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Mitochondria: The Pivotal Players in Veterinary Health and Disease

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Abstract

The powerhouse of the eukaryotic cells, Mitochondria, has a dynamic structure and role in animals. Structurally consisting of a double membrane along with cristae promotes oxidative phosphorylation and calcium signalling along with ATP production. Mitochondrial dysfunctions from mutations or environmental factors cause diverse disorders in animals. neurodegenerative diseases, cardiac issues, muscular disorders, hepatic ailments to metabolic syndromes. The interplay of mitochondrial dynamics, fusion, fission, and mitophagy is crucial for maintaining cellular homeostasis and responding to stress conditions. Understanding mitochondrial biology is necessary for prospering veterinary clinical strategies and their profound impact on animal health and disease.

Keywords: Mitochondria, electron transport chain, calcium signalling, genetic mutations, neurodegenerative diseases, animal health

Introduction

Mitochondria, also known as the powerhouse of the cell, is one of the most important cell organelles in eukaryotic organisms. It is generally called so for its vital role in adenosine triphosphate (ATP) generation. Apart from this, the powerhouse is involved in the citric acid cycle (Krebs cycle), fatty acid oxidation and many more metabolic pathways. Due to its role in such metabolic reactions, its structure is a double membrane-bound with an outer membrane and foldings called cristae on the inner membrane, which increases the surface area for such reactions to take place. The most important electron transport chain (ETC) takes place in the inner membrane. Another important element for oxidative phosphorylation, i.e., ATP synthase, is also found here (Yousaf, Z. et al., 2024). Mitochondria has vital roles in calcium signalling pathways, regulating the intercellular calcium levels, maintaining cellular homeostasis, and programmed cell death (apoptosis) by releasing cytochrome C and production of reactive oxygen species (ROS) along with antioxidant defence mechanisms to maintain redox balance. They have immense metabolic importance as they play a key role in cellular metabolism, amino acid metabolism, lipid metabolism, and heme biosynthesis. So, any dysfunction in their performance can greatly affect hugely to the animal body by causing various disorders such as neurodegenerative and metabolic disorders, ageing-related ailments, etc. They contribute overall to cellular adaption and its health, so understanding the role of mitochondria is essential in both veterinary clinical medicine and basic cell biology.

Origins and evolution

Dr. Lynn Margulis stated the endosymbiotic hypothesis of mitochondria which highlights its origin in prokaryotes, the formation of a symbiotic relationship with eukaryotic cells and the supply of energy in trade of protection leading to evolutionary advancements and metabolic capacities in eukaryotes (Sagal L., 1967). The biostructural theory by Eugene Macovschi challenges the endosymbiotic hypothesis by stating that living cells are made up of biostructure matter and coexistent molecular matter, so the origin of life is a single uniform cell (Macovschi E., 1969).

Currently, the nucleus of the cell consists of 1200 protein shapes and maintains the mitochondria, including their DNA having 37

genes (Calvo, S.E. et al., 2016). So, they are mainly reliant on the nucleus for their needs. The powerhouse provides ATP as the energy source is present in all cells of the body except RBCs which have a different mechanism of energy production. In skeletal muscles, mitochondria constitute a corresponding network to stimulate energy production efficiently (Kirkwood, S.P. et al., 1986).

Homeostasis: the interplay of fission, fusion, and mitophagy

Mitochondria have multi-faceted roles, so the maintenance of homeostasis, and balancing mitochondrial biogenesis, dynamics, and degradation is crucial for cellular health. Any disruption in this harmony can lead to several disorders. There is fusion and fission in mitochondria for their proper functioning. The former helps to reduce stress by combining the contents of partly impaired mitochondria as a form of complementation, while the latter is necessary for the removal of damaged mitochondria stimulating mitophagy (Xia, M. et al., 2019). Fusion is regulated by mitofusins (Mfn1 and Mfn2) which enables the outer mitochondrial membrane (OMM) fusion and optic atrophy 1 (OPA1) helps in inner mitochondrial membrane (IMM) fusion (Olichon, A. et al., 2006). Mitochondrial DNA (mtDNA), proteins, and lipids are distributed by fusion ensuring optimal mitochondrial function and morphology. Fission is vital for quality control of mitochondria and mitophagy of damaged ones being regulated by Dynamic-related protein 1 (Drp1) that moves to the OMM assembling into a spiral structure, constricting and dividing the mitochondrion.

Damaged mitochondria are selectively degraded by a process known as mitophagy, which is regulated by PTEN-induced putative kinase 1 (PINK1) and E3 ubiquitin ligase Parkin. In healthy animals, mitochondria are degraded simply by PINK1, whereas during mitochondrial injury, PINK1 gathers on OMM and recruits Parkin. Ubiquitination of various OMM proteins by Parkin helps in mitochondrial degradation by autophagy. This prevents increased ROS production, which leads to cell damage (Kim, S.J. et al., 2015).

Biogenesis and quality control

The growth and development of mitochondria are regulated by peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) also known as the master regulator that coactivates nuclear respiratory factors (NRF1 and NRF2). They induce the expression of mitochondrial genes that help in oxidative phosphorylation, mitochondrial DNA replication, and transcription (Lin, J. et al., 2005). They also regulate mitochondrial transcription factor A (TFAM) necessary for mtDNA replication and maintenance (Virbasius, C. A. et al., 1994). The most important lifestyle factor that helps in the induction of PGC-1α and a potent stimulator of the biogenesis of mitochondria is physical exercise (Handschin, C. et al., 2008). Unfolded protein response (UPRmt), proteostasis, and mitophagy help in mitochondrial quality control (Haynes, C. M. et al., 2010). During mitochondrial stress, there is activation of UPRmt that refolds and degrades misfolded proteins, hence reviving mitochondrial function. The balanced synthesis and degradation of mitochondrial proteins is known as proteolysis. The mitochondrial protease Lon and the AAA+ proteases CLPP and AFG3L2 help in the degradation of damaged proteins (Quiros, P. M. et al., 2016).

Various diseases associated with mitochondrial dysfunction

When the function of the energy producers is compromised due to various factors such as genetic mutations, environmental factors, or a combination of both, it can lead to a wide array of disorders. Some disorders arise due to genetic mutations in mitochondrial DNA or nuclear DNA called primary mitochondrial diseases (Lawless, C. et al., 2020). Some diseases arise due to oxidative stress, environmental toxins, and lifestyle factors called secondary mitochondrial diseases (Le, C.H. et al., 2020).

A decrease in the efficiency of mitochondria leads to a decrease in energy and an increase in reactive oxygen species leading to cellular damage and impaired cellular function. Such mitochondrial dysfunction contributes to the ageing process and age-related diseases (Jang, J.Y. at el., 2018).

Neurodegenerative diseases

There is calcium homeostasis, reactive oxygen species (ROS) regulation, apoptosis, and cellular metabolism along with ATP production in neurones and gial cells. Mitochondria also provides energy for neurogenesis i.e. generation of new neurones from neural stem cells (NSCs) (Khacho et al., 2016). The TCA cycle produces alpha-ketoglutarate, a precursor for the synthesis of the neurotransmitter glutamate (Schon & Przedborski, 2011).

Canine neurodegenerative diseases

In Canine degenerative myelopathy (DM), there is an inefficiency of oxidative phosphorylation, oxidative damage, and alterations of mitochondrial dynamics which leads to degeneration of white matter of the spinal cord, axonal degeneration, loss of motor function in the hind limb and paralysis in older dogs. Dogs show symptoms like hind limb weakness, ataxia, and loss of coordination. As the disease prolongs for a longer period the paralysis ascends to forelimbs and loss of bladder and bowel control. Eventually, it can lead to complete paralysis and respiratory failure. According to some studies, there is a genetic mutation of the superoxide dismutase 1 (SOD1) gene in association with DM that causes mitochondrial dysfunction and oxidative stress in affected spinal cord tissues. As there is no proper cure for the disease supportive care like physical therapy, anti-inflammatory medications and nutritional support can be implemented. Therapeutic strategies like antioxidants and mitochondrial biogenesis enhancers help in the reduction of disease and improved diagnosis in affected dogs (Toedebusch et al., 2018).

A neurodegenerative disorder similar to Alzheimer's disease in humans is commonly found in older dogs named Canine Cognitive Dysfunction (CCD). There is an accumulation of beta-amyloid plaques and tau tangles in the brain causing neuronal anomaly and death. Mitochondrial dysfunction like impaired oxidative phosphorylation increased ROS production, and mtDNA damage (Head et al., 2008) occurs. The clinical signs include behavioural transformations, disorientation, reduced interaction, changes in sleep patterns, house soiling, and ultimately severe damage and impairment. Dietary supplementation with antioxidants, omega-3 fatty acids, and neuroprotective agents is given to the animals. Behavioural enrichment and environmental modifications are also advised to improve cognitive function. Research into potential therapies targeting mitochondrial function and amyloid clearance is ongoing (Cotman et al., 2002).

Feline neurodegenerative diseases

Feline spinal muscular atrophy (FSMA) and Neuroaxonal dystrophy (NAD) are commonly seen diseases due to mitochondrial dysfunction in felines. Muscle weakness due to spinal cord motor neurone degeneration is seen in FSMA. Mitochondrial dysfunction like impaired energy production and increased oxidative stress also causes neurone and muscle atrophy (Fyfe et al., 2006).

Degeneration of axons and neurones causing motor deficits and cognitive impairment is seen in NAD. Impaired mitochondrial transport and bioenergetic deficits are the abnormalities occurring in the affected animals (Griffin et al., 2005). Therapeutic strategies like antioxidants, mitochondrial cofactors (e.g., coenzyme Q10), and mitochondrial dynamics modulators play an important role in the diagnosis.

Feline spongiform encephalopathy is a rare disorder seen in cats as similar to prion diseases in other species. There is an accumulation of abnormal prion proteins in the brain that leads to neurogenic failure and spongiform changes. Mitochondrial dysfunction, like impaired oxidative phosphorylation, increased ROS production, and mitochondrial structural abnormalities (Bartz et al., 2004) causes behavioural changes, ataxia, cognitive decline, tremors, hyperesthesia, seizures and in severe cases, neurological impairment and eventual death. It lacks any proper treatment and supportive management strategies are provided. Research into probable cures focusing on prion propagation and mitochondrial function is ongoing (Aguzzi & Calella, 2009).

Equine neurodegenerative diseases

Equine neuroaxonal dystrophy (eNAD) and equine degenerative myeloencephalopathy (EDM) are the most common diseases seen in equines as a consequence of mitochondrial dysfunction. Degeneration of axons and neurones in the brain and spinal cord leads to abnormalities in gait and neuronal death (Finno et al., 2016). eNAD in horses is caused due to impaired oxidative metabolism and mitochondrial oxidative damage. It is also caused by vitamin E deficiency and genetic predilection. Symptoms like ataxia, hind limb muscle weakness, difficulty in coordination and an abnormal gait.

In EDM, there is degeneration of the spinal cord white matter, causing ataxia and paralysis in the animals. Impaired ATP production and bioenergetic depletion are the mitochondrial dysfunction that causes axonal degeneration and loss of motor function (Finno et al., 2018). Therapeutic strategies like antioxidants, mitochondrial cofactors, and dietary modifications like vitamin E supplements help in the diagnosis of the disorder.

The spinal cord and brainstem are affected by Equine Motor Neurone disease (EMND). Mitochondrial dysfunctions like chronic vitamin E deficiency, oxidative stress, impaired mitochondrial respiratory function, increased ROS

production and mitochondrial deterioration are found (Divers et al., 2006). Supportive therapies like antioxidant therapy are used along with neuroprotective agents and vitamin E supplementation for the management of the disease.

Cardiac diseases

In highly strenuous tissues like the heart, mitochondria play a vital role in maintaining its consistent and rhythmic contractions. Mitochondria's multi-faceted roles in such cells help in the proper functioning of the body.

Canine cardiac diseases

Dilated cardiomyopathy (DCM) occurs predominantly in large breeds like Doberman Pinschers, Boxers, and Great Danes, where there is dilation and impaired contraction of ventricles. Mitochondrial dysfunction is abnormal mtDNA, ETC, along with increased oxidative stress, is seen. Clinical signs such as exercise intolerance, lethargy, coughing, difficulty breathing, fainting, ascites, and in some cases sudden death due to arrhythmias are seen (O'Brien, P. J., & Jeoung, N. H. 2021). For proper management of the disease, antioxidant supplementation like Coenzyme Q10 and vitamin E is administered. Much research on resveratrol, (Beauchamp, G., et al. (2009) a mitochondrial biogenesis stimulator is going on to be implemented in the diagnosis

Feline cardiac diseases

Thickening of the heart muscle due to obstructive blood flow and heart failure is the characteristic of Hypertrophic Cardiomyopathy (HCM). It is commonly seen in cat breeds like Ragdolls and Maine Coons. Functional and structural mitochondrial abnormalities like mutations in the encoding of genes increased ROS, and abnormal oxidative phosphorylation lead to hypertrophic effects and cardiac dysfunction. Clinical signs like rapid and open-mouth breathing, lethargy, loss of appetite and even collapse or sudden death are seen. Antioxidants like N-acetylcysteine (NAC) have shown effective results for the management of this disease. Research on activating peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is going on to be implemented in the treatment (Schober, K. E., & Maerz, I. 2006).

Equine cardiac diseases

Horses suffer from ischemic heart disease due to Ischemia-reperfusion injury causing significant mitochondrial damage. Clinical signs like poor performance, difficulty breathing, increased heart rate, and signs of congestive heart failure like oedema, jugular vein distension and myocardial ischemia are seen. Administration of antioxidants along with some preconditioning techniques that expose the heart to short periods of ischemia before a prolonged ischemic effect has been quite effective for the management of the disease (Cohen, N. D., et al. 2010).

Muscular diseases

In muscle cells, the role of ATP is crucial for contraction of the muscles, relaxation and cellular metabolism. It also influences calcium homeostasis, which is vital for muscle function and the generation of reactive oxygen species (ROS) along with apoptosis.

Canine muscular diseases

Canine Duchenne Muscular Dystrophy (DMD) is commonly found in breeds like Golden Retrievers due to mutations in the dystrophin gene that lacks a functional dystrophin protein. During the contraction of the muscle cell membrane, the integrity is maintained by dystrophin. The absence of dystrophin leads to an increased susceptibility to muscle damage and mitochondrial dysfunction, which includes impaired oxidative phosphorylation, increased ROS production, and mitochondrial DNA (mtDNA) deterioration. Symptoms like muscle weakness, atrophy, exercise intolerance, and difficulty in rising, walking, and climbing stairs are seen. Chronic conditions lead to respiratory distress and cardiomyopathy. Therapeutic strategies like physical therapy, anti-inflammatory medications, antioxidants, mitochondrial-targeted therapies and nutritional support along with recent advances in gene therapy and exon skipping techniques help in restoring partial dystrophin function and improving muscle health (Kornegay et al., 2012).

An inflammatory muscle disease with an idiopathic cause, along with immune-mediated and mitochondrial abnormalities commonly found in dogs, is Polymyositis. Some of the clinical signs include muscle weakness, stiffness, pain, difficulty in swallowing (dysphagia), lethargy, muscle atrophy, and breathing difficulties. Immunosuppressive therapy, such as corticosteroids, to reduce inflammation along with physical therapy and nutritional support and antioxidant supplementation is given (Shelton, 2002).

Feline muscular diseases

Feline mitochondrial myopathy occurs when there are mutations in mtDNA or nuclear DNA encoding mitochondrial proteins. This causes defects in the ETC, which results in impaired ATP production and increased oxidative stress. In cats, mutations in mitochondrial tRNA genes and

components of the ETC complexes are associated with mitochondrial myopathy. Some of the clinical signs and symptoms include muscle weakness, exercise intolerance, lethargy, difficulty jumping, and muscle atrophy. Few neurological signs like seizures and ataxia can also be seen. Therapeutic strategies like antioxidant supplementation, such as coenzyme Q10 and vitamin E, dietary modifications along with specific gene therapies, and mitochondrial-targeted treatments are followed (Fyfe et al., 2006).

Equine muscular diseases

Equine mitochondrial myopathy is caused by genetic mutations in nDNA or mtDNA that damage the mitochondria leading to abnormal ATP production and oxidative stress. Some of the clinical signs shown by affected horses include exercise intolerance, muscle weakness, stiffness, muscle cramps, immobility, muscle atrophy and even rhabdomyolysis. A proper diet with high antioxidants, minerals and vitamins should be given to the horses. Any kind of strenuous activities should be avoided and controlled exercise should be performed to enhance mitochondrial functioning (Finno et al., 2018).

Hepatic diseases

The liver, a highly metabolic organ in the body relies on mitochondria for various vital functions such as energy production, metabolism (Gluconeogenesis, β-oxidation of fatty acids, Ketogenesis etc.) ammonia detoxification, biotransformation, regulation of apoptosis, and reactive oxygen species (ROS) signalling.

Canine hepatic diseases

In canines, hepatopathies are caused due to mitochondrial dysfunction like impaired oxidative phosphorylation and increased ROS production that leads to inflammation and cellular damage. In chronic hepatitis, such dysfunctions cause inflammatory responses that lead to fibrosis and cirrhosis. Clinical signs include lethargy, anorexia, vomiting, diarrhoea, jaundice, ascites and even hepatic encephalopathy and coagulopathies. Administration of antioxidants like S-adenosylmethionine and vitamin E along with dietary supplements like zinc and lactulose (Hirschberger, J., et al., 2007).

In breeds like Terriers, Doberman Pinschers and Labrador Retrievers, copper-associated hepatopathy is seen, which is caused due to excessive copper accumulation triggering oxidative damage. This yields ROS, resulting in mitochondrial dysfunction, abnormal ATP production, and hepatocytic damage. Clinical signs include lethargy, decreased appetite, weight loss, jaundice, ascites, and hepatic encephalopathy. Therapeutic strategies include copper chelators, e.g., D-penicillamine, zinc supplements, and antioxidant therapy (Webb, C. B., & Twedt, D. C., 2003).

Feline hepatic diseases

Fatty liver syndrome also known as Hepatic lipidosis is considered a life-threatening disease in cats. Excessive fat deposition in hepatocytes causes mitochondrial dysfunction such as impaired fatty acid metabolism and excessive ROS production. Clinical signs include jaundice, vomiting, lethargy, weight loss, anorexia and hepatic encephalopathy. Enteral feeding with high-protein, low-carbohydrate, antioxidants like S-adenosylmethionine and vitamin E has proved to be effective against this disease (Center, S. A., 2009)

Equine hepatic diseases

Serum hepatitis commonly called Theiler's disease, is considered a prominent cause of acute hepatic failure in horses. Though the actual pathological mechanism behind this disease is unknown, it is believed that mitochondrial dysfunction induces abnormal energy production and oxidative stress, leading to enormous hepatocytic death. Clinical signs like lethargy, anorexia, jaundice, photosensitivity, and hepatic encephalopathy are commonly seen. Therapeutic strategies include intravenous fluids, anti-inflammatory medications, and antioxidants (Peters, E. B., et al. 2005).

Hepatic lipidosis is less common but prevalent in ponies, miniature horses, and donkeys. Similar to felines, abnormal fatty acid oxidation causes ROS production, hepatocytic death, and liver dysfunction. Lethargy, anorexia, weight loss, jaundice, and hepatic encephalopathy are some of the common signs observed in affected animals. Adequate nutritional support and administration of antioxidants are the common treatment methods followed (Garcia, J. A., et al. 2005).

Metabolic diseases

Canine metabolic diseases

The most common metabolic disease seen in dogs is Diabetes mellitus, which causes chronic hyperglycaemia due to insulin deficiency or resistance. Due to increased oxidative stress, there is damage to beta cells of the pancreas causing abnormal secretion of insulin. There is also insulin resistance in muscle and liver due to mitochondrial dysfunction that reduces glucose uptake and use. Common signs seen in diabetes mellitus include polyuria, polydipsia, polyphagia, weight loss, cataracts, and neuropathy. Treatment for the disease consists of insulin therapy, dietary

strategies to check blood sugar and antioxidant supplementation, e.g., alpha-lipoic acid (Greco, D. S. 2014).

Obesity in dogs is a rising concern these days, which leads to many metabolic disorders like insulin resistance and cardiovascular disease. Due to a decrease in mitochondrial biogenesis and function, there is an accumulation of lipids triggering inflammation and insulin resistance. Such affected animals are at high risk for diabetes mellitus, hypertension, and hyperlipidemia. Clinical signs seen in obesity include reduced exercise tolerance, respiratory distress, and joint pain. There should be proper weight management and controlled exercise programs to ensure a reduction in obesity. Supplements like omega-3 fatty acids and L-carnitine can also be given to promote sound mitochondrial roles (Nelson, R. W., & Reusch, C. E., 2014).

Feline metabolic diseases

Insulin resistance and failure of pancreatic beta cell function are seen in feline diabetes mellitus. Mitochondrial dysfunction occurring in this condition consists of impaired oxidative phosphorylation, increased ROS production, pancreatic beta cell injury, abnormal insulin secretions and its resistance in peripheral tissues. This decreases the glucose uptake and use in the body of affected animals. Animals show polydipsia, polyphagia, weight loss, and neuropathy. Therapeutic strategies include insulin therapy, dietary adaptations to manage blood glucose levels, and antioxidant supplementation (Greco, D. S. 2014).

Equine metabolic diseases

Equine metabolic syndrome (EMS) is characterised by obesity, insulin resistance, and a high risk of laminitis. The main cause, i.e. mitochondrial dysfunction like impaired oxidative phosphorylation, fatty acid oxidation, inflammation results in insulin resistance, and hyperglycaemia that triggers laminitis. Equines show obesity, recurrent laminitis, insulin resistance, and many metabolic disorders. Therapeutic strategies include a proper diet with less sugar intake, regular exercise, and administration of supplements like omega-3 fatty acids (Frank, N., & Tadros, E. M. 2014).

Conclusion and future perspectives

Mitochondria is a key player in various cellular metabolism and processes. Their dynamic structure and role have a huge influence on animal physiology. It is very crucial to understand mitochondrial function as well as dysfunction for proper management and diagnosis of an array of diseases. Future perspectives in research aim to explore many more therapeutic strategies such as gene therapies, mitochondrial-targeted antioxidants, high-resolution imaging, functional assays, and pharmacological modulators to create a huge impact on the field of veterinary science by early detection of diseases, precise treatment, and elevating the quality of life of animals worldwide.

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