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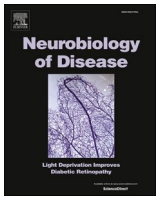

Review

Glucocorticoid impairs mitochondrial quality control in neurons

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ABSTRACT

Neurons are particularly vulnerable to mitochondrial dysfunction due to high energy demand and an inability to proliferate. Therefore, dysfunctional mitochondria cause various neuropathologies. Mitochondrial damage induces maintenance pathways to repair or eliminate damaged organelles. This mitochondrial quality control (MQC) system maintains appropriate morphology, localization, and removal/replacement of mitochondria to sustain brain homeostasis and counter progression of neurological disorders. Glucocorticoid release is an essential response to stressors for adaptation; however, it often culminates in maladaptation if neurons are exposed to chronic and severe stress. Long-term exposure to high levels of glucocorticoids induces mitochondrial dysfunction via genomic and nongenomic mechanisms. Glucocorticoids induce abnormal mitochondrial morphology and dysregulate fusion and fission. Moreover, mitochondrial trafficking is arrested by glucocorticoids and dysfunctional mitochondria are subsequently accumulated around the soma. These alterations lead to energy deficiency, particularly for synaptic transmission that requires large amounts of energy. Glucocorticoids also impair mitochondrial clearance by preventing mitophagy of damaged organelle and suppress mitochondrial biogenesis, resulting in the reduced number of healthy mitochondria. Failure to maintain MQC degrades brain function and contributes to neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and Huntington's disease. However, mechanisms of glucocorticoid action on the regulation of MQC during chronic stress conditions are not well understood. The present review discusses pathways involved in the impairment of MQC and the clinical significance of high glucocorticoid blood levels for neurodegenerative diseases.

1. Introduction

Mitochondria are multifunctional organelles that supply energy. The normal function of mitochondria is critical for cell survival, and dysfunction can result in cell apoptosis. The unique polarized morphology and energy demands of neurons necessitate mitochondrial transport to maintain synaptic plasticity in neurons. Mitochondrial function is strictly regulated by the mitochondrial quality control (MQC) system to ensure adequate energy supplies in brain tissue. If MQC is impaired, disrupted mitochondrial health results in dysfunctional neuronal metabolism, which is an early feature of several neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) (Yao et al., 2009; Reeve et al., 2018; Intihar et al., 2019; Wiedemann et al., 2002). Therefore, restoration of mitochondrial function is a key therapeutic strategy for preventing progression rather than removal of toxic molecules that appear in later stages of neurodegenerative diseases. For example, mitochondria-targeted antioxidant therapy is helpful for preventing cognitive and neuropathological progression in animal models of AD and PD (McManus et al., 2011; Langley et al., 2017). Elucidating the mechanisms of mitochondrial dysfunction that accompany neurodegenerative changes caused by certain stressors will assist the development of effective treatment strategies for neurodegenerative diseases.

Mitochondria respond to various stress mediators via two distinct neuroendocrine signaling pathways; the sympathetic adrenal medullary pathway (SAM) and the hypothalamic pituitary adrenal (HPA) axis. Activation of the SAM pathway is typically short-lasting and involves autonomic nervous system responses that result in increased circulating levels of epinephrine and norepinephrine derived from the adrenal medulla and sympathetic nerve terminals, respectively. The second stress response system is initiated in the hypothalamus and descends to the adrenal cortex via corticotrophin-releasing hormone. Glucocorticoid hormone (cortisol in human or corticosterone in rodents) release from the adrenal cortex is stimulated by

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Abbreviations

Aβ	Amyloid β
ACTH	Adrenocorticotropic hormone
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
Bcl-2	B-cell lymphoma 2
BNIP3	BCL2 interacting protein 3
BNIP3L/NIX	BCL2 interacting protein 3 like/NIX
CMA	Chaperone-mediated autophagy
Drp1	Dynamin-related protein
ER	Endoplasmic reticulum
GR	Glucocorticoid receptor
GRE	Glucocorticoid responsive element
Hap1	Htt-associated protein 1
HD	Huntington's disease
HPA	Hypothalamic pituitary adrenal
Htt	Huntingtin
KIF5	kinesin-related protein 5
Mfn	Mitofusion
MQC	Mitochondrial quality control
mtDNA	mitochondrial DNA
OPA1	Optic atrophy 1
ROS	Reactive oxygen species
SAM	Sympathetic adrenal medullary pathway
TRAK	Trafficking protein kinesin-binding
PD	Parkinson's disease
PGC1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PINK1	PTEN-induced kinase 1.

adrenocorticotropic hormone (ACTH). Unlike the SAM pathway, activation of the HPA axis by stress is slow and its physiological effects on metabolism, immune function, emotional state, and reproductive function are prolonged. Mitochondria allocate cellular resources to make stored energy available for meeting demands induced by stressful stimuli, particularly in tissues required for stress adaptation, such as the brain. ACTH activation in the adrenal gland induces steroidogenic acute regulatory protein to transport cholesterol across the mitochondrial membrane. This movement is the rate-limiting step in glucocorticoid productions. Cholesterol is converted to pregnanolone in the mitochondrial matrix and transferred to the endoplasmic reticulum (ER) where it is converted to 11-deoxycorticosterone (rodents) or 11-deoxycortisol (humans). Finally, 11β-hydroxylase makes corticosterone or cortisol in the mitochondrial matrix which is then released into the circulation. Mitochondria influence the cellular responses in the body and brain by adapting to local levels of glucocorticoids. However, chronic stress can lead to altered levels of HPA axis hormones and failure to response to stress ultimately results in negative impacts on cellular physiology. Further, chronic stress may produce physiological alterations that exceed the adaptability of mitochondria, inducing a condition termed as stress vulnerability. Failure to adapt to stress alters neural activity and brain shrinkage. Glucocorticoids, the primary stress-responsive steroid hormones, are the main cause of stress vulnerability. Acute and mild-to-moderate stress produces a protective glucocorticoid response that aids mitochondrial adaptation to stress and assists neuronal homeostasis. By contrast, chronic exposure of glucocorticoid is typically detrimental to the neural development/homeostasis, and may result in brain atrophy (Ma et al., 2017). An altered HPA axis, which produces hormones required for the normal stress response, is observed in various neurodegenerative diseases (Du and Pang, 2015). Long-term activation of the HPA-axis characterized by hypercortisolemia is highly correlated with mitochondrial abnormalities. Therefore, the treatment of hypercortisolemia reverses brain atrophy via restoring the ability of the HPA axis and mitochondria to appropriately cope with stress. The present review focuses on the ways via which long-term exposure of glucocorticoids affects mitochondrial dysfunction in neurons and produces subsequent neurodegenerative phenotypes.

1.1. Biphasic effect of glucocorticoids on neuronal mitochondria

Munck and Náray-Fejes-Tóth suggested that physiological responses of glucocorticoids follow a biphasic, inverted U-shape dose-response curve. Glucocorticoids thus show disparate effects depending on concentration, duration and frequency of release into the circulation (Munck and Náray-Fejes-Tóth, 1992). Glucocorticoids exhibit strengthening effects of synaptic functions at basal levels but show suppressive effects at high concentrations (Cain and Cidlowski, 2017). Many functions associated with stress responses such as lipolytic or glycogenolytic actions, immune response stimulation, growth promotion, and energy mobilization are triggered in various tissues by mild to moderate levels of glucocorticoids. By contrast, chronic and repeated exposure to high levels of glucocorticoids suppress inflammation-related cytokines, induce muscle-wasting, weaken bones, and promote hyperglycemia.

Glucocorticoids are widely known for biphasic effects in neural tissue. The acute stress response in the brain is essential for the survival and mobilization of energy stores to enhance neural plasticity. Glucocorticoids usually enhance synaptic functions such as synaptic transmission, long-term potentiation, and learning at this stage. However, increased amounts and frequency of glucocorticoid release produces a contrasting suppressive effect on synaptic function (Wiegert et al., 2005). Further, repeated or chronic stress adversely affects the brain morphological changes in dendritic spines and neurogenesis. These effects can lead to a reduction in neural plasticity and initiation of seizures, strokes, or head trauma (Cain and Cidlowski, 2017). Finally, pathophysiological levels of glucocorticoids induce brain aging with the accumulation of extra-synaptic glutamate and free radicals in the neurons and glia. Therefore, appropriate concentration and duration of glucocorticoids appear to be pivotal for maintaining normal function.

A relatively low concentration (physiological plasma concentration) of glucocorticoids is approximately between 7 and 35 ng/mL in humans. High concentrations, considered 'stress' levels, start at 70 ng/mL (Ábrahám et al., 2006). Glucocorticoid action is mediated by mineralocorticoid receptors at relatively low plasma concentration because this receptor has up to a 10-fold higher affinity for glucocorticoids than that of glucocorticoid receptor (GR). At high levels of glucocorticoids, effects are primarily controlled via GR (De Kloet et al., 2005; Kitchener et al., 2004). Glucocorticoids display both circadian and ultradian rhythms involving the occurrence of oscillation peak. These rhythms maintain the transcriptional activity of glucocorticoids to sustain normal levels of neuronal homeostasis. This action is mainly mediated by mineralocorticoid receptor even at peak levels of glucocorticoids (Oster et al., 2017). However, stress-induced increases in glucocorticoids activate a stress response that is not blocked by the mineralocorticoid receptor antagonist spironolactone.

Interactions between glucocorticoids and mitochondrial physiology also differ depending on the duration and concentration of glucocorticoids in neurons. Therefore, alterations in mitochondrial function related to neuroprotection can be differentially induced by varying doses and durations of exposure to glucocorticoids., i.e., glucocorticoids also show a biphasic effect towards mitochondrial function. Physiological levels of glucocorticoids enhance mitochondrial calcium holding capacity and membrane potential, both of which enhance energy production and maintains cytosolic Ca^{2+} levels (Nilsen and Brinton, 2003;

da Silva et al., 2020). Thus, mild-to-moderate stress shows neuroprotective effect via regulation of mitochondrial function. By contrast, under pathological doses of glucocorticoids, mitochondrial reactive oxygen species (ROS) production and reduced mitochondrial membrane potential are observed (Du et al., 2009a). Detrimental effects of glucocorticoids on mitochondria are exerted via the downregulation of binding between GR and cytoprotective protein B-cell lymphoma 2 (Bcl-2) in mitochondria; increased interaction between GR and Bcl-2 is observed under physiological levels of glucocorticoids. This downregulation caused by high levels of glucocorticoids results in alteration of mitochondrial function, such as reduced calcium buffering capacity. Another example of biphasic effects of glucocorticoids on transcription of mitochondrial DNA (mtDNA) also exists. The mtDNA includes 37 genes; some of these genes include glucocorticoid responsive element (GRE) sites recognized by mitochondrial GR (Du et al., 2009b). Acute and chronic stress produced different mtDNA gene expression in ChIP-sequencing data; rats with high levels of plasma glucocorticoids showed complex I deficits in the hippocampus, which is also observed in the progression of neurodegenerative diseases such as AD (Hunter et al., 2016). Therefore, glucocorticoids exhibit biphasic effects on mitochondrial function and are highly correlated with neuron survival (Du et al., 2009a).

1.2. Glucocorticoid signaling: genomic and nongenomic pathways in neuronal mitochondria

GR belongs to the superfamily of nuclear hormone receptors and is encoded by the gene *NR3C1*. GR is expressed in the cytosol, at the cellular membrane, and on mitochondria. In the genomic pathway, cytosolic GR translocates to the nucleus and binds to GRE and acts as a transcription factor for the regulation of cellular functions, including inflammatory cytokine production, glucose metabolism, and mitochondrial homeostasis (Mitre-Aguilar et al., 2015). For example, nuclear GR upregulates BAX expression, which destabilizes the mitochondrial outer membrane to decrease mitochondrial membrane potential and causes cytochrome *c* to be released into the cytosol (Zhang et al., 2006). Further, several reports have demonstrated that the existence of mitochondrial GR. Localization signal of mitochondria and nucleus signal are located at different domains of GR (Sionov et al., 2006). Furthermore, data from immunogold electron microscopy demonstrated that GR was located within the inner space of mitochondria both in human cells and rat brain (Moutsatsou et al., 2001; Scheller et al., 2000). Then, GR translocates to the mitochondrial matrix and acts as a transcription factor of mtDNA to modulate mitochondrial electron transport (Du et al., 2009b; Hunter et al., 2016; Psarra and Sekeris, 2011). By contrast, GR at the cellular membrane or on mitochondria alters cellular function independent from transcription. This process is considered the nongenomic pathway (Choi et al., 2018; Choi et al., 2017). The nongenomic pathway of glucocorticoids includes the binding of GR with Bcl-2 or BAX to regulate caspases or regulating various kinases that participate in mitochondrial function (Kassel et al., 2001). Therefore, the genomic and nongenomic pathways crosstalk to evoke stress responses at the cellular level to regulate various functions.

In the brain, glucocorticoids trigger various pathways to impair mitochondrial function. Low levels of glucocorticoids induce the hippocampus to release glutamate via the nongenomic pathway. Conversely, high levels of glucocorticoids inhibit presynaptic glutamate and GABA release via endocannabinoid formation (Hill and Tasker, 2012). Subsequently, glutamate binds to the NR2a subunit of the NMDA receptor associated with mitochondria to enhance calcium buffering capacity, which increases ATP production and neuroprotection (Gough, 2012). Conversely, other studies have indicated that glutamate-induced intracellular calcium signaling or ROS production culminates in mitochondrial dysfunction and neuronal cell death (Cassano et al., 2016; Kumari et al., 2012). These contradictory results can be related to the duration and concentration of glucocorticoids because there is a difference in the effects of the glutamate receptor trafficking process between acute and chronic exposure to glucocorticoids (Yuen et al., 2009; Yuen et al., 2011; Gourley et al., 2009). Moreover, glucocorticoids trigger the ligation between ER and mitochondria that affects mitochondrial calcium capacity and ATP production, inducing microtubule destabilization in hippocampal neurons and SH-SY5Y neuroblastoma cell lines (Choi et al., 2018). This process involves another nongenomic pathway of glucocorticoids. Genomic pathways of glucocorticoids also regulate neuronal mitochondria. Ligand-bound GR translocates into the nucleus or mitochondria and alters the mitochondrial biogenesis (Hunter et al., 2016). For example, nuclear GR has been found to directly regulate peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) expression in hippocampal neurons and SH-SY5Y cell lines. This factor is a master regulator of mitochondrial biogenesis. Moreover, GR also downregulates NF-κB and activator protein 1 that translocate into mitochondria and act as transcription factors (Psarra and Sekeris, 2011). GR can also translocate into mitochondria in the presence of ligands to alter mitochondrial gene expression. Cumulatively, glucocorticoids can negatively contribute to mitochondrial health in neuronal cells via various signaling pathways (Fig. 1).

1.3. Glucocorticoids and mitochondrial quality control

Mitochondria undergo constant mitochondrial dynamics, mitochondrial trafficking, mitophagy, and biogenesis; all of which interact with each system to maintain a healthy mitochondrial pool. Mitochondria are highly dynamic organelles that respond to various stress factors. It has been widely known that severe stress disrupts MQC and impairs mitochondrial homeostasis; however, it is less clear how glucocorticoids disrupt MQC at molecular levels. Therefore, we described below the importance of MQC in mitochondria maintenance and how MQC is disturbed by glucocorticoid exposure at molecular levels.

1.3.1. Mitochondrial dynamics

Mitochondria are dynamic organelles that undergo morphological changes via fission and fusion. In response to extracellular or intracellular stimuli, mitochondrial shape is altered into a tubular or fragmented form to adapt to energy demands and maintain MQC. Defects in the regulation of mitochondrial dynamics lead to ATP depletion and ROS production, followed by mitochondrial dysfunction. Therefore, an

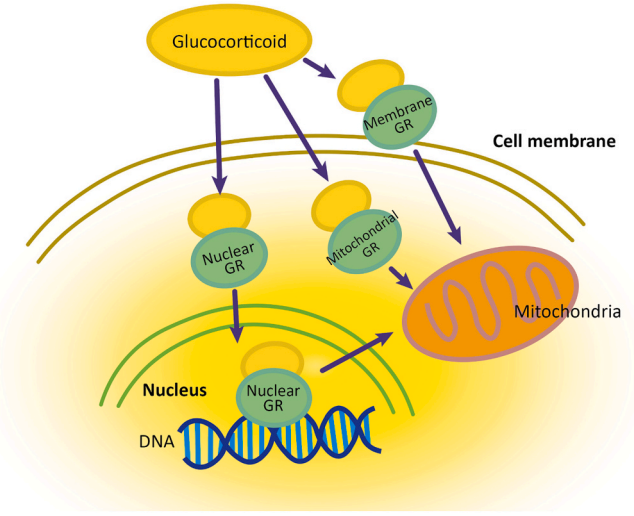

Fig. 1. The genomic and nongenomic pathways of glucocorticoid signaling affect mitochondrial function. Glucocorticoids attach to membrane GR or cross the membranes to bind to nuclear and mitochondrial GR for transcription of nuclear or mitochondrial DNA. This process is termed genomic pathway. Membrane GR activate second messengers to affect mitochondrial function. Furthermore, mitochondrial GR tether various organelles to alter mitochondrial function. These processes are called nongenomic pathway.

imbalance of mitochondrial dynamics is closely related to numerous neurodegenerative diseases (DuBoff et al., 2012; Mortiboys et al., 2010; Guedes-Dias et al., 2015).

Mitochondrial fusion typically occurs to facilitate the inter-complementation of mtDNA and the protection of mitochondria from various cellular stresses. Major proteins involved in mitochondrial fusion are the dynamin-related GTPases; mitofusion (Mfn) 1/2 on the outer mitochondrial membrane and optic atrophy 1 (OPA1) on the inner mitochondrial membrane. Mfn1/2 tethers membranes together via the formation of homo- or hetero- oligomers. OPA1 mediates inner membrane fusion and cristae remodeling with Mfn1/2 (Song et al., 2009). By contrast, mitochondrial fission is necessary for the elimination of aged or damaged mitochondria from the cell. But, mitochondrial biogenesis aids mitochondrial fission by increasing the number of mitochondria to supplement energy. Several main regulators are involved in mitochondrial fission. Dynamin-related protein (Drp1) is a large GTPase localized in the cytosol, but recruited to the mitochondrial outer membrane by several Drp1 adaptors such as Fis1, mitochondrial fission factor, and mitochondrial dynamics proteins of 49 and 51 kDa during fission (Osellame et al., 2016). Oligomerization of Drp1 at the outer membrane forms a ring-like structure and constricts mitochondria for asymmetric division (Kim et al., 2017).

Stress adaptation requires energy; circulating neuroendocrine factors guide adaptation in brain tissue that shows the greatest energy demand among the body organs (Picard et al., 2018). High levels of glucocorticoids acutely interact with GR to trigger processes to aid cellular homeostasis. Supraphysiological levels of glucocorticoid initially begin to promote moderate oxidation, maintain mitochondrial membrane potential, and promote Ca^{2+} sequestration; however, these actions for neuroprotection fail in neurons when exposure to glucocorticoid lasts (Picard et al., 2018). Subsequently, neurons usually respond to the lack of mitochondrial energy supply or damaged mitochondria by fragmentation of longer mitochondria into shorter globular organelles. For example, mitochondrial fission by Drp1 in injured motor neurons was induced after nerve injury for adaptive response (Kiryu-Seo et al., 2016). When the detrimental stress lasts, the inability of fragmented mitochondria to produce ATP ultimately impairs their role to chelate excess ROS or buffer intracellular Ca^{2+}, contributing to neurological pathology (Qi et al., 2011; Zemirli et al., 2018). Mitochondrial fission was also observed to increase in other tissue cells under glucocorticoids. In hepatoma cells, dexamethasone, a synthetic GR agonist, decreases Mfn1/2 and upregulates Drp1 and Fis1. Drp1 then modulates mitochondrial membrane fluidity to trigger ATP synthesis. The increase in ATP synthesis in response to glucocorticoids is a key factor for gluconeogenesis, which requires considerable amount of ATP and GTP (Hernández-Alvarez et al., 2013). Hyper-fission with the recruitment of GR into mitochondria was observed in the gut mucosa of a rodent stress model and culminated in mitochondrial dysfunction (De et al., 2017). However, the stimulatory effect of glucocorticoids on mitochondrial fission remains controversial. Dexamethasone was recently reported to suppress mitochondrial fission. Abnormal mitochondrial fusion with impaired energy generation by fission subsequently induced cell death in SH-SY5Y cells, presynaptic regions of the aging cortex, and dopaminergic neurons (Suwanjang et al., 2019; Hara et al., 2014; Pham et al., 2012; Tapias et al., 2017). Moreover, dexamethasone also induced Mfn1 and OPA1 expression, resulting in oxidative stress production and calcium deregulation in SH-SY5Y cells (Suwanjang et al., 2016). In other tissue cell types, dexamethasone also decreased Drp1 but increased Mfn2 proteins in adipocytes and mouse liver, suggesting that insulin-resistance was acquired via mitochondrial dysfunction (Troncoso et al., 2014). In other cases, glucocorticoids upregulate or downregulate both fission and fusion-related proteins simultaneously. Dexamethasone conversely downregulated both fusion and fission proteins in skeletal muscle via the AMPK/FOXO3 signaling (Liu et al., 2016). Few studies have demonstrated that glucocorticoids inhibit or promote both fusion and fission proteins in neurons.

The effects of glucocorticoids on mitochondrial dynamics are different. However, at high concentrations, glucocorticoids induce cell apoptosis through downregulating mitochondrial calcium buffering capacity and producing excessive mitochondrial ROS. Because glucocorticoids have a biphasic effect, the regulation of mitochondrial dynamics may vary depending on the concentrations and exposure times. As mentioned above, fission and fusion can increase to try to adapt to the stress situation by upregulating the number of mitochondria and protecting themselves, respectively. However, chronic exposure to high levels of glucocorticoids eventually direct mitochondrial shape into aberrant morphology, that is, the fission, according to the increase of the damaged mitochondria. Thus, fragmented mitochondrial will be observed a lot, which will lead to neurodegeneration. Following chronic exposure to stress or glucocorticoids, damaged mitochondria that failed to adapt to stress finally undergo fission to be cleared by MQC. Attempts to elucidate the effects of glucocorticoids on mitochondrial dynamics demonstrate that cells respond differently according to conditions and energy demands (Lapp et al., 2019; Picard et al., 2014). Biphasic effects of glucocorticoids or different responsiveness of cell types or brain regions render responses complicated, which leave the necessity of additional investigation to completely elucidate these processes (Du et al., 2009a; Du et al., 2009b).

1.3.2. Mitochondrial trafficking

Mitochondria are trafficked to where they are needed in response to local energy demand. Some parts of mitochondria in neurons are mobile. Many remain stationary, especially mitochondria localized in neuronal extremities where ATP demands are high for maintaining synaptic homeostasis, growth cones, and nodes of Ranvier (Zhang et al., 2010). Post-mitotic neurons must maintain an appropriate number of mitochondria near synapses and should rapidly degrade dysfunctional mitochondria via autophagy in the soma to avoid apoptosis signaling. Mitochondrial trafficking is thus strictly controlled (Lin et al., 2017; MacAskill and Kittler, 2010).

Microtubule-based mitochondrial movement is the major mechanism for organelle transport (Shen et al., 2018). Approximately half of the motile mitochondria move anterograde, away from the cell body. Mitochondria moving anterograde, and binding to motor protein kinesin, considered as new organelles required to meet synaptic energy demands. Conversely, mitochondria moving retrograde and binding to motor protein dynein are considered dysfunctional. However, recent studies have demonstrated that mitochondria moving retrograde are not always damaged or aged (Verburg and Hollenbeck, 2008). Several proteins that anchor mitochondria to motor proteins are found to link mitochondria and microtubules for efficient transport. Rho GTPases Miro 1/2 are outer mitochondrial membrane proteins that have two GTPase domains flanking two EF-hand Ca^{2+} binding domains and a transmembrane domain targeting mitochondria (Fransson et al., 2003). Binding to Ca^{2+} in Miro1/2 triggers a conformational change and detachment from mitochondria, and the motor protein-mediated mitochondrial motility is stopped (MacAskill et al., 2009). Owing to this trafficking system, mitochondria are appropriately localized. The motor adaptors for Miro are trafficking protein kinesin-binding 1 (TRAK1) and TRAK2. The latter is also known as Milton1/2 that binds to Miro and motor proteins (Barel et al., 2017; Modi et al., 2019). TRAK1 binds to both dynein and kinesin motor proteins, but TRAK2 only binds to dynein for retrograde movement. Members of kinesin-1 family, known as kinesin-related protein 5 (KIF5), are key regulators for mitochondria trafficking in neurons. Mammals have three KIF5 motor isoforms that bind to KIF5 receptor Miro and KIF5 adaptor TRAK1/2 to regulate mitochondrial movement. However, other proteins, such as synaptabulin, fasciculation and elongation protein zeta 1, and RAN binding protein 2 also interact with KIF5 and mediate anterograde mitochondrial trafficking (Ikuta et al., 2007; Cho et al., 2007). The Miro-TRAK1/2-dynein complex is critical in a retrograde movement to avoid mitochondrial accumulation in axon termini. Moreover, Arp11/Arp10p has

recently been reported to act as an important mediator for the retrograde movement of mitochondria in neurons (Mandal and Drerup, 2019). Miro1/2 interacts with Mfn2 to increase the microtubule-dependent mitochondrial motility, both anterograde and retrograde. Loss of Miro or Mfn2 halts mitochondrial movement and prevents the spread of dysfunctional mitochondria along neurons (Misko et al., 2010). Syntaphilin is another neuron-specific anchoring protein for mitochondria docking. These proteins keep the organelle stationary by bridging it with microtubules (Kang et al., 2008).

Another mechanism for mitochondrial movement is the actin cytoskeleton-dependent transport. Mitochondria-associated myosin, such as Myo19, is typically associated with increased mitochondrial motility (López-Doménech et al., 2018; Oeding et al., 2018). By contrast, myosin V and VI may have the contrasting role of resisting microtubule-based mitochondrial movement (Pathak et al., 2010). The myosin motor aids mitochondrial positioning and relatively short distance transport (Quintero et al., 2009). Considering the complexity of mitochondrial trafficking in neurons for distribution of organelles over long distances, an understanding of transport machinery is important for uncovering the dynamic life of mitochondria and the related neurodegenerative mechanism.

Stress normally induces motility arrest of mitochondria, forming hyperelongation or donut formation to aid cell survival at the early stage. However, chronic stressors finally cause substantial remodeling of mitochondrial morphology dominated by fission at the late stage in the various tissues including the brain (Eisner et al., 2018). Several mechanisms have demonstrated that glucocorticoids directly impair microtubule stability. Green et al. observed that hyperphosphorylation of tau was strongly triggered by glucocorticoids that can destabilize microtubules and reduce organelle trafficking in neurons (Green et al., 2006). Further, the ubiquitination of the microtubule destabilizing enzyme, stathmin 2, is reduced via glucocorticoid-mediated autophagy dysfunction in SH-SY5Y cells and the hippocampus (Choi et al., 2018). Therefore, kinesin-dependent mitochondrial trafficking is decreased and perinuclear clumping of mitochondria occurs. These findings are hallmarks of neurodegenerative diseases (Amadoro et al., 2014). Glucocorticoid effects on mitochondrial adaptor proteins include the downregulation of Mfn1/2 expression in neurons (Liu and Zhou, 2012). Chronic exposure to glucocorticoids promotes mitochondrial motility arrest and evokes a depression-like phenotype in a mouse. Further, Drp1 regulates dynein-based retrograde transport via interaction with the dynein-dynactin complex (Drerup et al., 2017). Reduction in Drp1 activity or expression by glucocorticoids would impair retrograde transport of mitochondria; however, the opposite could also occur. To date, the relationship between glucocorticoids and Miro1/2 or TRAK1/2 remains unclear. Uncovering the direct effect of glucocorticoids on mitochondrial adaptor proteins responsible for motility is necessary to reverse defects in mitochondrial distribution and motility.

Glucocorticoid increases oxidative stress that damages neurons by increasing intracellular levels of glutamate or calcium as well as by decreasing levels of antioxidant enzymes (Manoli et al., 2007). These ROS reportedly arrested mitochondrial motility. Debattisti et al. demonstrated that ROS induced p38α activation that inhibits TRAK and Miro complex binding to microtubules (Debattisti et al., 2017). Liao et al. also showed that ROS inhibited mitochondrial axonal transport via increasing neuronal Ca^{2+} levels and JNK activity (Liao et al., 2017). Another mechanism for mitochondrial arrest was triggered by extracellular glucose. Glucocorticoids induce gluconeogenesis and increase blood glucose levels, and extracellular glucose indirectly decreases mitochondrial motility (Pekkurnaz et al., 2014). Besides, excessive levels of glucocorticoids lead to a failure of the calcium buffering, thereby decreasing mitochondrial calcium buffering. Such stress vulnerability affects neuronal mitochondrial motility because Ca^{2+} levels play a pivotal role (Picard and McEwen, 2018). Disturbed homeostasis in levels of Ca^{2+} decreased mitochondrial motility and resulted in energy supply deficits.

Transport defects induced by glucocorticoids cause perturbation of mitochondrial turnover (Fig. 2). Abnormal turnover is one aspect of the pathology of numerous neurodegenerative diseases (Schon and Przedborski, 2011). Precise mechanisms of glucocorticoid modulation of mitochondrial transport in neurons will be necessary for the development of therapeutic strategies.

1.3.3. Mitophagy and mitochondrial biogenesis

Autophagy is a conserved non-selective lysosomal degradation pathway that involves the engulfment of cargo containing proteins or organelles to be degraded after delivery by a double-membrane organelle called an autophagosome. Autophagosomes are formed during trafficking; to neuronal soma along axons or dendrites. These organelles fuse with lysosomes to form autolysosomes (Evans and Holzbaur, 2020). Autophagy can be recruited in response to starvation to degrade proteins to amino acids as substrates for energy production. Further, autophagy participates in cell death, showing typical morphologies in dying cells. Therefore, autophagy is either a protective or detrimental mechanism depending on cell types, nature and extent of the injury, and cellular responses. Autophagic processes are classically categorized into three major subtypes; macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) (Redmann et al., 2016). Macroautophagy, a major pathway of autophagy, mostly involves selective and non-selective degradation of dysfunctional organelles including mitochondria, peroxisomes, ER, and ubiquitinated proteins. In microautophagy, lysosomes directly engulf and digest small amounts of cytosolic substrates (Oku and Sakai, 2018). CMA is a highly specialized form of autophagy degrading certain misfolded proteins such as amyloid β (Aβ) or α-synuclein with the help of heat shock cognate protein. CMA differs from other types of autophagy in that it does not require vesicular trafficking. Autophagy occurs differently depending on cell types. Basal autophagy is responsible for the continuous turnover of intracellular components and organelles whereas induced autophagy is mostly activated in response to stress. Thus, autophagy can randomly sequester and eliminate cytosol to maintain cellular homeostasis (Martinez-Vicente, 2017). Autophagy is also important in neuronal homeostasis because dysfunction in this process is strongly correlated with neurological disorders. The decreased autophagic function is evident in several neurodegenerative diseases that may be closely associated with accumulated toxic proteins. Further, mutations in autophagy-associated genes are observed to induce neurological diseases such as ALS, AD, and familial PD.

Damaged mitochondria in normal neurons undergo asymmetrical fission and are targeted by autophagosomes known as mitophagosome. Mitophagosomes return to the soma and fuse with lysosomes to form mitolysosomes, for subsequent degradation (Lin et al., 2017; Bhujabal et al., 2017). This selective autophagic process (mitophagy) maintains an appropriate number of healthy organelles in the mitochondrial pool. Although the process shares machinery with general autophagy, mitophagy initiation signals are different. Furthermore, mitophagy at distal neurons is observed when local damage exists at distal neurons. Lysosomal degradation at distal axons in PD is more likely to occur than in soma (Ashrafi et al., 2014). Further, transcellular mitophagy which means that neuronal mitochondria undergo mitophagy in adjacent astrocytes has been reported (Chung-ha et al., 2014; Gao et al., 2019). However, until recently, mitophagy was typically considered to be confined to the soma in most neurons.

Mitophagy can be largely classified into ubiquitin-dependent and ubiquitin-independent processes. Ubiquitin-dependent mitophagy can be categorized further as parkin-mediated and parkin-independent mitophagy. PTEN-induced kinase 1 (PINK1) is normally cleaved by various proteases in mitochondria. On mitochondrial membrane depolarization, PINK1 becomes stabilized and activated on the outer mitochondrial membrane. Activated PINK1 phosphorylates both ubiquitin and cytosolic E3-ubiquitin ligase parkin. Phospho-ubiquitin then binds with a high

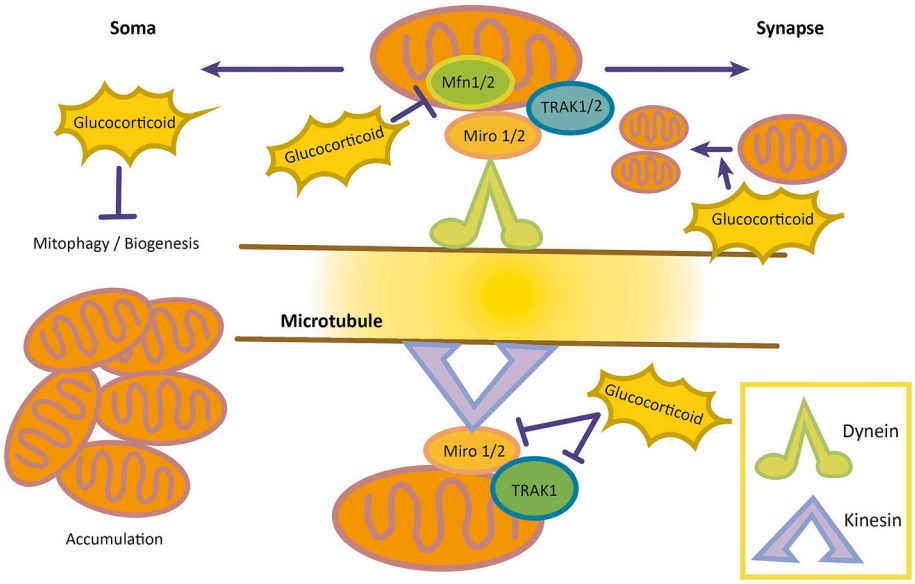

Fig. 2. Glucocorticoids impair mitochondrial trafficking and subsequently induce mitochondrial accumulation. Mitochondria move towards synapse or soma via kinesin or dynein-dependent trafficking along microtubules, respectively. Miro1/2 bridges dynein/kinesin to mitochondria with help from adaptor proteins, TRAK1/2 which tethers Miro 1/2 and mitochondria. Mfn1/2 also aids mitochondrial attachment to microtubules via interacting with Miro1/2. Glucocorticoids directly downregulate Mfn 1/2 via genomic pathway. Furthermore, glucocorticoids may indirectly inhibit Miro 1/2 and TRAK1/2 functions via altering mitochondrial calcium capacity. Glucocorticoids also suppress mitophagy induction and mitochondrial biogenesis, resulting in accumulation of aged or dysfunctional mitochondria in soma. Therefore, glucocorticoids arrest mitochondrial motility and subsequently induce perinuclear clumping.

affinity to phosphorylated parkin to trigger its conformational change and recruits parkin. Parkin polyubiquitinates several substrates such as voltage-dependent anion-selective channel, Mfn1/2, and Miro (Geisler et al., 2010; Tanaka et al., 2010; Wang et al., 2011). Other E3 ligases such as Gp78, SMAD specific E3 ubiquitin protein ligase 1, siah E3 ubiquitin protein ligase 1, and mitochondrial E3 ubiquitin protein ligase 1 can also recruit LC3 adaptors, such as optineurin, NDP52, and Tax1-binding protein1 to form mitophagosomes (Moore and Holzbaur, 2016; Zhang et al., 2015; Igarashi et al., 2020; Szargel et al., 2016). These E3 ligases can act independently from parkin-mediated mitophagy, but mediate parkin-dependent mitophagy (Lazarou et al., 2015). Ubiquitin-independent mitophagy is mediated by mitophagic receptors that do not require LC3 adaptors. Instead, it involves direct binding to LC3 via its LC3 interacting region motif (Palikaras et al., 2018). The BH3 domain containing mitophagic receptor proteins are BCL2/adenovirus E1B 19-kDa interacting protein 3 (BNIP3) and BNIP3 like (BNIP3L/NIX). These proteins are located on the outer membrane of mitochondria and are activated upon phosphorylation to bind to LC3. Furthermore, FUN14 domain-containing protein 1, BCL2L13, FK506-binding protein 8, prohibitin 2, and cardiolipin act as mitophagic receptors that interact with LC3. Mitophagic receptors independently induce mitophagy via the parkin-mediated pathway, however, recent research observed that NIX is highly associated with parkin-mediated mitophagy and other proteins also act as parkin substrates under specific conditions (Sarraf et al., 2013). Therefore, the interplay between ubiquitin-dependent and ubiquitin-independent mitophagy required extensive investigation.

Physiologically, mitophagy occurs constitutively, termed “basal/physiological” mitophagy. This process refers to continuous mitochondrial housekeeping. Regulation of basal mitophagy in long-lived or post-mitotic cells such as cardiomyocytes, renal tubule cells, and neurons is most important where energy demands are high (McWilliams and Muqit, 2017). PINK1/parkin-mediated pathways help ensure that mitochondrial integrity and function are maintained in some neurodegenerative diseases because proper and efficient elimination of damaged mitochondria serves as an early neuroprotective mechanism. PINK1-parkin induced mitophagy is mainly induced in pathological states, although other receptor-mediated mitophagy could compensate. However, PINK1 and parkin showed minor participation in basal mitophagy because physiological levels of parkin are insufficient to induce mitophagy (Kerr et al., 2017; Villa et al., 2018; Lee et al., 2018). The PINK1/parkin-mediated pathway compensates for acute, chemical insult-mediated mitochondrial dysfunction (Palikaras et al., 2018). In reality, numerous patients with neurodegenerative diseases exhibit suppression of receptor-mediated mitophagy, indicating that boosting basal mitophagy is a viable potential therapeutic target for neurological disorders. Two paradigms currently exist for the importance of basal mitophagy in neurological disorders, and further extensive investigation is necessary to identify appropriate therapeutic targets among various neurodegenerative diseases.

Information about the direct correlation between neuronal mitophagy and levels of glucocorticoids is scarce. Recently, Choi et al., demonstrated that glucocorticoids suppressed NIX-dependent mitophagy via repressing PGC1α expression in mouse hippocampal neurons and SH-SY5Y cells (Choi et al., 2021). These results are important that boosting PINK1-parkin pathway was not sufficient to compensate for the reduced mitophagy and basal mitophagy was solely responsible for maintaining MQC in neurons under glucocorticoids. This research suggested the new paradigm that MQC in neurons can be regulated through the enhancing NIX protein independently of PINK1-parkin-mediated mitophagy, not only dependent on hypoxia and parkin expression. Furthermore, glucocorticoids reduce PGC1α expression, which is also responsible for inducing mitophagy, in oligodendrocytes, followed by cell death (Trousson et al., 2009). In contrast, another study demonstrated that dexamethasone triggered parkin-mediated mitophagy, resulting in cardiomyocytes via LC3 recruitment and lysosomal aggregation (Zhou et al., 2020). The authors from this research with dexamethasone used physiological levels of glucocorticoids to treat the cells compared with the levels used in other studies that investigated high concentrations. Therefore, a state of prolonged severe stress can strongly and negatively affect mitophagy. The activation of mitophagy in neuronal cells in the presence of excess glucocorticoid may be an important therapeutic target for neurodegenerative disease.

After mitophagy, mitochondrial biogenesis normally follows to maintain the mitochondrial pool. The effect of glucocorticoids on the inhibition of mitochondrial biogenesis has been more investigated than that on the inhibition of mitophagy. Perinuclear clumping of mitochondria caused by glucocorticoids might imply a reduction in mitophagy and subsequent inhibition of the mitochondrial biogenesis, which is typically induced after mitophagy. Picard et al., and Manoli et al., explained that chronic exposure to glucocorticoids induced oxidative damage to neurons via the inhibition of mitochondrial biogenesis, ATP production, and mtDNA replication (Picard et al., 2018; Manoli et al., 2007). Glucocorticoids reduced mRNA levels of genes responsible for mitochondrial biogenesis such as PGC1α, sirtuin 1,

nuclear respiratory factor 1, and brain-derived neurotrophic factor in various tissue (Yu et al., 2014; Lee et al., 2013; Jeanneteau et al., 2018). These genes also participate in upregulating mitophagy-associated proteins, including PINK1, parkin, and NIX. Moreover, glucocorticoids damage mtDNA via mutation and deletion. Altered mtDNA induces mitochondrial damage, which is not followed by mitophagy that would normally be activated (Picard and McEwen, 2018). Further, Mfn1/2 and SOD1/2 that participate in mitophagy are downregulated by chronic exposure to corticosterone and stress. These actions cause mitochondria to become stationary and unlikely to undergo mitophagy (Jha et al., 2017). Cumulatively, the MQC is impaired by chronic stress, resulting in neurodegenerative diseases (Picard et al., 2014).

1.4. Glucocorticoid-induced mitochondrial dysfunction and neurodegenerative diseases

1.4.1. Alzheimer's disease

AD is a chronic neurodegenerative disease that causes 60%–70% of the cases of dementia due to the accumulation of amyloid plaque and fibrillary tangles. Characteristics of the affliction are severe issues with learning and memory. Nowadays, mitochondrial dysfunction has been suggested to play a primary role in the development of neurodegenerative disease or contribute to disease progression (Flannery and Trushina, 2019). Thus, mitochondria-targeted therapeutics are emerging to prevent the exacerbation and treat the early stage of neurodegenerative diseases. Dysfunction in MQC also results in the accumulation of damaged mitochondria and subsequent AD pathogenesis. For example, reduced fusion protein expressions but increased expression or activity of fission proteins were observed in the AD brain (Wang et al., 2009). Similarly, an increase in S-nitrosylation of Drp1 mediates mitochondrial fission, contributing to the pathogenesis of AD (Cho et al., 2009). Furthermore, compromised autophagy and mitophagy were observed in the AD brain. Mutations in gene for the presenilin 1 disrupt lysosomal proteolysis and therefore inhibit mitochondrial clearance (Lee et al., 2010). Mitochondrial biogenesis is also thought to be impaired in AD. The proteins regulating mitochondrial biogenesis such as NRF1/2, TFAM, and PGC1α were reduced in the hippocampus of the AD brain (Qin et al., 2009; Sheng et al., 2012). Therefore, boosting MQC system maintains efficient functional mitochondria against AD causes. To prevent AD progression, caloric restriction or exercise are often used clinically as adjuvant treatments to improve mitochondrial biogenesis and mitophagy (Onyango et al., 2016).

Glucocorticoids are known to directly trigger AD via increasing expression of beta-secretase 1 and hyperphosphorylation of tau (Choi et al., 2017; Green et al., 2006). Prolonged severe stress which releases high levels of glucocorticoids is therefore a major etiology of AD. Long term glucocorticoid treatment for anti-inflammatory/immunosuppressive therapy can also increase the risk of AD. A low-dose regimen of glucocorticoids (less than 60 mg of hydrocortisone daily or its therapeutic equivalent in other glucocorticoids) was shown to be not useful in the treatment of inflammation of the AD brain and even triggered behavioral decline compared to those with placebo treatment (Aisen et al., 2000). As AD patients primarily suffer from hypercortisolemia due to dysregulation of the HPA axis, long term glucocorticoid treatment for therapeutics can exacerbate AD pathology (Notarianni, 2013). After AD progressed, deficiency in intracellular GR does not help alleviate inflammation. Rather, glucocorticoid resistance induces neuroinflammation through microglia activation in that the anti-inflammatory function of prednisone may not be effective (Ros-Bernal et al., 2011). Therefore, severe stress or glucocorticoid therapy should be avoided for preventing AD progression.

Besides directly involved in APP processing, glucocorticoid-induced mitochondrial dysfunction can be an early pathological feature of AD because the hippocampus displays the most GRs among the brain regions and is vulnerable to chronic exposure to glucocorticoids. The hippocampus is among the first areas affected in AD, and the effect of glucocorticoids on mitochondria is a risk factor for AD (Canet et al., 2020). Prolonged hyperglycemia induced by high levels of glucocorticoids alters mitochondrial morphology causing excessive fragmentation and neuronal apoptosis (Lee et al., 2004; Medikayala et al., 2011). Moreover, chronic stress decreases OXPHOS gene expression via reduced mitochondrial GR trafficking, thereby altering mtDNA transcription. Accumulation of reactive species in numerous brain regions, reduction in mitochondrial membrane potential, and decrease in calcium buffering capacity alter mitochondrial physiology. The activation of caspase 3 driven by glucocorticoid-induced mitochondrial damage, such as excessive fission, increases the ratio of BAX to Bcl-2 and triggers tau aggregation, leading to AD progression (Vyas et al., 2016). Further, increased Aβ accumulation in mitochondria typically activates mitophagic machinery for removal of dysfunctional mitochondria; however, mitophagy is typically blocked by high levels of glucocorticoids, which in turn exacerbates Aβ-induced hippocampal toxicity. Therefore, glucocorticoids might trigger AD via various signaling pathways disrupting MQC in the hippocampus.

1.4.2. Parkinson's disease

PD is a neurodegenerative disease that mainly affects the motor system. Major signs are tremor, rigidity, and difficulty walking. Substantial loss of dopaminergic neurons in the substantia nigra pars compacta with significant dopamine deficiency is representative of PD. Postmortem PD brains showed the presence of Lewy bodies, large aggregates of misfolded α-synuclein protein. Mitochondrial dysfunction is typical for PD because genes associated with familial PD (5%–10% of the cases) such as α-synuclein, leucine-rich repeat kinase 2, parkin, PINK1, ATPase 13A2, vacuolar protein sorting-associated protein 35, and coiled-coil-helix-coiled-coil-helix domain containing 2 are highly regulated in mitochondrial biology (Grünewald et al., 2019). Further, sporadic PD occurs due to undetermined genetic or environmental factors. Factors that evoke mutations or upregulations/downregulations of familial PD genes in dopaminergic neurons can become environmental factors of PD. Examples include oxidative stress, iron accumulation, MQC failure, mitochondrial biogenesis reduction, and dysfunctional electron transport (Reeve et al., 2018). Failure to maintain MQC leads to the degeneration of dopaminergic neurons in PD patients. Sporadic PD induces α-synuclein aggregation and reactive chemical species production, resulting in the inactivation of parkin (Wang et al., 2011; Ge et al., 2020; Glauser et al., 2011). Both PINK1 and parkin facilitate degradation of mitochondrial fusion proteins Mfn1/2 and drives fission through upregulating the activity of fission protein and decreasing trafficking proteins such as Miro 1/2; however, the inactivated PINK-parkin pathway arrests the damaged mitochondria and slows the turnover of mitochondrial proteins (Pryde et al., 2016). With the removal of dysfunctional mitochondria by the PINK1-parkin pathway, mitochondrial biogenesis subsequently occurs because PINK1-parkin pathway triggers the expression of PGC1α (Stevens et al., 2015; Shin et al., 2011). However, suppression in this pathway by PD pathogenesis decreases mitochondrial turnover, resulting in the reduction of MQC.

Glucocorticoids are also a risk factor for dopaminergic neuronal degeneration. Patients with PD show higher plasma cortisol levels compared with control subjects because the HPA axis is unbalanced. Hypercortisolemia diminishes microglial activation and removes this source of protection from dopaminergic neurons (Herrero et al., 2015; van den Heuvel et al., 2020). Similarly, glucocorticoids are observed to increase the susceptibility of substantia nigra dopaminergic neurons to MPTP toxicity via regulating GR in astrocytes (Maatouk et al., 2019). Moreover, glucocorticoids trigger PD by impairing mitochondrial function. Glucocorticoids evoke mitochondrial dysfunction, deregulate intracellular calcium levels, cause oxidative stress, and damage proteostasis related to α-synuclein aggregation in PD (Corti et al., 2011). Glucocorticoids can regulate MQC by altering Mfn1/2 expression, PINK1-parkin-mediated mitophagy, and Miro1 activation, all of which are strongly correlated with PD. Chronic levels of glucocorticoids

worsen the motor deficits and neurodegeneration in nigrostriatal system; however, the precise mechanism of high levels of glucocorticoids in motor control following nigrostriatal lesions via mitochondrial dysfunction remain unclear (Smith et al., 2002). However, PD models with dexamethasone treatment maintained optimal levels showed better motor activity through its anti-inflammatory actions (Ham et al., 2017; Castano et al., 2002). But in reality, epidemiological studies showed that PD patients did not show enhanced motor activity and maintaine catecholamine against depletion when exposed to glucocorticoids for anti-inflammation (Singh et al., 2007; Bartels and Leenders, 2007). These effects only correspond to the early stages of PD because severe side effects such as chronic inflammation with the long-term use of glucocorticoids is unable to be a neuroprotective therapy in PD patients, replacing the NSAIDs for alleviating neuroinflammation (Ros-Bernal et al., 2011; Hirsch and Hunot, 2009).

1.4.3. Huntington's disease

HD is an inherited disorder that results in the degeneration and death of nerve cells in the central area of the brain. The disease causes movement, mood, cognition, and psychiatric disorders. An autosomal dominant mutation in the huntingtin (Htt) gene causes the synthesis of the polyglutamine tract and mainly triggers mitochondrial dysfunction, oxidative and metabolic stress, and ion-channel alterations. Deficiency in mitochondrial protein transport is induced by the inactivation of GAPDH with mutated Htt and thereby mtDNA damage and deletion are reported in HD brains (Jha et al., 2017). The dysfunction of MQC in HD brains can be also observed. Increased expressions of the fission proteins and downregulated fusion proteins were induced by HD, resulting in excessive mitochondrial fission (Shirendeb et al., 2011). Mutant Htt aggregates also reduced mitochondrial trafficking and disrupted neuronal transport culminated in neurodegeneration (Chang et al., 2006). However, mitochondrial clearance was inhibited because mutated huntingtin proteins reduced the mitophagosome formation by mitophagy receptors, resulting in the accumulation of damaged mitochondria (Franco-Iborra et al., 2020). Transcriptional dysregulation and mitochondrial damage are interconnected processes in HD via the reduction in PGC1α among other several dysregulated proteins (Intihar et al., 2019; Bano et al., 2011). Restoration of this protein is likely to restore neurodegeneration via the activation of mitochondrial biogenesis and receptor-mediated mitophagy.

Similar to AD and PD, hyperactivity of the HPA axis and increased cortisol levels have been reported in HD patients (Hubers et al., 2015; Aziz et al., 2009). Therefore, HPA axis hyperactivity can be an early feature of HD and long-term usage of glucocorticoid therapy also exacerbates HD progression. As mentioned above, glucocorticoids reduce PGC1α protein, accelerating the progression of HD by decreasing mitophagy and mitochondrial biogenesis. Htt-associated protein 1 (Hap1) binding to Htt protein stabilizes GR in mouse hypothalamic neurons. Moreover, glucocorticoid treatment in mice resulted in increased expression of Hap1, which strengthens glucocorticoid action in HD (Chen et al., 2020). Unlike AD and PD, HD is a genetic disorder, and glucocorticoids play a role in the exacerbation of HD. The development of a novel approach to reduce levels of glucocorticoids, which are elevated in HD mouse models may delay the progression of the disease (Dufour and McBride, 2019).

2. Conclusion

Mitochondria are essential for sustaining energy homeostasis and cellular survival, particularly neurons that have unique morphology and demand tremendous energy. Therefore, elucidation of MQC via the interplay among mitochondrial dynamics, trafficking, clearance, and biogenesis is critical for understanding the effect of mitochondrial energy production in locations such as synapses, on neuronal physiology and subsequent brain responses.

Considerable attention has been devoted to the impact of stress on the mitochondrial function that is regarded as a pivotal environmental factor for neurological disorders. However, this review presented a pathophysiological understanding of the interplay between specific aspects of mitochondrial functions and stress-induced glucocorticoid action, which have not been clearly investigated. The brain adapts to stress via the induction of multiple signaling cascades. The major stress-induced steroid hormone glucocorticoids also induce various signaling pathways depending on concentration and receptor distribution. Therefore, we described that glucocorticoids appear to show an inverted U-shape effect including both protective and detrimental effects on MQC (Fig. 3). Numerous studies demonstrated that chronic exposure to high levels of glucocorticoids induces ROS production that leads to mtDNA damage and degradation of mitochondrial membrane potential. We put our efforts to describe that these changes finally culminated in the disruption of MQC. We explained that glucocorticoids trigger instability in mitochondrial dynamics, thereby dysregulating morphological control through various mechanisms. Furthermore, impaired MQC owing to deficient trafficking/removing of dysfunctional mitochondria and mitochondrial biogenesis through genomic and nongenomic mechanisms contributes to mitochondrial allostatic load, indicating that mitochondria can no longer maintain homeostasis. This process contributes to increasing allostatic load. Defining cellular mechanisms of the detrimental effects of chronic stress on mitochondrial health and related neuronal responses promotes an understanding of the suppression of MQC and associated strategies for treating neurological disorders. In addition to the numerous glucocorticoid-dependent targets for restoring MQC we have described, future studies should systemically investigate the implications of multifaceted regulation by glucocorticoids on neuronal mitochondrial functions to develop innovative interventions for ameliorating the current burden of neurodegenerative diseases including AD, PD, and HD.

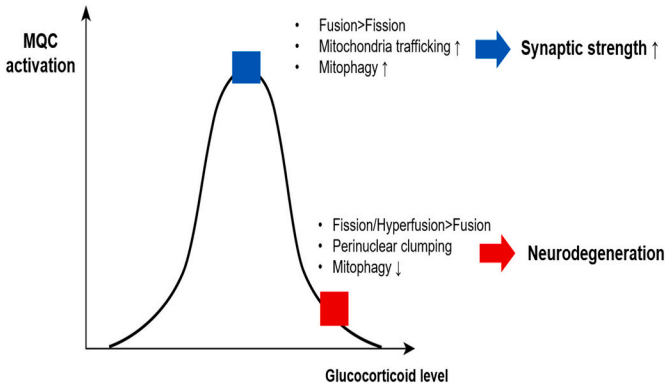

Fig. 3. Biphasic effects of glucocorticoids on MQC following inverted U-shape curve. Glucocorticoid is necessary to maintain cell homeostasis. Under physiological to mild stress-induced glucocorticoid levels, MQC activation is induced. As a result, the fusion of mitochondria is more likely to appear than fission. Further, transport of healthy mitochondria into the synapse and aged/damaged mitochondria towards soma for degradation via mitophagy occurs, resulting in the enhancement of synaptic strength. In contrast, chronic exposure of high glucocorticoids reverses these effects. Fission or hyperfusion overwhelms the mitochondrial fusion. Glucocorticoids also arrest mitochondrial trafficking, which induces perinuclear clumping and suppresses mitophagy. Thus, the exacerbation of neurodegeneration follows the failure of MQC.

Author contributions

G.E. Choi and H.J. Han contribute to literature research and drafted work.

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Declarations of interest

The authors declare no competing financial interests.

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