Photomodification of Blood Using Low-Intensity Optical Radiation

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INTRODUCTION

The optical radiation effect on blood in blood vessels and tissues, used for therapeutic purposes, is one of the methods of a phototherapy (PT) that is the fastest-growing field of modern medicine. Laser medicine originated in the second half of the twentieth century; it should be viewed as a PT subset that is one of the oldest therapeutic methods. PT was initially utilized in medical practice as solar therapy, then light therapy, and then as ultraviolet blood irradiation that has been in use in medicine for 70 years. Currently, PT performed as intravenous and overvein blood irradiation with low-intensity optical radiation is considered as a method of biostimulation suitable for treating a wide range of diseases. Evidence has emerged that the combined effects of phototherapy and drug treatment improve treatment outcomes.

So far, the expansion of the scope of applications of intravenous and overvein blood irradiation has been empirical. The widespread use of these methods in medical practice was limited by a lack of generally accepted ideas about the primary molecular mechanism of the optical radiation action on blood irradiated *in vivo*. The previously proposed biostimulation mechanisms, based on the analysis of various secondary reaction products, obtained by irradiating cell cultures and biotissues, remained at the level of the hypotheses unable to explain many experimental facts. In addition, it was impossible to predict the PT effects on a living organism by the processes detected in cell cultures and in isolated tissues. It appeared that a direct comparison of the effects observed in model experiments and in a living organism poses great difficulties. The same PT methods, with identical energy densities of light exposure, initiated improvements in some patients and unpredictable negative reactions in others. The positive and negative treatment results were not explained scientifically. Such topical photobiostimulation problems remained unresolved, as the development of methods for assessing their effectiveness for individual patients and the creation of methods for standardization and control.

In this regard, the study of photoreactions initiated in blood by therapeutic doses of the optical radiation at different wavelengths, the determination of laws of blood photomodification, and the identification of factors that most affect the individual patient sensitivity to the blood irradiation are among the urgent tasks of PT. Solving these problems will

contribute to deepening our understanding of PT mechanisms and also further expand the applications of laser-optical technologies in medicine.

ABOUT THE STRUCTURE OF THE BOOK

The book is founded on the experimental results of the authors. The main purpose of this book is to propose and substantiate PT molecular mechanisms with the implication of photophysical processes initiated by low-intensity optical radiation. The book is organized in four chapters, a conclusion and a bibliography.

According to the basic law of photochemistry, a photochemical reaction in blood can occur only if irradiated blood is capable of absorbing incident light. In Chapter One, we studied the spectral characteristics of whole blood, red cells and plasma before and after UV extracorporeal, intravenous and overvein blood irradiation by low-intensity laser-optical radiation at different wavelengths. The spectral manifestations of photochemical processes initiated in blood under PT were explored and explaind in order to examine the irradiation effects at the molecular level. Fluorescent spectroscopy was adopted to investigate possible structural changes in plasma macromolecules after the blood irradiation *in vivo*.

In Chapter Two, the research objects were blood gas composition, a degree of hemoglobin oxygen saturation in venous and arterial blood, acid-based balance indices, erythrocyte and hemoglobin concentrations, as well as contents of some metabolic products under PT. A study of changes initiated by PT in the partial pressure of blood gases and in the degree of hemoglobin oxygen saturation is a further step in identifying the photoacceptor molecule. Based on these data, the blood irradiation effect on the oxygen status of venous and arterial blood, the oxygen supply to the organs and tissues, and the oxygen utilization was studied. The blood oxygenation dynamics during the PT courses was defined as well. The changes in hematocrit, hemoglobin concentration, and erythrocyte count at low-intensity optical radiation doses were monitored during the PT course. Special attention was given to the susceptibility of individual patients to blood irradiation, and methods for its control were suggested.

A significant part of this chapter was devoted to metabolic processes under PT. Using glucose and lactate (playing an important role in metabolic processes), as an example we studied the PT effect on their concentrations. We showed that therapeutic doses of the optical radiation absorbed by blood cause short- and long-term changes in lactate and glucose concentrations in blood of patients. The dependences of

concentration changes initiated by PT on both the initial concentrations and the photoinduced variations in the blood oxygenation were analyzed.

Using the optical radiation of various wavelengths, we investigated the PT effects on blood coagulation parameters in different patients. The concentration changes in total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were estimated. A relationship between the photoinduced changes in blood oxygenation characteristics and the concentrations of metabolic products was analyzed. Possible molecular mechanisms were considered for the effects observed.

Chapter Three was devoted to analyzing the molecular mechanism of the PT action. First, a brief review based on the analysis of literature data was presented. It covered the proposed mechanisms of therapeutic action of laser-optical radiation. It should be noted that before our studies, the PT effect on a living organism had not been sufficiently analyzed at the molecular level.

The hypothesis that local heating of blood or tissues in the absorption zone is a starting mechanism for biostimulation has been actively discussed to date. We therefore performed a computer simulation of thermal fields and estimated heating temperatures at the tissue surface, in tissues, and in venous blood at low- and high-intensity laser irradiation. Computer modeling of low-intensity optical radiation effects in mucosal tissues was used to explore the mechanism of the optical radiation action on tissues stained by photosensitizers.

The choice of a wavelength for PT is another medical problem, for the solution of which the optical properties of blood and tissues are extremely important. The optical properties of blood and human tissues were briefly summarized. Based on these data, spectra of the radiation penetration depth into blood and skin tissues were calculated in the wavelength range of 405–950 nm. The wavelengths optimal for PT were then determined. Molecular oxygen is effectively formed during intravenous and overvein blood irradiation with the optical radiation at these wavelengths.

Based on the results obtained, we proposed a molecular mechanism for the therapeutic action capable of explaining a number of effects that had not been interpreted unambiguously for many years. The main photoactivation stages of the organism were suggested. The possible role of reactive oxygen species in the therapeutic action of low-intensity optical radiation was considered. The applicability of the proposed PT mechanism was discussed to explain the therapeutic effects observed in treating a wide range of diseases.

In Chapter Four, which deals with rat experiments, the radioprotective possibilities of low-intensity optical radiation were used to study the actual problem of counteracting the destructive action of ionizing radiation. The available literature data have no convincing confirmation of the radioprotective capability of low-intensity optical radiation. The effect of *in vivo* blood irradiation with the laser radiation on the hematological parameters and the antioxidant protection enzymes for gamma-exposed rats was examined. The quantitative changes caused by low-intensity laser radiation and gamma radiation in blood cells were analyzed. Differences in the individual radiosensitivity of rats were investigated. The molecular mechanisms of the radioprotective effect of low-intensity optical radiation, as well as the factors affecting the individual sensitivity of rats were discussed.

In conclusion, the results obtained by the authors of the book were summarized. The most important results were emphasized. In our opinion, they will contribute to a further successful use of PT in medical practice. Some important issues, which remained unresolved despite a rapid growth of a number of PT studies, were considered. Further research areas are outlined.

The book summarizes the interdisciplinary research results, and will be of interest to researchers in photophysics, biophysics, physiotherapy, as well as to physicians using phototherapy in complex treatment and rehabilitation of patients. The book is also intended as a teaching tool either for graduate students or students interested in physical medicine problems.

ABBREVIATIONS

ACS	–	Acute coronary sindrome
AOS	–	Antioxidant system
aPPT	–	Activated partially prothromboplastin time
$AVDO_2$	–	Arteriovenous oxygen difference
Ca^{2+}	–	Calcium ions
CO_2	–	Carbon dioxide
$ConO_2$	–	Consumption of oxygen
CVD	–	Cardiovascular disease
CAT	–	Catalase
C_{util}	–	Coefficient of oxygen utilization
ct_aO_2	–	Oxygen capacity in arterial blood
ct_VO_2	–	Oxygen capacity in venous blood
DRA	–	Deoxyribonucleic acid
2,3-DFG	–	2,3-Diphosphoglycerate
DO_2	–	Delivery of oxygen
EFME	–	Electrophoretic mobility of erythrocyte
EMT	–	Extracorporeal magnetotherapy
$F_V(HbO_2)$	–	Content of oxyhemoglobin fraction
GRA	–	Granulocyte
Gy	–	Gray
Hct	–	Hematocrit
Hb	–	Hemoglobin
H^+	–	Hydrogen ions
H_2O_2	–	Hydrogen peroxide
HbO_2	–	Oxyhemoglobin
HCO_3^-	–	Hydrocarbonate ion
IR	–	Ionizing radiation
INR	–	International normalized ratio
IVBI	–	Intravenous blood irradiation
k_{enh}.	–	Resolution enhancement factor
KRS	–	Thallium bromide iodide mixed crystal
LED	–	Light emitting diode
LILR	–	Low intensity laser radiation
LIOR	–	Low intensity optical radiation

LPO	–	Lipid peroxidation
LYM	–	Lymphocyte
MCV	–	Mean erythrocyte volume
MetHb	–	Methemoglobin
MF	–	Magnetic field
MT	–	Magnetic therapy
NO	–	Nitrogen oxide
ODC	–	oxyhemoglobin dissociation curve
OTFB	–	Oxygen transport function of blood
OVBI	–	Overvein blood irradiation
O_2		Oxygen
$^1O_2$	–	Singlet oxygen
O_2^-	–	Superoxide anion radical
PMM	–	Primary molecular mechanism
PPA	–	Primary photoacceptor
pH	–	Blood acidity
P_{50}	–	Oxygen partial pressure at which hemoglobin is 50% saturated
$\Delta p_V O_2$	–	Oxygen partial pressure in venous blood
$p_V CO_2$	–	Carbon dioxide partial pressure in venous blood
r	–	Pearson linear correlation coefficient
RBC	–	Erythrocyte
RNA	–	Ribonucleic acid
ROS	–	Reactive oxygen species
SOD	–	Superoxide dismutase
TCT	–	Trombin cloting time
UV	–	Ultraviolet
UVBI	–	Ultraviolet blood irradiation
$S_V O_2$	–	Hemoglobin oxygen saturation in venous blood
V_{er}	–	Volume of red blood cell
WBC	–	Leukocyte
γ	–	Gamma radiation
η_{bl}	–	Blood viscosity
η_{pl}	–	Plasma viscosity
λ	–	Wavelength
$\Delta\nu_{1/2}$	–	Half width of absorption band

CHAPTER ONE

THE EFFECT OF LOW-INTENSITY OPTICAL RADIATION ON THE SPECTRAL-LUMINESCENT CHARACTERISTICS OF BLOOD IRRADIATED *IN VIVO*

1.1 Electronic absorption spectra of whole blood, erythrocytes and plasma

Absorption spectroscopy is widely used to study the physicochemical properties of biological objects [1–3]. The position of absorption bands, and their half-width and intensity provide information on a qualitative and quantitative ratio of the components of biological systems and on their structural organization in the ground electronic state.

In the wavelength range of 210–250 nm, a number of blood components are absorbed: residues of aliphatic amino acids of proteins, free aliphatic amino acids of blood plasma, lipids of a membrane and plasma, polysaccharides, and some other non-protein organic components of blood plasma. In the range of 250–300 nm, the absorption occurs due to residues of aromatic amino acids: tryptophan, tyrosine, and phenylalanine. Of these, tryptophan has the highest absorption coefficient at a wavelength of 254 nm which is used in UV devices for the blood irradiation. Free amino acids and radicals of blood plasma that play an important role in initiating photooxidation reactions of unsaturated fatty acids are also absorbed within this range. It should be noted that UV radiation at 254 nm used for therapeutic purposes is photochemically active and can cause a breakdown of nucleic acids, proteins and lipids.

The absorption spectra of whole blood, erythrocytes and plasma are shown in Fig. 1-1. The shortwave absorption band, with a maximum wavelength of λ_{max}= 280 nm, is present in the spectra of all proteins containing aromatic amino acid residues.

The absorption bands of deoxyhemoglobin at λ_{max} = 430 and 555 nm, as well as the oxyhemoglobin bands at λ_{max}= 344, 415, 541 and 577 nm,

which appear in the blood and erythrocyte spectra, are caused by the absorption of iron porphyrin being part of hemoglobin [4]. Hemoglobin is a protein globule-tetramer. It is formed by four polypeptide chains, each of which is an individual molecule containing a protoporphyrin chelate complex with iron (heme), capable of attaching ligands (O_2, CO, NO, etc.). In the UV range, the absorption bands at λ_{max}=274 nm for deoxyhemoglobin and λ_{max}=276 nm for oxyhemoglobin, corresponding to their shortest wave transition, are masked by the absorption of proteins.

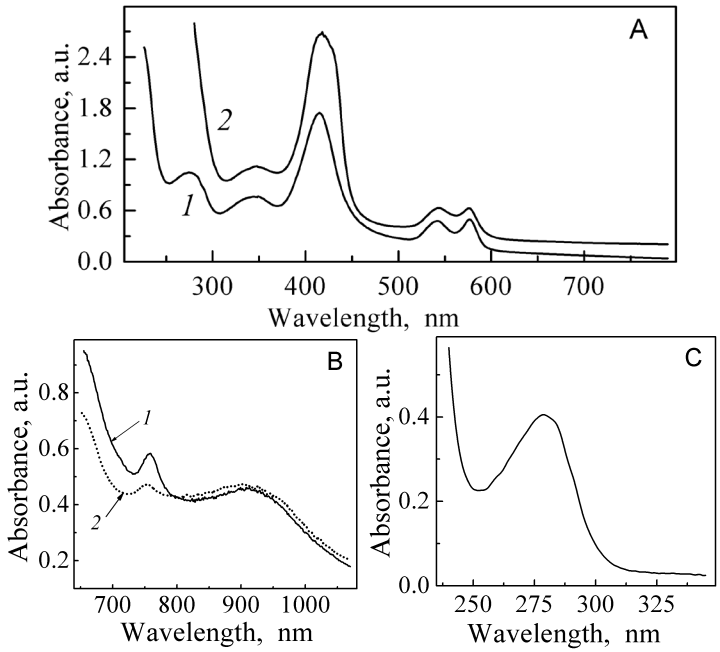

Fig. 1-1 Absorption spectra: whole blood (A1) and erythrocytes (A2), whole blood with a higher concentration of oxyhemoglobin (B2) and with a lower one (B1); plasma (C)

In the absorption spectrum of all hemoglobins, the most intense among iron-porphyrin bands is the Soret band (k= 140 $mM^{-1}\cdot cm^{-1}$), the maximum of which can be between 410 <λ_{max}<430 nm. According to the data [5], in the range of the Soret band, the electronic absorption spectra of porphyrins have two resolved high-intensity bands which belong to transitions, polarized mutually perpendicularly. High-frequency asymmetry of the band contour is due to the vibrational structure. The assignment of the