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REVIEW ARTICLE

Mitochondria and Synaptic Plasticity in the Mature and Aging Nervous System

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Abstract: Synaptic plasticity in the adult brain is believed to represent the cellular mechanisms of learning and memory. Mitochondria are involved in the regulation of the complex processes of synaptic plasticity. This paper reviews the current knowledge on the regulatory roles of mitochondria in the function and plasticity of synapses and the implications of mitochondrial dysfunctions in synaptic transmission. First, the importance of mitochondrial distribution and motility for maintenance and strengthening of dendritic spines, but also for new spines/synapses formation is presented. Secondly, the major mitochondrial functions as energy supplier and calcium buffer organelles are considered as possible explanation for their essential and regulatory roles in neuronal plasticity processes. Thirdly, the effects of synaptic potentiation on mitochondrial gene expression are discussed. And finally, the relation between age-related alterations in synaptic plasticity and mitochondrial dysfunctions is considered. It appears that memory loss and neurodegeneration during aging are related to mitochondrial (dys)function. Although, it is clear that mitochondria are essential for synaptic plasticity, further studies are indicated to scrutinize the intracellular and molecular processes that regulate the functions of mitochondria in synaptic plasticity.

Keywords: Aging, ATP, calcium, learning and memory, long-term potentiation, mitochondria, synaptic plasticity.

INTRODUCTION

Neuronal plasticity can be defined as structural and functional adaptations of neuronal circuits to changes due to learning and memory, environmental influences and brain damage [1, 2]. These dynamical processes in the neuronal system underlie the ability of the brain to change and to behaviourally adapt to a continuous changing environment. The two most important examples of neuroplasticity are long-term potentiation (LTP) and long-term depression (LTD) [3]. Both neurophysiological features can be found in neuronal synapses in response to a brief repeated stimulation. The cellular and molecular mechanisms behind this structural and functional changes of the neuronal network include pre- and postsynaptic neurotransmission alterations, cytoskeletal remodelling, membrane trafficking, gene transcription, protein synthesis and activation [4-7].

LTP is also assumed to be the cellular mechanism of learning and memory [8, 9]. Several studies have documented that changes in mitochondria, vital organelles presented in all eukaryotic cells, occur during synaptic activation and LTP [9]. For example, during LTP, mitochondrial energy production changes [10], mitochondrial calcium pump activity increases [11] and mitochondrial gene expression is enhanced [12].

The mitochondria are essential organelles found in all eukaryotic cells that are composed of compartments with specialized functions [13]. Mitochondria consist of outer membrane, intermembrane space, inner membrane and internal matrix. The outer and inner mitochondrial membrane have different properties. The outer mitochondrial membrane contains large numbers of integral proteins called porins. These porins form channels that allow small molecules (<500 Da) to freely diffuse from one side of the membrane to the other. In contrast, the inner membrane is not freely permeable, under physiological conditions. However, it contains specific transport proteins that regulate metabolite passage into and out of the matrix. Also, diverse proteins with different functions, including those involved in the electron transport chain and ATP synthesis [2].

The most prominent role of mitochondria is to produce cellular energy, in form of ATP through respiration, and to regulate cellular metabolism. Another important function of mitochondria in neurons is the regulation of calcium and redox signalling [14]. Mitochondria are able to remove calcium from the cytoplasm, in response to calcium influx into the cell and may also release calcium in response to certain stimuli [15, 16].

Given the oxidative, metabolic, and calcium buffering functions of the mitochondria, they are candidates to regulate

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and modify synaptic transmission and thus also related processes of functional and structural plasticity. For that matter, multiple lines of evidence have suggested that synaptic function and plasticity depend on mitochondria [2, 17-21].

A reciprocal influence between alteration of mitochondrial functionality and synaptic activity has already been reported for peripheral synapses [22]. Several pharmacological studies have revealed that the inhibition of mitochondrial activity results in impaired synaptic potentiation and neurotransmission [23, 24]. Acutely blocking mitochondrial function during intense stimulation also leads to depressed synaptic transmission [25, 26], whereas an increase in synaptic density is promoted *in vitro* through pharmacological enhancement of mitochondrial respiration [27]. These and other studies, which will be discussed here, suggest that mitochondria not only respond in various ways to synaptic activity but also regulate synaptic plasticity [16].

Here we review that mitochondria play important roles in regulating adult neuroplasticity. More specifically, we will discuss the role of mitochondria for dendritic spine growth and synaptogenesis, how mitochondrial ATP production and calcium buffering regulate neuroplasticity, and the relation between synaptic plasticity and mitochondrial gene expression. Finally, we review the role of mitochondrial dysfunctions on synaptic plasticity during aging.

DENDRITIC MITOCHONDRIA AND SYNAPTO-GENESIS

Synaptic plasticity in the mature nervous system involves structural and morphological modifications, such as dendritic spine growth and synaptogenesis [16, 28]. These modifications are the cellular response to changes in neuronal activity and are believed to be responsible for learning and memory [29, 30]. Mitochondria are present in axonal terminals and dendrites of neurons and are assumed to play a prominent role in synaptic plasticity [16].

Neuronal mitochondria are highly dynamic organelles that divide, fuse, and move purposefully within the different cell compartments of the neuron. The mitochondrial transport throughout the neuron and the recruitment of mitochondria to regions with high metabolic demands are essential for the proper functions of the neuronal network [14]. In dendrites, mitochondria are located mainly in the dendritic shafts and are also found to be associated with spines [31-33]. In response to synaptic stimulation, mitochondria redistribute toward dendritic protrusions and enhance their activity. It has been shown that the number of dendritic mitochondria increases simultaneously with synapse and spine morphogenesis, either following repetitive depolarization or in response of local electrical stimulation [27].

As reported by Li *et al.* [27], reducing the dendritic mitochondrial content led to loss of synapses and spines, whereas the number of spines and synapses significantly increased by accumulation of mitochondria in the dendrites. Furthermore, recent *in vitro* studies showed that the reduction of dendritic mitochondrial content through increased mitophagy leads to inhibition of dendrite growth during neuronal polarization [18] and to dendrite shortening in mature neuronal cultures [34]. Taken together, sufficient dendritic mitochondrial content is required for proper development and maintenance of dendrites, as well as synapse- and spine-formation.

Synaptic excitation affects the motility and subcellular distribution of mitochondria in dendrites. Electric stimulation in hippocampal organotypic slice culture leads to enlargement of the dendritic spines and recruitment of mitochondria to the active side [27]. On the other side, new spine and synapse formation is, in turn, enhanced by aggregation of mitochondria in dendrites [27]. Thus, there are mechanisms for mutual regulation of synaptic plasticity and mitochondrial distribution and activity.

Although these various functions and features of mitochondria are described, the functional role of mitochondria in dendritic protrusions remains to be determined. As in axonal growth cones [35], it is possible that changes in ATP demand and required calcium buffering capacity underlie the number of mitochondria in growing spines.

MITOCHONDRIAL ATP AND SYNAPTIC PLASTICITY

In every biological system energy supply is fundamental in a wide range of cellular function. Neuronal functions supported by mitochondrial ATP production also include the assembly of the actin cytoskeleton for the development of pre- and postsynaptic compartments, membrane potential generation, synaptic vesicle recruitment and release, as well as protein phosphorylation reactions [33, 36-38]. All of these processes are critical for neuroplasticity and can be modified by changes in ATP production and release [9]. Mitochondria play important roles in controlling the complex processes of neuroplasticity, including neurotransmitter release and dendritic remodelling by generating energy in the form of ATP [2, 33].

As mentioned above, LTP (enduring increase in neuronal excitability) is an established experimental model of the cellular mechanisms of learning and memory [8]. Blocking the mitochondrial oxidative phosphorylation, the metabolic pathway in which mitochondria produce ATP, leads to significant impairment of LTP [39]. Uncoupling the respiratory chain from the oxidative phosphorylation by carbonyl cyanide-4-(trifluoromethoxy) phenylhydrazone (FCCP) but also inhibiting the mitochondrial complex I by rotenone in synaptosomes led to reduced amplitude of synaptic vesicle release as a result of dysfunctional mitochondria and impaired ATP production [20]. Furthermore, Verstreken *et al.* [37] demonstrated in Drosophila neuromuscular junctions that the recruitment of reserve synaptic-pool vesicles is sufficient for the maintenance of normal neurotransmission during intense stimulation and depends on mitochondrial ATP production. A lack of synaptic mitochondria as well as application of oligomycin, an inhibitor of mitochondrial ATP production, resulted in a disability to mobilize reserve pool vesicles, which was partially rescued by addition of ATP [37]. These findings suggest that mitochondrial energy production is critical not only for a proper transmitter release *via* vesicle exocytosis, but also for mobilization of reserve synaptic-pool vesicle and regulation of synaptic strength (see Fig. **1**).

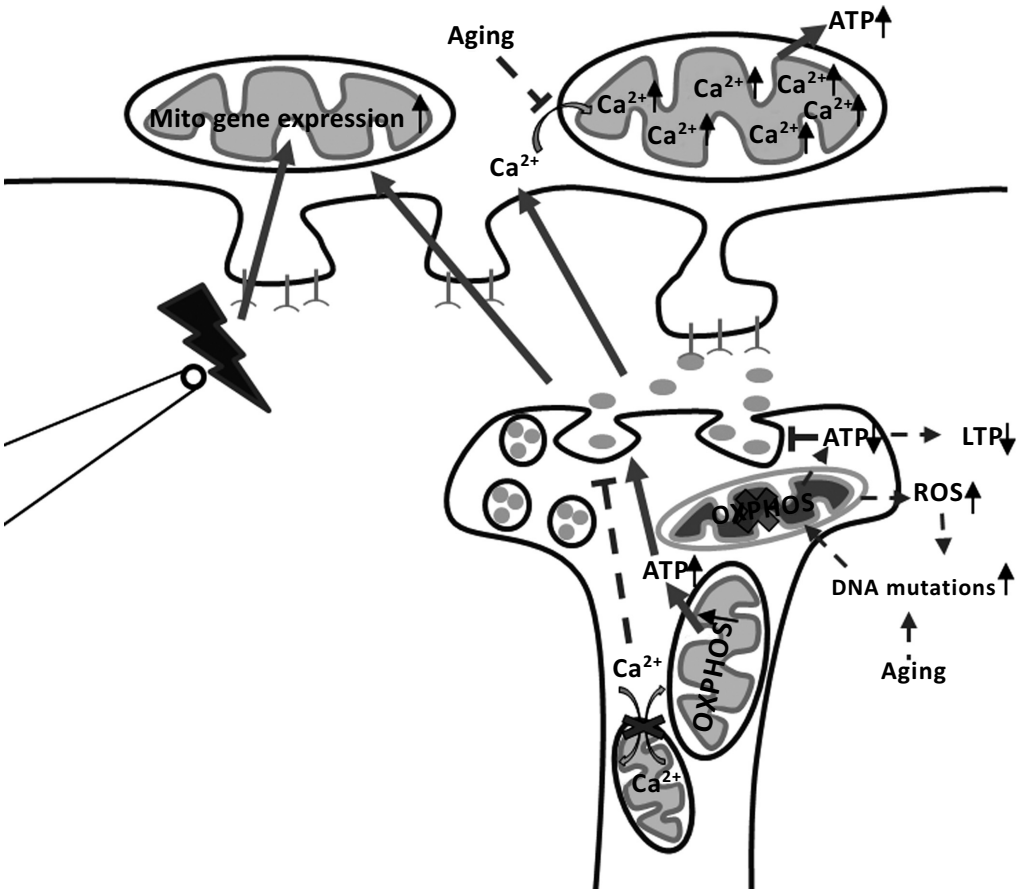

Fig. (1). Mitochondrial function in adult synaptic plasticity. Long-term potentiation (LTP) (effects indicated by solid lines) leads to enhanced mitochondrial respiration and thereby ATP production. Cellular ATP concentration influences, on its side, neurotransmitter release. On the other hand, blocking the mitochondrial oxidative phosphorylation (OXPHOS) leads to decrease in ATP levels, drop in neurotransmitter release and significant impairment of LTP. Furthermore, inhibition of the mitochondrial calcium uptake and release machinery results also in impaired synaptic neurotransmission. On the postsynaptic side, mitochondrial calcium uptake as well as mitochondrial gene expression increase following high-frequency stimulation (indicated by and electrode) resulting in enhanced energy production. Therefore, mitochondria play important role in controlling synaptic activity by generating energy in the form of ATP and regulating the intracellular calcium homeostasis.

Aging (effects indicated by dashed lines) results in increased incidence of DNA mutations. Certain DNA mutations lead to alteration in OXPHOS resulting in decreased ATP production and impaired LTP. In addition, DNA mutations increase reactive oxygen species (ROS) levels and oxidative stress. In parallel, high levels of ROS cause DNA mutations resulting in mitochondrial damage, which is a vicious circle. Furthermore, aging is associated with a loss of calcium uptake capacity of mitochondria. This leads to alterations in calcium homeostasis and a decrease in ATP production. Therefore, aged-related LTP deficits can be partially explained by mitochondrial dysfunctions associated with DNA mutations.

Signalling molecules such as glutamate and brain-derived neurotrophic factor BDNF regulate synaptic plasticity and also modify cellular energy metabolism [40, 41]. Glutamate plays critical roles in synaptic plasticity by activating receptors coupled to calcium influx [16]. It also regulates downstream signalling-pathways *via* activation of kinases (such as PKA, PKC and ERKs) and transcription factors that are important for long-term alterations of plasticity [42]. The protein activation processes are often ATP-dependent and glutamate also stimulates an increase in mitochondrial oxygen consumption and thereby ATP production [16, 43]. BDNF in turn modifies synaptic plasticity and has been shown to play a crucial role in hippocampus-dependent learning and memory [44]. BDNF could promote synaptic plasticity, in part, by enhancing mitochondrial energy production through increase of glucose utilization [45] and mitochondrial respiratory coupling at Complex I [46, 47]. Furthermore, a recent study showed that BNDF-signalling regulates mitochondrial transport and localization. In cultured hippocampal neurons, application of BDNF led to reduced mitochondrial motility in the axon and accumulation of mitochondria at presynaptic sites followed by an enhancement of the synaptic transmission [17].

In summary, ATP is essential for several cellular mechanisms that are associated with different processes in synaptic plasticity. Experimental studies show that mitochondria play a role in neurotransmitter release *via* vesicle exocytosis, but also reserve pool vesicles mobilization and protein phosphorylation reactions. Mitochondrial energy production (ATP levels) is also influenced by signalling pathways that regulate synaptic plasticity (see Fig. **1**). The available evidence indicates that the mitochondrial ATP production is homeostatically linked to synaptic plasticity.

However, how mitochondrial energy metabolism and neuronal plasticity are inter-related requires further systematic studies.

MITOCHONDRIAL CALCIUM BUFFERING

Synaptic mechanisms of plasticity are besides ATP also calcium-dependent processes. Reduction of extracellular calcium as well as intracellular injections of the calcium binding ethylene glycol tetraacetic acid (EGTA) block the induction of LTP in hippocampal neurons [48, 49]. Furthermore, a persistent increase in the uptake and retention of calcium parallels hippocampal LTP [50]. Indeed, cellular, and specifically mitochondrial, calcium-buffering could be very important in LTP expression.

The regulation of calcium concentration in neuronal cells is provided by plasma membrane pumps, cytoplasmic buffers, and two intracellular organelles: mitochondria and endoplasmic reticulum [51]. It has been shown that an increase in mitochondrial pump activity is associated with hippocampal LTP: mitochondrial calcium uptake was persistently increased after the induction of LTP in perforant path-dentate gyrus synapses [11]. Also, to increase the frequency of vesicular fusion events on the presynaptic side of hippocampal neurons, the regulator of adult synaptic plasticity BDNF requires *inter alia* full mitochondrial calcium stores [21]. In comparison, a pharmacological study of the neuromuscular junction on crayfish leg muscles suggests that synaptic alteration in response to intense stimulation is being produced by mechanism involving mitochondrial calcium uptake during stimulation and subsequent calcium release into cytoplasm [24]. The slow mitochondrial efflux of calcium results in a minutes-lasting plateau of calcium concentration, which in turn causes facilitation of the synaptic response [52]. Thus, mitochondria influence neurotransmitter release from axon terminals, which can be prevented by blocking the mitochondrial calcium release [16, 53].

As mentioned above, mitochondria consist of two membranes – inner and outer mitochondrial membrane. The permeability of the outer membrane is essential for the ability of mitochondria to regulate local calcium concentration levels [19] and is conferred by family of porin proteins that are substance of the permeability transition pore [54]. In order to study the synaptic modification due to impaired mitochondrial permeability during LTP, Levy *et al.* [55] blocked the mitochondrial permeability transition pore using low dose of cyclosporine A. Cyclosporine A treatment resulted in an increase in basal synaptic transmission and deficit in synaptic plasticity in hippocampal slices due to increase in the resting calcium concentration in presynaptic terminals. These data are consistent with earlier reports on the role of mitochondrial calcium buffering [24, 25] suggesting that mitochondria could regulate synaptic function and plasticity through their ability to take up and release calcium.

An electrophysiological study showed that synaptic plasticity is impaired in homozygote porin knockout mice [54]. In hippocampal slices both short-term and long-term synaptic plasticity were found to be impaired. Accordingly, the porin-deficient mice showed impaired fear conditioning and spatial learning abilities as compared to the wild-type mice. On the other hand, the reduced permeability of mitochondrial outer membrane in heterozygote porin knockout mice led to enhanced mitochondrial function and increased synaptic protein expression [19]. Mitochondrial membrane permeability regulates mitochondrial membrane potential and therefore mitochondrial functions such as oxidative phosphorylation and/or release of apoptotic factors. Thus, it is not surprising that fine-tuning the mitochondrial membrane permeability can affect the cell beneficially. Taken together, these results indicate that mitochondrial outer membrane permeability is essential for synaptic transmission due to regulation of local calcium concentration. Therefore the regulation of the mitochondrial permeability transition pore complex may play an essential role in synaptic plasticity.

In conclusion, mitochondrial calcium influx and release play important roles in regulating synaptic plasticity (see Fig. **1**). Further studies of the mechanisms of the mitochondrial involvement in the local regulation of cellular calcium homeostasis and signalling would be necessary for the understanding basic cellular mechanism underlying neuronal plasticity [53].

THE EFFECT OF SYNAPTIC PLASTICITY ON MITOCHONDRIAL BIOGENESIS

Synaptic plasticity involves structural changes at the synapses as a result of molecular remodelling of synaptic proteins, which could lead to long-lasting alterations of the synaptic response to subsequent neurotransmitter release. Several studies have reported that mitochondrial alterations such as changes in mitochondrial transmembrane potential, calcium uptake and release as well as mitochondrial gene expression are associated with LTP [12, 56]. A study using differential screening of a cDNA libraries from high-frequency stimulation (50 trains of 10 pulses; 400 Hz, 25 ms, 250 ms duration pulses) and control stimulation (0.05 Hz baseline stimulation) conditions showed that, following high-frequency stimulation, the postsynaptic mitochondrial gene expression was elevated. The analysis indicated a general up-regulation in mitochondrial gene expression which persisted for up to two weeks [12].

Furthermore, modulators of hippocampal synaptic plasticity and learning and memory such as oestrogen, growth factors and nitric oxide [57-60] are also known to modify mitochondrial biogenesis [12, 61-63]. Thus mitochondrial biogenesis is promoted by several signalling pathways that also regulate neuroplasticity.

Taken together, these findings suggest that changes in mitochondrial gene expression may be required for the maintenance of synaptic potentiation. Further work will be required to establish specific roles for different mitochondrial genes in the regulation and maintenance of synaptic plasticity.

SYNAPTIC PLASTICITY, MITOCHONDRIA AND AGING

Ageing is associated with specific impairments of learning and memory. These impairments can be caused, at least partly, by altered synaptic plasticity mechanisms, including deficits in the induction and maintenance of LTP

[64, 65]. Early studies of synaptic plasticity alterations reporting no difference in LTP induction in aged animals used high-frequency and high-amplitude stimulation protocols [66, 67]. However, when less robust protocols with lower stimulation intensity were used, aged animals show deficits in LTP induction, including an increased induction threshold [68, 69]. Examination of differences between young and old brains has also revealed that LTP maintenance is impaired in older animals [69, 70]. While in young animals LTP can last from hours to weeks [71], studies in the aged animals indicated a more rapid LTP decay in these preparations [67, 72]. In conclusion, aged-related LTP deficits are associated with increased threshold of LTP induction and decreased LTP maintenance duration.

Aged-related LTP deficits can arise from a number of different sources, including synaptic alterations, abnormalities in signal transduction pathways and different cellular functional alterations [64, 68, 70]. Here we concentrate on aged-related mitochondrial dysfunctions and their impact on synaptic plasticity in aging. As already mentioned, mitochondria play an important role in the maintenance of synaptic transduction through ATP generation and regulation of local intercellular calcium concentrations. Therefore, mitochondrial dysfunction and defects are predicted to affect various aspects of synaptic plasticity. Indeed, age-related mitochondrial dysfunctions are often associated with memory deficits and neurodegeneration diseases, such as Alzheimer's disease and Parkinson's disease [73, 74].

Ultrastructural analyses of mitochondrial morphology have demonstrated the appearance of age-related changes in these organelles, such as: microvacuolization, broken cristae, and accumulation of paracrystalline inclusions [70, 75]. Together with a decrease in the membrane potential of the inner mitochondrial membrane and decrease levels of some complexes of the electron transport chain (ETC) associated with aging [76], these changes could explain the impaired mitochondrial energy metabolism in the old brain. The age-related alteration in mitochondrial oxidative phosphorylation processes resulting in decreased ATP production and energy deficit not only may cause an impaired LTP induction and maintenance, moreover changes in cellular bioenergetics may as well induce neuronal apoptosis and neurodegeneration [69, 70].

The changes in mitochondrial bioenergetics could be due to a complex interplay between the aged-related accumulation of DNA mutations and abnormalities in redox-sensitive signalling pathways [70, 77]. Aging results in genetic instability and increased incidence of mutations both in nuclear and in mitochondrial DNA [78]. Certain DNA mutations may impair the ETC in the mitochondrial membrane and thereby the ATP synthesis. On the other hand, an increase in reactive oxygen species (ROS) levels causing oxidative stress is also associated with aging and age-related synaptic impairments [79]. Interestingly, deficiency in the ETC may result in increased production of ROS and, in parallel, high levels of ROS may cause DNA mutations resulting in mitochondrial damage and ECT deficits [80, 81]. However, whether DNA mutations and/or increased ROS levels are the cause or the consequence of aging is not a subject of this review.

Calcium plays a very important role for the increasing mitochondrial ATP production during neuronal stimulation [71]. Neuronal stimulation enhances mitochondrial calcium uptake resulting in an increased mitochondrial calcium concentration and mitochondrial depolarization [82, 83]. The ETC is thereby activated and the proton extrusion rate elevates inducing a recovery of the resting mitochondrial membrane potential and an increase in the ATP production. Additionally, calcium activates also some of the key enzymes of the Krebs cycle [84]. *In vitro* studies demonstrated that in aged neurons the mitochondrial repolarisation after stimulation was delayed which could be a sign of limited mitochondrial calcium uptake capacity [85, 86]. Moreover, quantitative analysis showed that the delay of mitochondria repolarisation correlates strongly with the recovery of the resting intracellular calcium concentration. Thus, age-related loss of calcium uptake capacity of mitochondria appears to impair the recovering of resting calcium values after stimulation and lead to alterations in calcium homeostasis (see Fig. **1**).

CONCLUSION

Synaptic plasticity in the mature nervous system involves structural modifications, such as dendritic spine growth or retraction, strengthening of synaptic transmission and even new synapses formation [16]. The plasticity processes occur in response to environmental stimuli and associated with changes in synaptic activity and are believed to be responsible for learning and memory [29, 30, 33]. In this review it is shown that, because of their molecular and functional complexity, mitochondria are not just involved in synaptic plasticity in the adult brain, but could also be essential regulators of these complex processes.

Li *et al.* [27] demonstrated that synapse formation was enhanced by mitochondrial aggregation in the dendrites. The dynamic mitochondrial distribution into the different neuron compartments is regulated by synaptic activity. Importantly, new synapse formation caused by potentiating stimuli depend critically on the proper distribution and function of mitochondria and is impaired by their absence [87]. Mitochondria are essential components of synaptic activity, mainly because of their functions as energy producer and calcium buffering organelles. ATP is required for maintenance and restoration of ion gradients, which enable synaptic transmission [33], but also for many different protein phosphorylation reactions involved in the regulation of LTP and other forms of synaptic plasticity [9, 38]. Verstreken *et al.* [37] demonstrated that during intense stimulation neurons with impaired mitochondrial functions could not maintain normal neurotransmitter release like controls. The evidence suggests that this effect was due to absence of mitochondrial ATP, which is required for the mobilization of reserve pool synaptic vesicles, since the synaptic transmission was rescued by ATP addition. The ability of mitochondria to rapidly buffer calcium during intense stimulation is also required for synaptic plasticity [55]. Blocking the mitochondrial calcium uptake resulted in a transient increase in presynaptic calcium

levels and impaired neurotransmission during intense stimulation [24].

The studies reviewed herein demonstrate that mitochondria are essential for both synaptic activity and plasticity, since they are required for the energy supply and metabolic control of the synapse but also for the regulation of calcium concentration and signalling pathways (see Fig. **1**). Mitochondria respond to synaptic plasticity in several ways *i.e.* aggregation of mitochondria in the pre- and post-synapses, elevation of ATP production, increase in mitochondrial calcium pump activity, and up-regulation of mitochondrial biogenesis. Moreover, accumulating evidence place mitochondrial alterations during aging in the focus of neurodegeneration studies [70, 73, 74]. The relation between mitochondrial dysfunctions and impaired synaptic plasticity in the old brain suggests a key role for mitochondria in the process of memory decline with aging. However, the precise involvement of mitochondria in the regulation of the cellular processes of learning and memory remains poorly understood. Advances in understanding the molecular and cell biology of mitochondria could lead not only to encoding the secret of memory but also to new approaches into the research of neurodegenerative diseases like different types of dementia.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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