Review

Exploring Therapeutic Applications of Autophagy in Spike Protein-Related Pathology

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Abstract: Fasting, a practice with historical roots in various cultures, has recently garnered significant interest in the field of medicine. In this article, we delve into the mechanisms underlying fasting-induced autophagy and its therapeutic applications for spike protein associated pathology. We explore the therapeutic potential of fasting on spike protein-related pathology. Additionally, we discuss factors that affect fasting, such as duration, type (dry vs. water), and the role of specific compounds like spermidine, resveratrol, rapamycin, and metformin. Furthermore, we analyse the interactions between fasting and other practices such as exercise, and highlight important considerations regarding participant characteristics, including pregnancy, breastfeeding, medication interactions, and metabolic disorders. In conclusion, fasting, coupled with an understanding of its nuances, holds promise as a therapeutic intervention with broad implications for human health.

Keywords: fasting; autophagy; long-COVID; post-vaccination syndrome; spike protein; mitochondria; mitophagy

1. Introduction

Fasting has been used by multiple different spiritual [1–8] and medicinal traditions [9], including ancient Greek medicine, traditional Chinese medicine, Ayurveda, Indigenous medicine of the Americas, shamanic medicine, the Islamic world (Table 1).

Table 1. An overview of fasting in different spiritual and medical traditions, showing wide use across the Earth.

Spiritual Tradition	World Region	Fasting Rituals
Islam	Middle East, Africa, Asia, and beyond	Ramadan: Observing a month-long fast from sunrise to sunset as a religious obligation [6].
Christianity	Europe, Americas, Africa, Asia, and beyond	Lent: Fasting for a period of 40 days leading up to Easter, often involving specific dietary restrictions [6].
Buddhism	East Asia, Southeast Asia, South Asia	Uposatha: Observing monthly fasting days to purify the mind and reaffirm spiritual commitments [6].
Hinduism	South Asia, Southeast Asia, Mauritius	Ekadashi: Fasting on the 11th day of each lunar fortnight, abstaining from grains and certain foods [6].
Judaism	Middle East, Europe, Americas, Africa, Asia	Yom Kippur: Observing a 24-hour fast as a day of atonement and repentance [6].
Bahá'í Faith	Global	Nineteen-Day Fast: Fasting from sunrise to sunset during the last month of the Bahá'í calendar [6].
Jainism	India, East Africa	Ayambil: Observing a one-day fast by consuming only boiled water and specific foods. [3]
Native American	Americas	Vision Quest: Fasting and solitary retreat to seek spiritual guidance and connection with nature.

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Spiritual Tradition	World Region	Fasting Rituals
		Sun dance: Fasting and dancing, without water for multiple straight days [4] Plant dietas: Preparation for ceremony [5]
Sufism	Middle East, South Asia, North Africa, Europe	Chilla: Engaging in extended periods of fasting and meditation for spiritual growth and purification. [7]
Mormonism (Church of Latter Day Saints)	North America	Fasting one day each month [6]
Medical Tradition	Region	Fasting Rituals
Ayurveda	India, South Asia	Upavasa: Observing occasional fasting as a means to cleanse the body, balance doshas, and support digestion [10].
Traditional Chinese Medicine	China, East Asia	Daoist Fasting: Engaging in intermittent or prolonged fasting to restore harmony and promote vitality [11].
Naturopathy	Europe, Global	Juice Fasting: Consuming only fresh fruit or vegetable juices for a specific duration to support detoxification and rejuvenation [12].
Siddha Medicine	India	Ekadashi Fasting: Observing fasting on specific lunar days to eliminate toxins, promote purification, and enhance energy levels [13].
Western Medicine	Global	Preoperative Fasting: Temporarily refraining from food and drink before surgical procedures to minimize the risk of complications [14].
Greek Medicine	Ancient Greece, Mediterranean	Fasting was used in the treatment of epilepsy [15].

There are a great many indigenous cultures that practice some form of fasting or food deprivation. Additionally, fasting may help in various diseases, particularly metabolic disorders, cancers and neurodegenerative diseases [16–18].

While fasting is identified for its therapeutic effect in these other instances, there is a potential therapeutic course for fasting in removing spike protein, an associated factor [19] and possible aetiological agent [20] in long COVID. This article describes the therapeutic potential of autophagy in treating spike protein related ailments, including long COVID-19 and post-vaccination syndrome from COVID-19 vaccines encoding the spike protein. Induction of autophagy can be facilitated via several therapeutic avenues, including fasting [21], fasting mimetics [22] and nutritional support [21]. Clinical use of autophagy is still limited, however, clinical trials are demonstrating positive results [23], and knowledge is disseminating from practitioners to the scientific field and vice-versa.

This review presents the pathophysiology of spike protein and its interference with the autophagic machinery of the body [24], and how autophagy can be used to clear its lingering damage, especially in mitochondria [25]. We then explore the various ways to upregulate autophagy and mitophagy, as well to restore mitochondrial function through promotion of mitogenesis and improving mitochondrial efficiency.

2. Pathophysiology related to spike protein

Spike protein can increase levels of pyroptosis, an inflammatory process for destroying cells [26], and downregulates autophagy [27], though spike protein can upregulate autophagy and apoptosis in ACE2 expressing cells [28]. In the latter case of spike protein-induced autophagy and apoptosis, this is a highly inflammatory process [28,29].

Spike protein S1 subunit, as well as the full trimer, can induce mitochondrial damage [25,30,31], lowering to decreased mitochondrial energy production [25,30] and the accumulation of ROS [25]. Under normal physiological conditions, damaged mitochondria are cleared via PINK1/Parkin mediated mitophagy [32–34], however, spike protein S1 subunit (S1) and Receptor binding domain (RBD) segments both inhibit mitophagy and increase mitochondrial ROS [24]. Here, the impact on mitophagy differs between vaccination and infection; in SARS-CoV-2 infection, the ORF10 element

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upregulates mitophagy [35], which may partially compensate for the inhibition of mitophagy by spike protein. In addition to damaging mitochondria [25,30,31], and inhibiting turnover via mitophagy [24], energy production can also be affected by blood clots interfering with tissue oxygenation, which many COVID-19 patients experienced [36,37]. Hypoxic conditions negatively impact mitochondrial energy production [38,39].

A wide variety of other harms are attributed to the spike protein [40], including inflammation [41–43], vascular damage [44–46], potential disruption of the blood-brain barrier [47], and the formation of aggregates [48,49]. Several autopsies from those deceased soon after vaccination show spike protein in cardiac [50–52] and brain [53] tissue. Lack of the nucleocapsid protein in these autopsies rules out SARS-CoV-2 infection as the cause of death [50,53], supporting vaccination as the primary cause of death.

3. Autophagy mechanism

Autophagy in mammals proceeds through a series of steps, whereby abnormal proteins are marked for degradation, and an autophagosome forms around the cell contents marked for degradation. Then, a lysosome fuses to the autophagosome, and the cellular contents of the lysosome break down the contents of the autophagosome. This can be induced towards the degradation of specific cell components or towards the degradation of general cytoplasmic contents.

It was observed in the initial experiments by Ohsumi that yeast cells deficient in genes necessary for autophagy rapidly died under nutrient starvation, whereas control yeast cells survived [54]. This difference in robustness was later attributed to the accumulation of defective mitochondria in the autophagy deficient yeast cells [55]. Several lines of evidence converge to the understanding that spike protein both impairs mitochondrial function [30,31,56], as well as the process of mitophagy [56]. Mitophagy is important for the maintenance of cellular energy production [57], and it is downregulated or completely inhibited in various cancers [58], neurodegenerative diseases [32,59].

One of the pathological features of COVID-19 is the negative impact on kidney function. This may possibly be through the induction of reactive oxygen species by damaged mitochondria [60], which may explain why those with pre-existing kidney disorders suffered far worse COVID-19 outcomes than other groups, [61,62].

Autophagy has two major roles in treating spike-protein related illness. As spike protein both damages mitochondria [30,31,56] and also inhibits their clearance through mitophagy [56], it is important to clear out the damaged mitochondria and restore proper energy function. Additionally, the other role is the removal of the spike protein itself, whether as a protein or composing an aggregate, where the aggregate can be composed of possibly misfolded proteins.

3.2. Regulation of Autophagy

Autophagy is regulated by a complex network of genes [63–65], and can broadly be divided into non-selective and selective autophagy, though both proceed through the formation of an autophagosome, fusion with a lysosome to form an autolysosome, and degradation of the contents (Figure 1). Selective autophagy requires the process of ubiquitination before autophagy, where the targets are marked by ubiquitin chains, which stimulate the formation of an isolation membrane around the target contents. Targets are usually damaged organelles, misfolded proteins, or aggregates, which are sensed by the ubiquitin-proteasome system [66].

Misfolded proteins are sensed by a network of protein specific chaperones, which can refold misfolded proteins [67]. In cases where the protein is irreversibly misfolded, the chaperone can induce protein degradation via the proteasome [68], or through the chaperone-mediated autophagy (CMA) pathway [69], presumed to be only present in mammals and birds [70,71]. The CMA pathway is stimulated by ketone bodies [72], which is a possible mechanism of its upregulation during fasting [73,74]. Dysregulation of CMA is observed in several disorders, and is a potential therapeutic moiety for several disorders, including age-related diseases and cancer [16–18].

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Non-selective or bulk autophagy occurs under conditions of nutrient starvation [75,76] and provides a source of nutrients for cells during periods of low or zero caloric intake [77]. Unlike selective autophagy, it does not require ubiquitin tagging of autophagic targets [63].

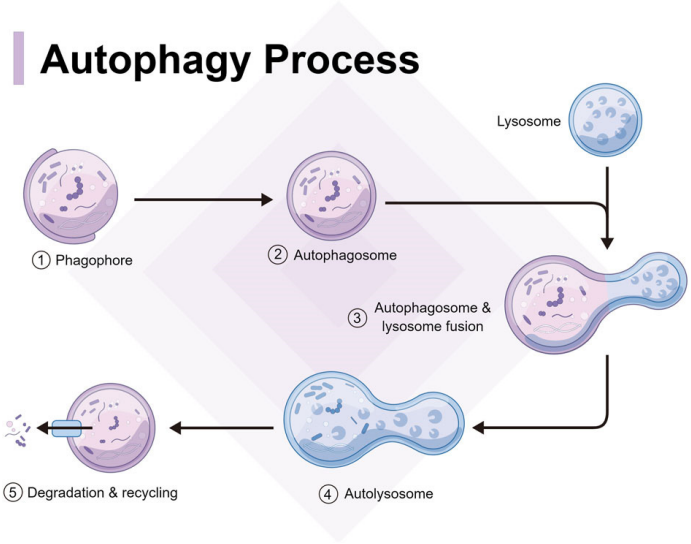

Figure 1. The process of autophagy. Degradation requires encapsulation by the isolation membrane (process shown in (1)) and the formation of the autophagosome (2). Lysosomes, containing proteases fuse to the autophagosome (3), forming the autolysosome (4). Contents can then be degraded and recycled (5). Reproduced from [78] under the terms of the Creative Commons Attribution License (CC BY).

4. Autophagy of spike protein and aggregates

Removal of spike protein can be accomplished in part by autophagy [79], which can be upregulated via interventions such as fasting, heat therapy and ozone. Additionally, there are also some specific compounds that may be taken to hasten the removal of spike protein. Concerningly, spike protein bodies have been found in the autopsies of both people dying from severe COVID-19 outcomes, as well as those dying in temporal relation to receiving COVID-19 vaccines.

Specifically, these compounds include nattokinase, which has been observed *in vitro* to degrade extracellular and membrane-bound spike protein [80], and also prevents SARS-CoV-2 infection *in vitro* [81]. In addition, for proteolytic agents to even have solvent access to proteins, it is necessary to break apart aggregates [82]. Nattokinase, is a fibrinolytic compound derived from the fermentation of soy [83,84] which functions as a thrombolytic and fibrinolytic compound [83,85–88]. It is likely that nattokinase breaks down spike protein incorporated in fibroid-amyloid clots [89] as well as membrane bound spike protein and extracellular spike protein [80]. Nattokinase' s ability to break down intracellular spike has not been tested, and little is known about its membrane permeability. However, computational prediction of membrane permeability for the nattokinase structure (PDB ID: 4DWW) [90] using the webserver BChemRF-CPPred [91] provides a permeability probability of 83%, so it is possible that nattokinase can enter the cell to degrade intracellular spike protein.

Bulk autophagy has some use in degrading cellular components indiscriminately, however, selective autophagy is useful for degrading specific targets, in our cases mitochondria (mitophagy) and aggregates (aggrephagy). Selective autophagy marks targets (often with ubiquitin) prior to encapsulation in the autophagosome and degradation in the autolysosome [63].

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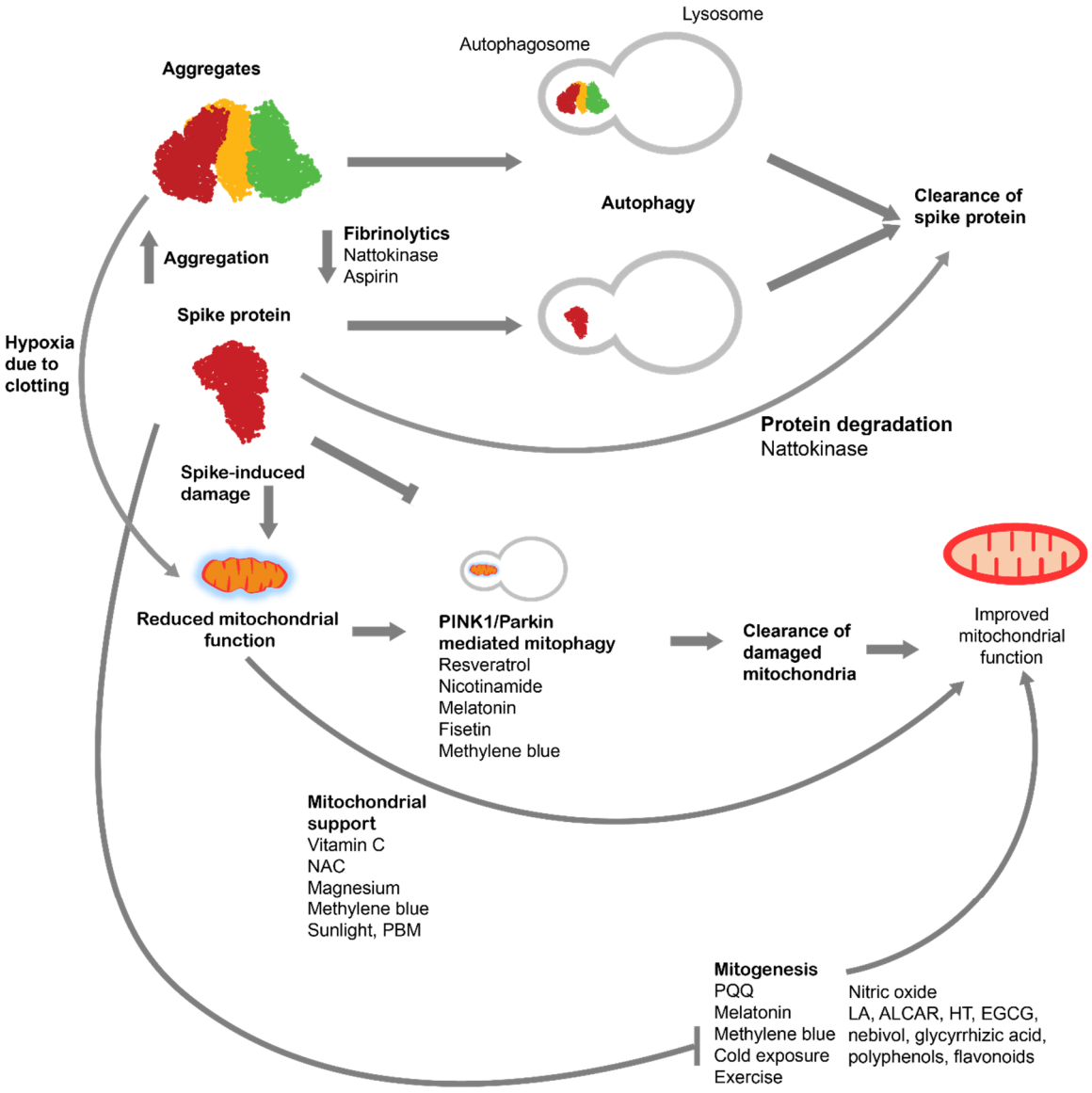

Figure 2. Pathways involved in the pathogenesis of spike-protein induced damage and available therapeutic pathways.

4. Autophagy for treatment of spike protein-induced pathologies

There are multiple points at which autophagy can be influenced, as there are many genes and signaling mechanisms regulating autophagy. The factors which influence autophagy are broadly broken into two classes, lifestyle (fasting) and pharmacological.

4.1. Fasting and autophagy

Time -restricted eating (TRE) and Intermittent fasting (IF) are effective methods to activate autophagy and mitophagy [92–95]. The mammalian target of rapamycin (mTOR) is a nutrient sensor and regulator of cell growth that is activated by glucose and protein (leucine) which switch on the pathway, inhibiting autophagy [96,97]. Under low nutrient conditions, mTOR is deactivated, which enables autophagy [98].

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Fasting, by definition, means abstaining from eating. TRE is a type of fasting where food intake is limited to a short window during the day (1 to 8 hours), with only fluids such as water, tea, or coffee for the rest of the day [99]. IF usually involves a longer period of fasting; the most common is alternative day fasting (24-hour fasting, followed by a 24-hour eating window) [8]. However, many people fast for several days (3-7 days, or up to 14 days) followed by slow refeeding. [100]

TRE and IF have many metabolic, cellular, and immunologic benefits [101–103]. It is important to emphasize that TRE/IF are not synonymous with caloric restriction (CR), though people do tend to eat less *ad libitum* following a fasting regimen [104]. Additionally, eating nutrient-dense [105] and high-protein [106] foods can decrease the sensation of hunger. More extended (1-2 days) fasting, can increase basal metabolic rate (BMR) [107,108] and growth hormone (GH) levels [109,110]. Calorie-matched studies show a greater improvement in metabolic parameters (insulin sensitivity) in individuals adopting IF as opposed to CR [111,112].

TRE/IF has a profound effect on promoting immune system homeostasis [113]. Fasting improves mitochondrial health [114–117] and protects hematopoietic stem cells from damage [118]. TRE/IF may be an effective therapy for the treatment of insulin resistance [119], metabolic syndrome [120,121], and type II diabetes [122,123]. In addition, Intermittent fasting has additional benefit in prolonging health-span, alleviating the symptoms/curing many chronic diseases as well as preventing cardiovascular disease [124], neurodegenerative diseases [125] (e.g. Alzheimer's Disease) and cancer [126].

4.2. Compounds for increasing autophagy

Increasing the level of autophagy is important to increase the rate at which foreign proteins and aggregates can be cleared. This section describes pharmacological strategies to induce or upregulate autophagy.

4.2.1. Spermidine

Spermidine is produced endogenously from the precursor putrescine. It is a polyamine which can stimulate autophagy via inhibition of the acetyltransferase EP300 [127]. It can be consumed exogenously and is found in high concentrations in wheat germ and other vegetables [128,129], though conflicting information exists on whether supplementation raises polyamine levels. Studies show that oral polyamine intake raises levels [130,131] supplementation does not appear to raise spermidine levels [132]. However, spermidine supplementation shows improvement in cognitive function in animal models [133]. In human trials, spermidine improved memory performance in older adults at risk for dementia [134] though this effect was not seen in a different study on older adults experiencing cognitive decline [135,136].

4.2.2. Caffeine

Multiple article have demonstrated a link between caffeine consumption and enhanced autophagy in *in vivo* studies [137,138].

4.2.3. Resveratrol

Resveratrol is a plant phytochemical (non-flavonoid polyphenol) that is a potent inducer of autophagy [139,140]. In addition, resveratrol has anti-inflammatory [141] and antiviral [142] (incl. SARS-CoV-2) properties and has beneficial effects on the microbiome [143]. Resveratrol activates the fasting state [144] and inhibits mTOR-related inhibition of autophagy [145].

4.2.4. Curcumin

Curcumin, the active ingredient in turmeric, has antiviral activity against SARS-CoV-2. In addition, this spice has anti-inflammatory, immune-modulating properties, and potent anti-cancer activity [146]. Curcumin activates autophagy. [147,148] Curcumin has low solubility in water and is poorly absorbed by the body [149]; consequently, it is traditionally taken with full-fat milk and black pepper,

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the latter of which greatly enhances bioavailability [150]. Nano-curcumin preparations or formulations designed to enhance absorption are recommended [149].

4.2.5. Other compounds

There is some that evidence that Epigallocatechin gallate (EGCG) may increase autophagy [151,152]. The diabetes drug rapamycin is also a potent inducer of autophagy [153–156]. There are other compounds which may increase autophagy through various pathways, and some have supporting *in vitro* evidence. These were covered in a recent review [157].

5. Improving mitochondrial function

In addition to clearing damaged mitochondria, it may be of therapeutic benefit to improve the mitochondrial function of the other mitochondria. Ideally, we do not want these processes to interfere.

5.1. Mitophagy

Spike protein can damage mitochondria [25,158], and is therefore important to both clear spike and restore the damaged mitochondria. Degradation of mitochondria via a selective form of autophagy, named mitophagy, is a fundamental mechanism conserved from yeast to humans that regulates mitochondrial quality and quantity control. Mitophagy is promoted via specific mitochondrial outer membrane receptors, or ubiquitin molecules conjugated to proteins on the mitochondrial surface (PINK1 and Parkin) leading to the formation of autophagosomes surrounding mitochondria. PINK1 is a protein that surveils for damaged mitochondria [33,159]. In healthy mitochondria, PINK1 is imported into the mitochondria, and then is subsequently cleaved by proteases (PARL and Oma1) on the inner mitochondrial membrane [160]. When mitochondria lose their membrane potential, PINK1 cannot reach the inner membrane [34] and accumulates in the outer mitochondrial membrane, where it begins to phosphorylate serine 65 on ubiquitin chains, which in turn activates Parkin [161–164], and subsequently signals mitophagy [165].

Disrupted mitochondrial membrane potential is the signal which ultimately leads to mitophagy, and several pathological mechanisms work by downregulating mitophagy via increasing the membrane potential [166]. There are several pharmacological pathways through which mitophagy can be induced [167]. Notably, this list includes the natural compounds resveratrol [168], fisetin [169], and nicotinamide [170], which have been examined for their potential therapeutic impacts in acute- or long-COVID [171–173]. Melatonin is another compound which can increase mitophagy [174–176]

5.2. Mitochondrial biogenesis

Clearing damaged mitochondria will leave a lack of energy production capacity in the cell if not replaced. Mitochondrial population is regulated through multiple processes, including mitochondrial fission (breaking apart to form more mitochondria), fusion [177] (two or more mitochondria fusing to reduce mitochondrial population), mitophagy [178] and mitochondrial biogenesis (MB) [179].

5.2.1. PQQ

Pyrroloquinoline quinone (PQQ) increases mitochondrial biogenesis via elevation of peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), a biochemical marker for mitochondrial biogenesis [180].

5.2.2. Cold exposure

Cold exposure increases the expression of PGC-1α in (soleus) muscle tissue [181]. When combined with endurance exercise (mice swimming for 30 to 60min), gene expression changes promoting mitochondrial biogenesis were highly upregulated [181].

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5.2.3. Endurance exercise

Endurance exercise induces the increase in mitochondrial density of skeletal muscle [182,183]. For the purpose of this investigation into treatment of spike protein related pathology, the reintroduction of exercise needs to be tempered [184].

5.2.4. Nitric Oxide

Additionally, one pathway which increases mitochondrial biogenesis is via the production of nitric oxide (NO) [185,185,186], which can be upregulated during exercise [187,188], ultraviolet A light [189]. Plant studies also observe an increase in NO production during cold stress [190,191]. NO can also be upregulated by ROS [192], estrogen [193], statins [194].

5.2.5. Melatonin

Melatonin is an important agent in upregulating mitochondrial biogenesis [174,195,196]. A recent review identified it as a molecule of interest for treating long COVID [197].

5.2.6. Others

Other compounds have demonstrated potential in improving both mitochondrial biogenesis as well as mitochondrial function [115,198,199].

Lipoic acid (LA) has demonstrated capability to increase mitochondrial biogenesis [200–202]. Acetyl-L-Carnitine (ALCAR) also shows benefits when combined with LA [202], and other studies show ALCAR increases the expression of gene pathways in mitochondrial biogenesis [203–205]. Hydroxytyrosol, a compound in extra-virgin olive oil may also stimulate mitochondrial biogenesis [206]. The compound nebivolol, a beta blocker, also stimulates mitochondrial biogenesis [207]. EGCG [208–210], green tea polyphenols [211], isoflavones [212], quercetin [213], mulberry [214,215], anthocyanins [216], rutin [217], curcumin [218], glycyrrhizic acid (licorice) [219], cyanidin-3-glucoside [220], citrus tangeretin [221], isorhamnetin [222], nobiletin [223], eriocitrin (citrus lemon compound) [224], sudachitin (a flavone found in citrus fruit) [225], Amla (Indian medicinal plant) [226], and *Platycodon grandiflorum* extract [227] also may stimulate mitochondrial biogenesis [199].

5.3. Improving Mitochondrial Function

In addition to removing damaged mitochondria and restoring tissue oxygenation via the removal of clotting bodies, it is important to increase mitochondrial energy production. Studies demonstrate deleterious impacts of the spike protein [25], SARS-CoV-2 [228] and the COVID-19 mRNA vaccines [229] on mitochondrial parameters.

Mitochondrial dysfunction is a hallmark of long COVID [230–233], and multiple agents with a mitochondrial mode-of-action are currently being investigated therapeutically for long COVID [79]. Below, we include several factors known to improve mitochondrial function.

5.3.1. Vitamin C

Vitamin C has important anti-inflammatory [234], antioxidant [235], and immune-enhancing properties [236]. It is transported into the mitochondria and confers protection against oxidative injury [235], though little is known about its influence on mitochondria [237].

Oral Vitamin C helps promote the growth of protective bacterial populations in the microbiome [238]. As gut dysbiosis is associated with long COVID [239,240], supplemental vitamin C may confer benefit to those experiencing long COVID [241]. Trials on the impact of L-Arginine combined with Vitamin C showed positive results for long-COVID [242,243].

5.3.2. N-acetyl cysteine

N-acetyl cysteine (NAC) is the precursor of hepatic glutathione (GSH) [244]. NAC penetrates cells where it is deacetylated to yield L-cysteine thereby promoting GSH synthesis [244]. GSH is an

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important intracellular antioxidant [245]. In addition, NAC has anti-inflammatory and immune-modulating properties [246]. NAC is well absorbed by the intestine and supplementation with NAC is effective for increasing GSH levels [247]. NAC acts as a protective factor for mitochondrial energy production [248] and supplementation with glycine improves mitochondrial markers in older adults [249].

5.3.3. Magnesium

Magnesium is an important mineral for health, as magnesium deficiencies are linked with many disease processes [250], as well as more severe COVID-19 outcomes [251]. Magnesium plays important roles in maintaining mitochondrial membrane potential [252,253].

5.3.4. Methylene Blue

Methylene blue (MB) induces mitophagy [254] and has neuroprotective [254–256] and antiviral properties [257]. It is capable of directly rerouting electrons in the mitochondrial electron transport chain to promote mitochondrial activity [255].

MB should be avoided during pregnancy [258]. Also, MB is a potent monoamine oxidase inhibitor that, in conjunction with an selective serotonin reuptake inhibitor, can potentiate serotonin syndrome, a life-threatening medical emergency [259].

5.3.5. Light therapy

Modern humans currently spend the majority of their time indoors [260], approximately 93% by one survey of medical students [261]. Early humans were exposed to sunlight daily, likely with profoundly important health benefits [262]. A recent large prospective study demonstrated that avoiding sun exposure is a risk factor for all-cause mortality, demonstrating lower life expectancies (0.6 to 2.1 years) in those avoiding sun exposure when compared to the highest sun exposure group [263]. Apart from UV radiation stimulating vitamin D synthesis [264], red and near-infrared (NIR) radiation have a profound effect on human physiology [265], notably acting as a mitochondrial stimulant and increasing ATP production [266]. Indeed, during the 1918 influenza pandemic, “open-air treatment of influenzae” appeared to be an effective treatment for seriously ill patients [267].

The most well-studied mechanism of action of PBM centers around enhancing the activity of cytochrome c oxidase, which is unit four of the mitochondrial respiratory chain, responsible for the final reduction of oxygen to water. [268] In addition, one of the most reproducible effects of PBM is an overall reduction in inflammation [269]. It has also been demonstrated that NIR light increases the expression of genes associated with mitochondrial biogenesis [270].

5.3.6. Others

Multiple other compounds have been identified which modulate mitochondrial function, including fucoidan, a brown marine algae, which improves mitochondrial membrane potential [271]. Investigational compounds are covered in recent reviews [272–274].

6. Conclusion

The spike protein, notably the S1 segment, is likely a pathogenetic factor leading to both long COVID and post-vaccination syndrome. Multiple intersecting and overlapping pathophysiologic processes contribute to the vast spectrum of pathology caused by spike-protein, including inflammation, clotting (fibrin-amyloid clots), autoantibodies, mitochondrial dysfunction, and endothelialitis. This is a novel pathology and requires the development of treatment protocols to meet this pressing need. Autophagy is a promising technique to remove foreign proteins and restore cellular function, as well as restoring cellular energy production.

Autophagy has a long and broad history in medicine as well as spiritual practice, its use in medicine, pending validation, is sure to increase, given its therapeutic potential. Modifiable lifestyle factors as well as pharmacological factors can upregulate autophagy. Further work is of course required

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in the development of spike-protein therapeutics, and their clinical validation, as well as extending the therapeutic use of fasting to other disorders. Autophagy has much potential in the future of medicine.

Abbreviations

ACE2	angiotensin converting enzyme 2
ALCAR	Acetyl-L-Carnitine
BMR	basal metabolic rate
CR	caloric restriction
CMA	chaperone-mediated autophagy
EGCG	Epigallocatechin gallate
GH	growth hormone
GSH	hepatic glutathione
IF	Intermittent fasting
LA	Lipoic acid
mTOR	mammalian target of rapamycin
MB	methylene blue
NAC	N-acetyl cysteine
NIR	Near-infrared radiation
NO	nitric oxide
PBM	photobiomodulation
RBD	Receptor binding domain
ROS	reactive oxygen species
S1	spike protein S1 subunit
TRE	Time -restricted eating
PGC-1α	peroxisome proliferator-activated receptor γ coactivator-1α
PQQ	pyrroloquinoline quinone

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