Nitric oxide mediates anti-inflammatory action of extracorporeal shock waves

Anna R. Ciampa[a], Alessandra Carcereri de Prati[a], Ernesto Amelio[b], Elisabetta Cavalieri[a], Tiziana Persichini[c], Marco Colasanti[c], Giovanni Musci[d], Ernst Marlinghaus[e], Hisanori Suzuki[a,*], Sofia Mariotto[a]

[a] *Dipartimento di Scienze Neurologiche e della Visione, Sezione di Chimica Biologica, Università degli Studi di Verona, Strada Le Grazie, 8, 37134 Verona, Italy*
[b] *Unità Operativa di Chirurgia della Mano, Servizio di Terapia con Onde d'Urto, Policlinico G.B. Rossi, Azienda Ospedaliera di Verona, Verona, Italy*
[c] *Dipartimento di Biologia, Università "ROMA TRE", Roma, Italy*
[d] *Dipartimento di Scienze Microbiologiche Genetiche e Molecolari, Università di Messina, Messina, Italy*
[e] *Applied Research Center, Storz Medical AG, Kreuzlingen, Switzerland*

Received 20 September 2005; revised 21 October 2005; accepted 11 November 2005

Available online 28 November 2005

Edited by Barry Halliwell

Abstract Here, we show that extracorporeal shock waves (ESW), at a low energy density value, quickly increase neuronal nitric oxide synthase (nNOS) activity and basal nitric oxide (NO) production in the rat glioma cell line C6. In addition, the treatment of C6 cells with ESW reverts the decrease of nNOS activity and NO production induced by a mixture of lipopolysaccharides (LPS), interferon-γ (IFN-γ) plus tumour necrosis factor-α (TNF-α). Finally, ESW treatment efficiently downregulates NF-κB activation and NF-κB-dependent gene expression, including inducible NOS and TNF-α. The present report suggests a possible molecular mechanism of the anti-inflammatory action of ESW treatment.

Keywords: Extracorporeal shock waves; Inducible nitric oxide synthase; Inflammation; NF-κB; Nitric oxide

1. Introduction

Nitric oxide (NO) is a highly versatile signaling molecule playing a critical role in the nervous, immune and cardiovascular systems. NO is generated in different cell types by at least three isoforms of NO synthase (NOS) through the conversion of L-arginine and oxygen into L-citrulline. Two enzymes, neuronal NOS (nNOS) and endothelial NOS (eNOS), are constitutively expressed and their enzymatic activity is Ca^{2+}/calmodulin-dependent. These constitutive NOS (cNOS) are responsible for the production of physiological levels of NO involved in events such as vasodilation, angiogenesis, and neurotransmission [1]. The third enzyme is an inducible and Ca^{2+}-independent isoform of NOS (iNOS), virtually expressed in all cell types after stimulation with LPS and/or with different cytokines, such as interferon-γ (IFN-γ), interleukin-1β (IL-1β), or tumour necrosis factor-α (TNF-α). Induction of iNOS expression occurs at the transcriptional level and is mediated by the early activation of some nuclear transcriptional factors, including NF-κB [2]. Massive amounts of NO produced by iNOS under pathological conditions (e.g., inflammatory diseases) are potentially harmful, especially when time-spatial regulation of iNOS expression becomes compromised.

Shock waves (SW), defined as a sequence of single sonic pulses characterized by high peak pressure (100 MPa), fast pressure rise (<10 ns), and short lifecycle (10 μs), are conveyed by an appropriate generator to a specific target area with the energy density in the range of 0.003–0.890 mJ/mm^2. Extracorporeal shock waves (ESW) therapy was first applied in patients in 1980 to break up kidney stones [3]. In the last ten years, this technique has been successfully employed as an anti-inflammatory therapy in a number of orthopedic diseases [4] such as pseudoarthrosis [5], tendinitis calcarea of the shoulder, [6,7] epicondylitis [8], plantar fasciitis [9], and several inflammatory tendon diseases. In particular, ESW treatment is able to induce an increase of neoangiogenesis in tendons [10] and the regeneration of muscle and tendon tissues [11]. More generally, an immediate increase in blood flow around the treated area has been frequently observed.

The clinical observation of an immediate vasodilatation and laboratory findings of an enhancement of angiogenesis around the ESW-treated area immediately give rise to the hypothesis that ESW may modulate the production of NO. In this respect, we have reported that NO is produced non-enzymatically by the treatment of a L-arginine/hydrogen peroxide mixture with ESW, although this NO production requires higher energy potencies (0.89 mJ/mm^2) than those employed clinically [12]. More recently, we have demonstrated that ESW, at a clinically compatible energy density, are able to induce the enhancement of enzymatic NO production in resting cells [13]. Indeed, we have showed that ESW quickly enhance eNOS activity and NO production in human umbilical vein endothelial cells (HUVEC).

*Corresponding author. Fax: +39 045 8027170.
E-mail address: hisanori.suzuki@univr.it (H. Suzuki).

Abbreviations: ESW, extracorporeal shock waves; HUVEC, human umbilical vein endothelial cells; IFN-γ, interferon-γ; IL-1β, interleukin-1β; MIX, mixture of 1 μg/ml LPS, 10 ng/ml IFN-γ plus 10 ng/ml TNF-α; L-NAME, N-nitro-L-arginine methyl ester; NO, nitric oxide; NOS, nitric oxide synthase; cNOS, constitutive NOS; eNOS, endothelial NOS; iNOS, inducible NOS; nNOS, neuronal NOS; TNF-α, tumour necrosis factor-α

0014-5793/$30.00
doi:10.1016/j.febslet.2005.11.023