Protein Disulfide Isomerase overexpression in vascular smooth muscle cells induces spontaneous preemptive NADPH oxidase activation and Nox1 mRNA expression: effects of nitrosothiol exposure.

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Mechanisms regulating NADPH oxidase remain open and include the redox chaperone protein disulfide isomerase (PDI). Here, we further investigated PDI effects on vascular NADPH oxidase. VSMC transfected with wild-type PDI (wt-PDI) or PDI mutated in all 4 redox cysteines (mut-PDI) enhanced (2.5-fold) basal cellular ROS production and membrane NADPH oxidase activity, with 3-fold increase in Nox1, but not Nox4 mRNA. However, further ROS production, NADPH oxidase activity and Nox1mRNA increase triggered by angiotensin-II (AngII) were totally lost with PDI overexpression, suggesting preemptive Nox1 activation in such cells. PDI overexpression increased Nox4 mRNA after AngII stimulus, although without parallel ROS increase. We also show that Nox inhibition by the nitric oxide donor GSNO is independent of PDI. PDI silencing decreased specifically Nox1 mRNA and protein, confirming that PDI may regulate Nox1 at transcriptional level in VSMC. Such data further strengthen the role of PDI as novel NADPH oxidase regulator. (Supported by FAPESP, CNPq, INCT de Processos Redox em Biomedicina – Redoxoma)

Palavras-chaves: *Protein Disulfide Isomerase, NADPH oxidase, overexpression, nitrosothiol, vascular smooth muscle cells*