Intranasal Light Therapy (ILIT)

Timon Cheng-Yi Liu

Laboratory of Laser Sports Medicine,
South China Normal University

liutcy@scnu.edu.cn
Introduction to ILIT
History of ILIT

- ILIT on local diseases such as rhinitis was put forward by Russian in 1986.

- ILIT on systemic diseases was put forward by Chinese in 1998
ILIT: intranasal light therapy

Clinical applications

Pain

Cerebral Palsy

Stroke (cerebral infarction, …)

Coronary Heart Disease

myocardial infarction

Inflammation

Depression

ILIT: intranasal light therapy

Clinical applications

- Hyperlipidemia
  - Blood hyperviscosity
- Insomnia
- Mild cognitive impairment
- Alzheimer’s disease
- Parkinson’s disease
- Schizophrenia
ILIT: intranasal light therapy

Possible applications in sports medicine

- Asthma
- Carpal tunnel syndrome
- Epicondylitis
- Exercise-induced muscle damage
- Osteoarthritis
- Upper respiratory tract infection
- Wound

Negative feedback

A makes B; B inhibits A

http://www.nature.com/nature/journal/v458/n7241/full/458969a.html
Negative Feedback on Proteins

Photobiomodulation (PBM) is a modulation of low intensity laser irradiation or monochromatic light (LIL) on biosystems, which stimulates or inhibits biological functions but does not result in irreducible damage.
Function-Specific Homeostasis (FSH)

- FSH is a negative feedback for a function to be fully performed
  - Proliferation-specific homeostasis (PISH)
  - Sleep-specific homeostasis (SISH)
  - Longevity-specific homeostasis (LoSH)


Physiological roles of the SIRT1

Liver
- SIRT1
  - TORC2
  - PGC-1α
  - FOXO1
  - Glucose production

Adipose tissue
- SIRT1
  - PPAR-γ
  - LXR
  - Fat mobilization
  - Lipid metabolism

Blood vessel
- SIRT1
  - FOXO1
  - eNOS
  - Angiogenesis
  - Vascular tone

Brain
- SIRT1
  - HCS1
  - ↓ Apoptosis
  - Δ Neuronal differentiation
  - ↑ Resistance to neurodegeneration

Pancreas
- ↑ SIRT1
  - ↓ UCP-2
  - ↑ Insulin secretion

Intestine
- ↑ SIRT1
  - ↓ β-catenin activity
  - ↓ Tumour formation
Handling stress

SIRT1 is a deacetylase that is activated by a variety of stressors and targets transcriptional regulators including p53, NF-κB, HSF1, FOXO1, 3, and 4, and PGC-1. These factors then control adaptive responses that modulate life span. AC: acetyl group;
Sirtuin 1 (SIRT1) activity potential well.

FSSA1 denotes function-specific homeostasis specific SIRT1 activity.

Function-specific homeostasis (FSH)

FSH-specific SIRT1 activity (FSSA1)
Economic FSH

Sirtuin 1 (SIRT1) activity potential well.

FSSA1 denotes function-specific homeostasis specific SIRT1 activity

PlSH of PC12 cells in glucose

- Functional optimum
- Resistance
- Lowest NAD/NADH and SIRT1 activity

PlSH of PC12 cells in glucose

- Normal glucose (nG)
- Low glucose (lG)
- High glucose (hG)

- NAD+/NADH
- SIRT1 / GAPDH

- Glu (mM)

- ** Indicates significant difference
PISH of PC12 cells in nucleotide
PISH of PC12 cells in glutamine
PISI of PC12 cells in temperature

**NAD+/NADH**

- Lowest
- Functional optimum
- SIRT1 activity

**SIRT1/GAPDH**

- Temperature (°C): 30, 35, 37, 40
Sleep-specific homeostasis


<table>
<thead>
<tr>
<th>Sleep duration</th>
<th>Weighted prevalence of fair/poor SRH, %</th>
<th>Age-adjusted OR (95% CI)†</th>
<th>Multivariable OR (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole population (n = 20,663)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 5 h</td>
<td>23.4</td>
<td>3.84 (3.18-4.62)</td>
<td>2.29 (1.86-2.83)</td>
</tr>
<tr>
<td>6 h</td>
<td>13.8</td>
<td>2.01 (1.71-2.35)</td>
<td>1.68 (1.42-2.00)</td>
</tr>
<tr>
<td>7 h</td>
<td>7.5 (Referent)</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>8 h</td>
<td>12.1</td>
<td>1.59 (1.37-1.84)</td>
<td>1.38 (1.18-1.61)</td>
</tr>
<tr>
<td>≥ 9 h</td>
<td>23.8</td>
<td>3.10 (2.63-3.66)</td>
<td>1.98 (1.63-2.40)</td>
</tr>
</tbody>
</table>

SRH, self-rated health; OR, odds ratio; CI, confidence interval.
Longevity-specific homeostasis (LoSH)

Car-specific Optimum Speed

Each car has its optimum speed
In FSH

Far from FSH

Far from FSH
PBM Biomechanism: FSS & FSSH

Negative feedback on stresses

FSH-specific stress (FSS)
FSSS-specific homeostasis (FSSH)
Successful stress: FSS in FSSH

Sirtuin 1 (SIRT1) activity potential well.

FSSA1 denotes function-specific homeostasis specific SIRT1 activity
Wound healing


Human Placental Extract (HPE)

Wound healing
Successful stress in FSSH

Chronic stress far from FSSH

FSH

FSS

mFSH

wFSHa

wFSHb

wFSHc

wFSHz

FSH Quality
Oxidative stress on insulin sensitivity


IRS1: insulin receptor substrate 1
Phases of wound repair. Wound healing has been arbitrarily divided into three phases:

- Inflammation (0-5 days)
- Proliferation (3-14 days)
- Maturation (week-year)

Sport-specific homeostasis (SpSH)

Pattern of performance measured with Plim5' test over the experiment. Dotted lines delimit the two phases of training: phase 1 with three training sessions per week and phase 2 with five training sessions per week. Values are mean ± SE.

Negative feedback and PBM

PBM Biomechanism: dPBM & iPBM

Direct photobiomodulation (dPBM)
Indirect photobiomodulation (iPBM)
dPBM

- There is no dPBM on FSH/FSSH
- dPBM modulates a chronic stress self-adaptively until it becomes a successful stress so that the FSH/FSSH is established
Low intensity laser irradiation or monochromatic light (LIL)
## Percutaneous coronary intervention

Major adverse cardiac events (MACE) and mean extent of narrowing on follow-up coronary angiogram at 6 months, stratified by diagnosis of restenosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Laser (n = 52)</th>
<th>Control (n = 49)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean narrowing on angiogram (%)</td>
<td>32.0 ± 22.1</td>
<td>43.5 ± 23.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Patients with restenosis (%)</td>
<td>59.1 ± 22.0</td>
<td>71.8 ± 16.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patients without restenosis (%)</td>
<td>27.5 ± 13.0</td>
<td>32.2 ± 17.8</td>
<td>0.128</td>
</tr>
<tr>
<td>Major adverse cardiac events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months</td>
<td>4 (7.7%)</td>
<td>7 (14.3%)</td>
<td>0.525</td>
</tr>
<tr>
<td>At 12 months</td>
<td>4 (7.7%)</td>
<td>9 (18.4%)</td>
<td>0.266</td>
</tr>
</tbody>
</table>

dPBM on hG induced dysfunction
Self-adaptive dPBM
Self-adaptive dPBM
Redundant genes

If genes $A$ and $B$ perform function $F$ with equal efficacy, then redundancy does not persist. For unequal mutation rates, the gene with higher mutation rate will become extinct.

Redundant pathway
iPBM

A function in its FSH has three kinds of subfunctions in terms of their respective homeostasis (sFSH)
- The FSH inhibits the establishment of sFSH (iFSH)
- The FSH does not modulate the establishment of sFSH (nFSH)
- The FSH promotes the establishment of sFSH (pFSH)

iPBM self-adaptively modulates a subfunction far from its pFSH until the pFSH is established and then the FSH is upgraded into enhanced FSH (eFSH).
pFSH

FSH

nFSH

iFSH

eFSH

Light

iPBM

promotion

inter-promotion

dPBM

Homeostasis Quality

eFSH: enhanced FSH
nFSH: non-modulated FSH
iFSH: inhibited FSH
pFSH: promoted FSH

inter-inhibition

non-modulation
iPBM on PISH in nG
Redundancy mediated iPBM

The FNSH is differentiation-specific homeostasis
Collagen deposition and cellularity in preconditioned surgical wounds


http://www.ncbi.nlm.nih.gov/pubmed/18580963
ILIT Biomechanisms

Pathways mediating ILIT
Olfactory, autonomic and central nervous system
Olfactory, autonomic and central nervous system

Blood

Bone

Acupoints and meridians
ILIT Biomechanism: blood mediation
Thermal Texture Map before and after ILILT treatment

Before

After

From Prof. Liu SH
Improved regional cerebral blood flow

before

net increase

after

SPECT for old men before and after ILIT from Prof. Xiao XC
Peripheral red cells from an unrelated control individual (+/+, dashed line) and an individual homozygous for AQP1 deficiency (subject IIa, -/-, solid line) were analyzed by osmotic gradient ektacytometry, a technique that determines whole cell deformability while the osmolality of the suspending medium is continuously being changed. Consistent with a small reduction in membrane surface area and a small decrease in surface-to-volume ratio, the Colton-null red cells exhibit a minor reduction in maximum deformability (at 290 mosM/kg) and a small shift in the osmolality value at which red cells exhibit minimum deformability in hypotonic medium (140 mosM/kg).
Low-intensity He-Ne laser irradiation (LHNL) was irradiated at 5 mW (4.4 mW/cm²) for 5 minutes.
Aquaporin 1 mediated LPBM

HgCl₂ is an inhibitor of aquaporin 1

1 echinocytes, 2 LIL, 3 HgCl₂+LIL
Volunteer Subjects

- Coronary Heart Disease (CHD) was diagnosed on electrocardiogram and coronary angiography,
- Cerebral Infarction (CI) was diagnosed on coronal CT appearance.

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients (n)</th>
<th>Gender</th>
<th>Age (years)</th>
<th>CHD (n)</th>
<th>CI (n)</th>
<th>CHD&amp;CI(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Group</td>
<td>60</td>
<td>34</td>
<td>26</td>
<td>76.6±7.81</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Control Group</td>
<td>30</td>
<td>15</td>
<td>15</td>
<td>75.5±9.52</td>
<td>13</td>
<td>14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>t Value</th>
<th>0.358</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>t Value</th>
<th>0.561</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>t Value</th>
<th>5.157</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>
Rehabilitation of dPBM

Before

After

Blood Corpuscle Examination
### Blood Viscosity Index (mean ± SEM)

<table>
<thead>
<tr>
<th>BV</th>
<th>Treatment Group(n)</th>
<th>Verified Statistics</th>
<th>Control Group(n)</th>
<th>Verified Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>t</td>
<td>P</td>
</tr>
<tr>
<td>BV(l)</td>
<td>8.34 ± 1.91</td>
<td>8.15 ± 1.91</td>
<td>0.545</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>BV(h)</td>
<td>4.23 ± 0.82</td>
<td>3.94 ± 0.74</td>
<td>2.020</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PV</td>
<td>1.23 ± 0.02</td>
<td>1.14 ± 0.22</td>
<td>2.233</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RBCP</td>
<td>39.88 ± 7.72</td>
<td>41.66 ± 4.79</td>
<td>1.526</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>RV(l)</td>
<td>17.35 ± 4.03</td>
<td>15.24 ± 2.82</td>
<td>3.323</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RV(h)</td>
<td>6.99 ± 0.75</td>
<td>6.63 ± 0.55</td>
<td>2.120</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RBCA</td>
<td>2.15 ± 0.41</td>
<td>1.95 ± 0.24</td>
<td>3.263</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**BV**: Blood Viscosity,  
**l**: low shear  
**PV**: Plasma Viscosity,  
**RBCP**: Red Blood Cell Pressure,  
**RV**: Redox Viscosity,  
**RBCA**: Red Blood Cell Aggregation
Olfactory, autonomic and central nervous system
ILIT Biomechanism: bone mediation

Mesenchymal stem cells/marrow stromal cells (MSCs) mediated ILIT
Mesenchymal stem cells (MSCs)
Effects of LIL on infarct size (a) and ventricular dilatation (b) in infarcted control non-laser-treated (open column), LIL applied to the heart (dashed column), and LIL applied to the BM (solid column) in rats. Rats were sacrificed 3 weeks post-MI, and LIL was applied 20 minutes post-MI.

*P < 0.05 and **P < 0.01.
Effect of LIL application on the density of c-kit in the entire left ventricle (a) or infarcted area (b) in control non-LIL-treated (open column), LIL applied to the heart (dashed column), or LIL applied to the BM (solid column) in rats. *P < 0.05 and **P < 0.01.

Extracellular matrix (ECM)


Extracellular matrix (ECM)


**Donor Effects**

**ejection fraction (EF)**

**end-systolic volume (ESV)**

**end-diastolic volume (EDV)**
MSC-mediated ILIT mechanism

- Improved MSCs
  - Nasal bone
  - Du meridian

- Improved ECM
  - olfactory nerve (melatonin),
  - blood cells,
  - autonomic nervous system
ILIT: intranasal light therapy

ILIT → MSCs

→ myocardial infarction
→ Carpal tunnel syndrome
→ Epicondylitis
→ Exercise-induced muscle damage
→ Osteoarthritis
→ Stroke (cerebral infarction, …)
→ Wound
Olfactory, autonomic and central nervous system
Targeted delivery

"Nose-to-brain" delivery

Tube to middle ear

Lymphoid tissues

Openings to the sinuses

No lung inhalation

Tube to middle ear

Lymphoid tissues

Openings to the sinuses

Less local irritation

single photon emission computed tomography (SPECT)
Improved regional cerebral blood flow

before

after

net increase

SPECT for old men before and after ILILT from Prof. Xiao XC
ILIT: intranasal light therapy

DMN: default mode network

Clinical applications

Cerebral Palsy
Depression
Insomnia
Mild cognitive impairment
Alzheimer’s disease
Parkinson’s disease
Schizophrenia

In Summary
Handling stress

SIRT1 is a deacetylase that is activated by a variety of stressors and targets transcriptional regulators including p53, NF-κB, HSF1, FOXO1, 3, and 4, and PGC-1. These factors then control adaptive responses that modulate life span. AC: acetyl group; TH: Tyrosine hydroxylase.

SIRT1 is activated by calorie restriction; oxidative stress; polyphenols.
Sirtuin 1 (SIRT1) activity potential well.

FSSA1 denotes function-specific homeostasis specific SIRT1 activity.

Function-specific homeostasis (FSH)

FSH-specific SIRT1 activity (FSSA1)
ILIT: intranasal light therapy

SIRT1: Sirtuin 1, one of longevity factors

Clinical applications

- Pain Relief
- Cerebral Palsy
- Stroke (cerebral infarction, …)
- Coronary Heart Disease
- Myocardial infarction
- Inflammation
- Depression
ILIT: intranasal light therapy

SIRT1: Sirtuin 1, one of longevity factors

Clinical applications:

- Hyperlipidemia
- Blood hyperviscosity
- Insomnia
- Mild cognitive impairment
- Alzheimer’s disease
- Parkinson’s disease
- Schizophrenia

Possible applications in sports medicine

ILIT: intranasal light therapy

SIRT1: Sirtuin 1, one of longevity factors

- Asthma
- Carpal tunnel syndrome
- Epicondylitis
- Exercise-induced muscle damage
- Osteoarthritis
- Upper respiratory tract infection
- Wound

SIRT1

ILILT

Discussion

"I think you should be more explicit here in step two."
Olfactory, autonomic and central nervous system
ILIT Biomechanism: Olfaction
Hierarchical regression analyses

- Proficiency in executive functioning and semantic memory contributed significantly to odor discrimination and identification performance (Hedner et al. 2010)
- Age, sex, education, cognitive speed and vocabulary were reliable correlates of performance in the odor identification task (Larsson et al. 2004).

Odor identification and decline in different cognitive domains in old age

- A person with a low odor identification score (6, 10th percentile) declined more than twice as rapidly in perceptual speed and episodic memory as a person with a high score (11, 90th percentile)
  - Lower odor identification score was associated with lower function at baseline in each cognitive domain
  - Lower score was also associated with more rapid decline in perceptual speed and episodic memory but not with rate of decline in semantic memory, working memory, or visuospatial ability.

Dysfunctional odor identification

- Neurodegenerative diseases such as Alzheimer’s and Parkinson's disease

- Schizophrenia

- Depression
Dysfunctional odor identification

- HIV infection

- Posttraumatic stress disorder (PTSD)

- Addiction
Age-sex adjusted Kaplan–Meier survival curves by severity of olfactory impairment among Blue Mountains Eye Study participants aged 60 years and older.


Odor identification Score (OIS) and mortality in old age

**Figure 1** Distribution of odor identification scores in participants who survived (green) and those who died (blue).

**Figure 2** Cumulative risk of death associated with a low (dotted line, 10th percentile) compared with high (solid line, 90th percentile) odor identification score, adjusted for age, sex, and education.

Olfaction might be recovered/enhanced with ILIT

- Numerous central nervous system disorders may be associated with olfactory dysfunction.
  - According to dPBM, ILIT might recover CNS disorders at least through olfaction recovery.

- Olfaction has been found to represent longevity. The stronger the olfaction, the longer the longevity.
  - According to iPBM, ILIT might extend the longevity at least through olfaction promotion.
Olfactory, autonomic and central nervous system

Blood

Bone

Acupoints and meridians
ILIT: intranasal light therapy
DMN: default mode network

Clinical applications

Cerebral Palsy
Depression
Insomnia
Mild cognitive impairment
Alzheimer’s disease
Parkinson’s disease
Schizophrenia

DMN might be recovered/enhanced with ILIT

- Numerous central nervous system disorders may be associated with dysfunctional DMN.
  - According to dPBM, ILIT might recover CNS disorders at least through DMN recovery.

- DMN connectivity has been found to represent cultural intelligence. The stronger the DMN connectivity, the higher the cultural intelligence.
  - According to iPBM, ILIT might extend the cultural intelligence at least through DMN connectivity promotion.
Acknowledgement

- The 2000-2002 summer student research grants of the American Society of Lasers in Surgery and Medicine;

- National Science Foundation of China (60878061, 60478048, 6027812, 60178003 and 69778003).