MITOCHONDRIAL MYOPATHY: A NEW THERAPEUTIC APPROACH

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MITOCHONDRIAL MYOPATHY: A NEW THERAPEUTIC APPROACH (Abstract): Restoration of deoxyribonucleic acid in mitochondrial myopathies may occur after a mechanical or chemical injury of striated muscle or by endurance training. Therapies with enzymes, gene therapies, or treatments with substances that stimulate mitochondrial biogenesis are used at the moment. Genesis of mitochondria may also come from myonuclei by releasing the nuclear respiratory factor-1/2 during muscle contractions. Multiplying of myonuclei depends on muscle satellite cell activation. Since the electromyostimulation increase the number of circulating stem cells that may participate in the genesis of new muscle fibers (adding to the deposit of specific stem cells of the muscle), and intermittent hypoxia stimulates the proliferation of muscle satellite cells, we propose to combine the two processes for the treatment of mitochondrial myopathies. Respective combined therapy may be useful for restoring damaged mitochondria by drug side effects. **Keywords:** ELECTROMYOSTIMULATION, INTERMITTENT HYPOXIA, MITOCHONDRIAL MYOPATHIES

The syndrome comprising mitochondrial myopathy, encephalopathy and lactic acidosis have genetic causes, being inherited through maternal line. Restoring muscle mitochondrial deoxyribonucleic acid (DNA) may be the consequence of the healing process after producing a chemical or mechanical lesion of striated muscle (1, 2). In patients with mitochondrial myopathies, endurance training based on concentric exercises stimulate the transformation of stem cells into new muscle fibers with mitochondrial DNA restoration (3). A subsequent study found that 12 weeks of endurance exercises for the lower limbs in patients with the same condition resulted in an increase in aerobic capacity, mitochondrial activity and number of muscle cells satellites, but not in a significant restoration of mitochondrial DNA (4). One case study showed how the force exercises have reduced the rate of a sporadic transfer ribonucleic acid (tRNA) point mutations at an adult with mitochondrial myopathy, but that work has not been evaluated the muscle performance nor the satellite muscle cells characteristics (3). The current therapeutic strategies for mitochondrial myopathies are based on therapies with enzymes, gene therapies, nucleoside therapies, and also on the stimulation of mitochondrial biogenesis by the administration of resvera-
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trol, 5-aminoimidazo-4-carboxamide ribo-
nucleotide, nicotinamide riboside, or even
antioxidants (5). In this paper we propose a
new therapeutic strategy, based on the
assessment of relations between the bio-
genesis of mitochondria and muscle stem
cells.

ELECTROMYOSTIMULATION
COMBINED WITH INTERMITTENT
HYPOXIA - POTENTIAL METHOD
TO RESTORE MUSCULAR
MITOCHONDRIA HYPOTESIS

The decrease in intramuscular ratio of
adenosine triphosphate/adenosine diphos-
phate (ATP/ADP) and of phosphocreatine
concentration activates adenosine mono-
phosphate-activated protein kinase
(AMPK), which promotes mitochondrial
biogenesis by peroxisome proliferator-
activated receptor-gamma coactivator-1
(PGC-1) and nuclear transcription factors
(NRFs) (6, 7). Subsequently it was estab-
lished that a factor arising from myonuclei
(nuclear respiratory factor-1/2 - NRF-1/2)
that stimulate mitochondrial biogenesis is
released due to physical exercise (8).

Given that muscular stem cells can gen-
erate myonuclei or differentiate into new
muscle cells (9) it follows that in both
modes have an indirect contribution to
mitochondria biogenesis. In vivo activation
of satellite stem cells is made by nitric
oxide (NO) released during exercise (10).
In support of this mechanism it comes that
at a young age, muscular stem cells activa-
tion is made by muscular attrition (11).
Practically after only 4 weeks of endurance
exercise the number of mitochondria in
muscle fibers almost doubled (12). Elec-
tromyostimulation (EMS) made with fre-
quency between 50 and 2,000 Hz per-
formed on human subjects for 21 days has
led to an increase in number of myonuclei
in muscular fibers and possibly to hyper-
plasia of striated muscle, process assumed
to be induced by proliferation of muscle
cell satellites (13). Correlating this fact
with the above observations strengthen the
hypothesis that electromyostimulation activ-
ates satellite stem cells and implicit mito-
chondrial biogenesis. Intermittent hypoxia
combined with surface electromyostimula-
tion cause circulating stem cell prolifera-
tion (14), which can add to satellite cells
during the formation of new muscle cells
(13). Moreover, hypoxia activates Notch
signals with role in muscular satellite cell
proliferation, the same action having the
stimulation of Wnt/B-catenin pathway (15).

It seems that mutant mitochondrial
DNA in muscle satellite cells is lost if their
replication to form new muscle fibers oc-
curs rapidly, creating new prospects for
treating mitochondrial myopathies (16).

Given the supposed effects of intermittent
hypoxia combined with electromyostimula-
tion on muscle stem cell activation and
implicitly on mitochondrial biogenesis, this
therapy could be indicated for myopathy
causds by mitochondrial defects.

DISCUSSION

An indirect argument for the fact that
electromyostimulation induce biogenesis of
mitochondria is that six weeks of low fre-
quency EMS (10 Hz) had the effect of in-
creasing muscle volume and degree of
pinnate, lower blood pressure and increase
aerobic capacity (i.e. the number of mito-
chondria of muscle) (17). In addition to the
combination with intermittent hypoxia,
EMS can be combined with modern thera-
pies of mitochondrial myopathies, and in
particular with the use of riboside-nicotinamide (compound believed to increase the intracellular synthesis of nicotinamide adenine dinucleotide - NAD+) (18) and therefore the efficiency of communication between the nucleus and mitochondria (19).

The combination electromyostimulation - intermittent hypoxia could be used to control quality and/or quality defects of mitochondria appeared as unwanted side effects of some drug therapies: analgesics and anti-inflammatory (aspirin, acetaminophen, naproxen), anesthetics (bupivacaine lidocaine, propofol) antiarrhythmic (amiodarone), antianginal (perhexilene, Dethylaminoothoxyhexesterol), antibiotics (tetracycline), antiepileptics (valproic acid), antidepressants (amitriptyline, amoxapine, citalopram, fluoxetine), antipsychotic agents (chlorpromazine, fluphenazine, haloperidol, risperidone, quetiapine, clozapine, olanzapine), anxiolytics (alprazolam, diazepam), barbiturates (amobarbital, aprobarbital, butobarbital, butalbital, methylphenobarbital, pentobarbital, phenobarbital, primidone, propofol, secobarbital, thiobarbital), cholesterol medications (statins - atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, bile acids - cholestyramine, clofibrate, ciprofibrate, colestipol, colesvealam), diabetes medication (metformin, troglitazone, rosiglitazone, buformin), chemotherapy (mitomycin C, proffiomycin, adriamycin), antiparkinsonian (tolcapone), lithium, disulfiram, medication anti HIV (abacavir sulphates, Hivid (ddC, zalcitabine), zidovudine, ddl, didanosine, d4T, stavudine) (20).

CONCLUSIONS

In our study, based on proven functional relationships between mitochondrial biogenesis and muscle stem cells, we propose the combination electromyostimulation-intermittent hypoxia to be used as mitochondrial myopathies treatment, possibly in association with gene therapy or administration of substances that stimulate mitochondrial biogenesis.

Electromyostimulation combined with intermittent hypoxia may potentially be used for the repair of mitochondrial damage caused by various drugs.

REFERENCES

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