, Corral-Debrinski M *et al*. (1995). Mitochondrial DNA mutations in human degenerative diseases and aging. Biochim Biophys Acta 127: 141–151.

Wang GJ, Thayer SA (2002). NMDA-induced calcium loads recycle across the mitochondrial inner membrane of hippocampal neurons in culture. J Neurophysiol 87: 740–749.

Wang X, Su B, Zheng L, Perry G, Smith MA, Zhu X (2009a). The role of abnormal mitochondrial dynamics in the pathogenesis of Alzheimer's disease. J Neurochem 109: 153–159.

Wang X, Su B, Lee HG, Li X, Perry G, Smith MA *et al*. (2009b). Impaired balance of mitochondrial fission and fusion in Alzheimer's disease. J Neurosci 29: 9090–9103.

Wilhelm F, Hirrlinger J (2011). The NAD^+/NADH redox state in astrocytes: independent control of the NAD^+ and NADH content. J Neurosci Res 89: 1956–1964.

Wong E, Cuervo AM (2010). Autophagy gone awry in neurodegenerative diseases. Nat Neurosci 31: 805–811.

Woo NH, Teng HK, Siao CJ, Chiaruttini C, Pang PT, Milner TA *et al*. (2005). Activation of p75NTR by proBDNF facilitates hippocampal long-term depression. Nat Neurosci 8: 1069–1077.

Wu A, Ying Z, Gomez-Pinilla F (2004a). The interplay between oxidative stress and brain-derived neurotrophic factor modulates the outcome of a saturated fat diet on synaptic plasticity and cognition. Eur J Neurosci 19: 1699–1707.

Wu X, Zhu D, Jiang X, Okagaki Mearow K, Zhu G, McCall S *et al*. (2004b). AMPA protects cultured neurons against glutamate excitotoxicity through a phosphatidylinositol 3-kinase-dependent activation in extracellular signal-regulated kinase to up-regulate BDNF gene expression. J Neurochem 90: 807–818.

Xie H, Leung KL, Chen L, Chan YS, Ng PC, Fok TF *et al*. (2010). Brain-derived neurotrophic factor rescues and prevents chronic intermittent hypoxia-induced impairment of hippocampal long-term synaptic plasticity. Neurobiol Dis 40: 155–162.

Xu X, Zhan M, Duan W, Prabhu V, Brenneman R, Wood W *et al*. (2007). Gene expression atlas of the mouse central nervous system: impact and interactions of age, energy intake and gender. Genome Biol 8: R234.

Yang JL, Tadokoro T, Keijzers G, Mattson MP, Bohr VA (2010). Neuron s efficiently repair glutamate-induced oxidative DNA damage by a process involving CREB-mediated up-regulation of apurinic endonuclease 1. J Biol Chem 285: 28191–28199.

Youle RJ, Strasser A (2008). The BCL-2 protein family: opposing activities that mediate cell death. Nat Rev Mol Cell Biol 9: 47–59.

Young KW, Piñón LGP, Dhiraj D, Twiddy D, MacFarlane M, Hickman J *et al*. (2010). Mitochondrial fragmentation and neuronal cell death in response to the Bcl-2/Bcl-xL/Bcl-w antagonist ABT-737. Neuropharmacology 58: 1258–1267.

Yu L-Y, Saarma M, Arumae U (2008). Death receptors and caspases but not mitochondria are activated in the GDNF- or BDNF-deprived dopaminergic neurons. J Neurosci 28: 7467–7475.

Yulug B, Ozan E, Gonul AS, Kilic E (2009). Brain-derived neurotrophic factor, stress and depression: a minireview. Brain Res Bull 78: 267–269.

Zuccato C, Ciammola A, Rigamonti D, Leavitt BR, Goffredo D, Conti L (2001). Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. Science 293: 493–498.