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The influence of low level laser irradiation on vascular reactivity

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ABSTRACT

Purpose: The mechanism of action of low level laser irradiation on tissues is unclear. Authors of publications present the positive clinical impact of low and medium power laser irradiation on vascular reactivity. The purpose of this study was to analyze the role of vascular endothelium in laser-induced constricted by endothelin-1 and phenylephrine.

Materials and methods: Experiments were performed on isolated and perfused rat tail arteries of weighing 250–350 g male Wistar rats. Contractility of arteries as a response to endothelin-1 and phenylephrine was measured after exposure to laser stimulation (10, 30 and 110 mW).

Results: Laser irradiation inhibits vascular smooth muscle contraction induced by endothelin-1 and an alpha-adrenergic receptor agonist, phenylephrine proportionally to the laser power. Concentration-response curves were shifted to the right with significant reduction in maximal response. Laser irradiation at the power of 10 mW, 30 mW, and 110 mW reduced the maximum response of arteries stimulated with phenylephrine sequentially to 88%, 72%, and 52%. Similar findings were observed during stimulation of endothelin-1. Laser irradiation at the power of 10 mW, 30 mW and 110 mW resulted in maximal response respectively reduced to 94%, 62% and 38%.

Conclusion: Our results strongly suggest that during low level laser irradiation vascular smooth muscle cells reactivity is reduced, this effect is present in arteries with normal endothelium. The mechanism of action of laser biosimulation on tissues is unclear. Authors of publications present the positive clinical impact of low level laser irradiation on vascular reactivity.

1. Introduction

Low –level laser irradiation also known as laser biostimulation have been clinically used for many years. Its application include wound healing, soft and hard tissue [1–8], treating pain syndromes, enthesopathy, peripheral nerve injury and peripheral neuropathy. Many studies also confirmed anti-inflammatory qualities of low-level laser irradiation (LLLI) [2,6,9]. LLLI modulate many of biological processes which manifests in an increase of mitochondrial respiration, an increase in ATP synthesis proliferation of mesenchymal stem cells and cardiac stem cells [10,11]. The biological effects of LLLI are still not well understood and stir a lot of controversy [12].

The influence of light on vascular smooth muscle have been studied from the early 20th century, when it was established that light affects its contractibility [13,14]. The studies were continued by Furchgott in the in the 1950s and 1960s [13]. From the 1980s there have been reports on the effect LLLI on the action of vascular smooth muscle. Experimental studies have proven that laser of power less than 100 mW cause relaxation of smooth muscle of blood vessels [14–17]. Clinical studies from the 21st century prove that LLLI may cause photorelaxation of blood vessels including coronary arteries and may prevent their restenosis after PTCA [11,18].

The goal of our study is to determine the mechanism in which LLLI affects vascular smooth muscle reactivity and the role of Nitric Oxide (NO) in this processes.

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2. Material and methods

2.1. Animals

The experiments were performed on isolated, perfused tail arteries of Wistar rats which were kept under a 12-h light/12-h dark cycle with food and water available ad libitum. The animals (n = 37) weighing 250–350 were anesthetized with an intraperitoneal injection of urethane (120 mg/kg), stunned and sacrificed by cervical dislocation. The study protocol was approved by the Local Ethics Committee and all experiments were carried out in accordance with the United States NIH guidelines [Guide for the Care and Use of Laboratory Animals (1985), DHEW Publication No. (NIH) 85-23: Office of Science and Health Reports, DRR/NIH, Bethesda, MD, U.S.A.].

2.2. Drugs and solutions

Krebs solution contained NaCl (71.8 mmol/L), KCl (4.7 mmol/L), CaCl2 (1.7 mmol/L), NaHCO3 (28.4 mmol/L), MgSO4 (2.4 mmol/L), KH2PO4 (1.2 mmol/L), and glucose (11.1 mmol/L). All reagents were obtained from Sigma Aldrich Chemical Company (Poznan, Poland).

2.3. Study design and conduction

Following dissection from the surrounding tissues, 2.5 to 3.0 cm long segments of rat tail arteries were cannulated and connected to a perfusion device. The distal part was ballasted with a 500 mg weight and the arteries were put in a 20-mL container filled with oxygenated Krebs solution at 37 °C. The perfusion pressure was continuously evaluated. A peristaltic pump was used to gradually increase perfusion solution flow up to 1 mL/min. The measurement of vasospasm induced with phenylephrine (an adrenergic alpha- 1 receptor agonist; PHE) and endothelin (agonist of endothelin receptor A) was based on an increase in perfusion pressure. Experiments were performed separately on arteries exposed to laser radiation and control arteries.

The agonists were applied directly to the solution in tissue perfusion chamber.

The study utilized a semiconductor laser (400 mW, wave length810 nm), operating in continuous-wave mode.

After achieving maximal vasospasm the arteries were rinsed and stabilized for a period of 30 min before exposition to laser irradiation. The arteries were placed on a plate and the laser header was positioned on a tripod approximately 1 cm from the irradiated tissue. The irradiation was applied directly on the blood vessels without utilization of a glass chamber. The laser power was applied in increasing doses of 10 mW (E = 1,8J), 30 mW (E-5,5J), 110 mW (E = 19,8J). Time of exposition was 3 min for each irradiation.

2.4. Data analysis and statistical procedures

The van Rossum method was utilized to calculate the concentration-response curves (CRCs). The points of maximal response between 20% and 80% of the CRCs were compared and analysed. The maximal response of tissue (Emax) was calculated as a percent of the maximal response for PHE. The half maximal effective concentration (EC50) was estimated using classical pharmacological methods with pD2, the negative logarithm of the EC50. The CRC and Emax were used in all the calculations estimating the statistical significance.

Results were presented as means ± standard deviations. We used the Shapiro-Wilk test to verify normal distribution of the variables. Statistical analysis was performed using the Newman-Keuls test for multiple comparison of means. Statistical significance was set at $P < 0.05$ (two sided).

Table 1
EC_{50}, maximal response and relative potency of phenylephrine for controls and in the presence of laser radiation at the power of 10 mW, 30 mW, 110 mW.

	n[a]	$\%E_{max}$[b]	EC_{50} [M]	pD_2	RP[c]
Controls	20	100	6,88 (±0,42) $\times 10^{-8}$	7,16	100%
+L1 (10 mW)	12	88	2,90 (±0,98) $\times 10^{-7}$*	6,54	24%
+L2 (30 mW)	10	72	6,12 (±1,06) $\times 10^{-7}$*	6,21	11%
+L3 (110 mW)	12	52	1,40 (±1,24) $\times 10^{-6}$*	5,89	5%

* p-value < 0.05 calculated in comparison to control values.
[a] Number of concentration-response curves used for calculations.
[b] Emax – calculated as a percent of maximal response for controls.
[c] RP – relative potency – calculated as EC_{50} for controls/EC_{50}.

3. Results

Laser irradiation at the power of 10 mW, 30 mW, and 110 mW reduced the maximum response of arteries stimulated with of an alpha-adrenergic receptor agonist, phenylephrine sequentially to 88%, 72%, and 52%. Furthermore, we found significant and power-dependent increase in EC50 value (the concentration of agonist at which 50% of the maximal effect is reached). EC50 in the presence of 10 mW, 30 mW and 110 mW laser irradiation was respectively 4.2, 9.5 and 20.3 times higher than in the controls. Relative potency was reduced in all laser irradiated subsets. The results are presented in Table 1.

Similar findings were observed during stimulation of endothelin-1. Laser irradiation at the power of 10 mW, 30 mW and 110 mW resulted in maximal response respectively reduced to 94%, 62% and 38%. The response pattern was similar to phenylephrine. Analysis of EC50 value revealed a significant and power-dependent reduction. EC50 in the presence of 10 mW, 30 mW and 110 mW laser irradiation was respectively 5.5, 50.7 and 89.4 times higher than in the controls. Relative potency of endothelin-1 was reduced in all laser irradiated subsets. The results are presented in Table 2.

Maximal perfusion pressure during phenylephrine as well as endothelin-1 induced vasospasm was significantly and power-dependent reduced during laser irradiation. The reduction was found during contraction resulted from calcium influx from intra and extracellular calcium stores. The results are presented in Tables 3 and 4.

In the first stage of the experiment, which reflected calcium influx from the intra cellular space, the maximal perfusion pressure achieved with PHE was 57.9 (±7.2). After laser irradiation, a reduction of pressure was observed to 1 (±3.3); 25.2 (±4.2); 18.2 (±4.7), respectively, to irradiation at the power of 10 mW; 30 mW oraz 110 mW. The reduction was statistically

Table 2
EC_{50}, maximal response and relative potency of endothelin-1 for controls and in the presence of laser radiation at the power of 10 mW, 30 mW, 110 mW.

	n[a]	$\%E_{max}$[b]	EC_{50} [M]	pD_2	RP[c]
Controls	20	100	7,51 (±0.78) $\times 10^{-9}$	8,12	100%
+L1 (10 mW)	12	94	4,10 (±0.92) $\times 10^{-8}$*	7,39	18%
+L2 (30 mW)	11	62	3,80 (±0.75) $\times 10^{-7}$*	6,42	2%
+L3 (110 mW)	12	38	6,20 (±0.98) $\times 10^{-7}$*	6,21	1%

* p-value <0.05 calculated in comparison to control values.
[a] Number of concentration-response curves used for calculations.
[b] Emax – calculated as a percent of maximal response for controls.
[c] RP – relative potency – calculated as EC_{50} for controls/EC_{50}.

Table 3
Maximal perfusion pressure during phenylephrine-induced contraction.

	Intracellular calcium Phase 1		Extracellular calcium Phase 2	
	n	Perfusion pressure (±SE) [mmHg]	N	Perfusion pressure (±SE) [mmHg]
Controls	20	57.9 (±7.2)	20	93.6 (±7.8)
+L1 (10 mW)	12	40.1 (±3.3)*	11	78.7 (±6.7)*
+L2 (30 mW)	11	25.2 (±4.2)*	11	47.4 (±7.5)*
+L3 (110 mW)	12	18.2 (±4.7)*	12	27.4 (±8.5)*

* $p < 0.0001$ vs. controls.

Table 4
Maximal perfusion pressure during endothelin-1 -induced contraction.

	Intracellular calcium Phase 1		Extracellular calcium Phase 2	
	n	Perfusion pressure (±SE) [mmHg]	N	Perfusion pressure (±SE) [mmHg]
Controls	19	52.7 (±6.1)	20	93.6 (±7.8)
+L1 (10 mW)	10	44.1 (±4.1)*	11	81.2 (±7.2)*
+L2 (30 mW)	11	31.8 (±5.1)*	11	49.1 (±6.3)*
+L3 (110 mW)	10	20.7 (±5.2)*	11	33.2 (±6.9)*

* $p < 0.0001$ vs. controls.

significant in relation to the control value and proportional to the irradiation power.

Similar relationships were observed in the second stage of the experiment, which reflected calcium influx from the extra cellular space. The PHE induced maximal perfusion pressure was 93.6 (±7.8), which fell to 78.7 (±6.7); 47.4 (±7.5) and 27.4 (±8.5) after applying laser irradiation at the power of, respectively, 10 mW; 30 mW and 110 mW. In all the cases, the reduction of pressure significantly differed from the control value. The results are shown in Table 3.

Similar relationships were observed after applying endothelin-1. In the first stage of the experiment, reflecting calcium influx from the intracellular space, the maximum perfusion pressure achieved by endothelin 1 was 52.7 (±6.1). After applying laser irradiation at the power of 10 mW; 30 mW and 110 mW, there was a reduction of pressure to, respectively, 44.1 (±4.1); 31.8 (±5.1); 20.7 (±5.2). The pressure reduction was proportional to the laser power. In the second stage of the experiment, which reflected calcium influx from the extracellular space, the perfusion pressure was, respectively, 81.2 (±7.2; 49.1 (±6.3); 33.2 (±6.9). The pressure reduction was statistically significant in relation to the control value and proportional to the laser power. The results are shown in Table 4.

4. Discussion

Vascular endothelium is the main source of NO which is considered as the most potent endogenous vasodilator and vasoconstriction preventing factor [19,20,21,22,23]. In the 1950s Furchgott proved that both visible and ultraviolet light irradiation cause relaxation of vascular smooth muscle. According to the author the vasodilatory effect was mediated by certain endogenous photosensitive factors activated by light. He also stated that photorelaxation was reversible and was not an effect of any damage to the muscle [13].

Activation of alpha-adrenergic and endothelin-1 receptors, both located in the vascular endothelium, produces strong vasospasm. Proper blood vessel tone is maintained by the balance in vasodilatory NO and vasoconstrictive action of endothelin [24,25]. In our experiments laser irradiation at the power of 10 mW, 30 mW and 110 mW resulted in inhibition of alpha-adrenergic and endothelin-1 receptor mediated vasospasm. The higher laser irradiation dosage was applied, the bigger inhibition of vasoconstriction was observed. Inhibitory effect of LLLI was observed for arteries with normal vascular endothelim.

Our previous investigations, presented as a poster during the 19th European Congress of Physical and Rehabilitation Medicine, Marseille 2014, showed the presence of the vasodilatative effect of LLLI in the blood vessel with preserved and functioning epithelium, as the LLLI did not have the vasodilative effect on the blood vessels with stripped epithelium or after applying an NO inhibitor [26].

In our study we proved that LLLI also inhibits vasoconstriction that is induced by endothelin.

We also managed to show that the inhibition of endothelin-induced calcium influx, both from extra and intra cellular space.

We observed that the pressures related to the calcium influx from extra and intra cellular spaces, induced by both phenylephrine and endothelin were reduced by LLLI, and the reduction was proportional to the increasing power of the irradiation.

Similar findings of LLLI induced vasorelaxation were observed by Gal and Steg [16,15]. They showed that laser irradiation at the power below 100 mW caused constant smooth muscle relaxation, whereas continuous wave laser at the power below 1W resulted in vasoconstriction. However contrary to our findings Gal and Steg proved that vasodilatory effect of laser is was not endothelium dependent as they were able to cause vasodilation without the presence of the endothelium. The experiments were performed both in vitro and in vivo. In vivo laser irradiation was generated from laser sources representing the ultraviolet, visible and infrared portions of electromagnetic spectrum. It was determined that all 3 wave lengths of light reverted histamine induced vasospasm.

Steg observed in vitro relaxation of smooth muscles induced by low pulsed low level laser even if the muscles had not been previously contracted [15].

Maegave and al also conducted studies on the effect of LLLI on arterioles and concluded that it acted as vasodilator. They suggested it was partially an effect of NO release, especially in the initial phase, whereas in the late phase LLLI induced reduction of Ca +2 in microvascular smooth muscles [27,28].

Both continuous wave low level laser at the power below 100mw and excimer laser which resulted in vasodilation were independent from an increase in temperature [15].

The in vitro and in vivo studies on the effect of low energy laser on vascular smooth muscle reactivity prompted clinical studies on the effects of LLLI in blood vessel disorders. De Sceerder et al. conducted studies in 80 patients who underwent PTCA with low power laser light of energy level 30 mW applied endovascularly using a balloon catheter system. Initial results prove that laser results in a decrease of in-stent restenosis when used during primary stenting. Laser was not as effective in patients with secondary stenting. The authors suggested that LLLI inhibits intimal hyperplasia in an unknown mechanism.

Plass et al. examined the effect of LLLI on human coronary arteries and internal thoracic artery. It was determined that photorelaxation was more prominent in healthy arteries than in atherosclerotic ones. They claimed that during laser irradiation intracellular photolabile store of NO gets activated which prevents the arteries from vasospasm. The authors also postulated other clinically important effects of LLLI, namely antithrombotic and inhibiting growth of arterial smooth muscle which may result in restenosis prevention [11]. Similar restenosis preventing mechanism was described by Kipshidze et al. in their in vitro studies in which they observed that LLLI stimulates vascular endothelial growth factor (VEGF) in smooth muscles, cardiomyocytes and fibroblasts [18]. Similar results were published by Hirakawa et al. who observed that ultraviolet B skin irradiation resulted in an increase of VEGF production promotes vessel dilatation and vascular proliferation [5].

LLLI may potentially become one of the modalities not only used in prevention of coronary artery restenosis but also it may become useful in treating lower extremity atherosclerosis. Percutaneous irradiation of atherosclerotic arteries would be cheap, noninvasive and side effect free method, however it requires further clinical studies.

5. Conclusion

Our results strongly suggest that during laser biostimulation vascular smooth muscle cells reactivity is reduced, this effect is present in arteries with normal endothelium

Conflict of interests

The authors declare no conflict of interests.

Financial disclosure

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