Abstract: Reactive oxygen species (ROS), generated by reduction-oxidation (redox) reactions, have been recognized as important chemical mediators that regulate signal transduction. It has been reported that increase in ROS generation may relate to a risk for cardiovascular diseases such as atherosclerosis, angina pectoris, and myocardial infarction. Therefore, understanding the ROS-generating biological processes and ROS-induced intracellular signaling will be informative to gain insights into the pathogenesis of these diseases. In this review, we focus on the sources and reactions of ROS in the cardiovascular system and the role of mitogen-activated protein (MAP) kinase pathway in redox-mediated signal transduction. Clinical implications of ROS and MAP kinase are then described to provide insight into the pathogenesis of various redox-sensitive cardiovascular diseases. The pathways responsible for ROS generation in the cardiovascular system may provide novel therapeutic targets. J. Med. Invest. 48: 11-24, 2001

Keywords: reactive oxygen species, mitogen-activated protein kinase, signal transduction, cardiovascular disease
A. Time course

H$_2$O$_2$ (1 mM) : 0 5 20 40 60 120 (min)

IB: phospho-ERK1/2 → pERK1/2

JNK in vitro kinase assay → pc-Jun

IB: phospho-p38 → pp38

B. Kinase activation (fold increase)

Time (min)  0  20  40  60  80  100  120

C. Concentration-response

H$_2$O$_2$ : 0 0.01 0.03 0.3 1 (mM)

IB: phospho-ERK1/2 → pERK1/2

JNK in vitro kinase assay → pc-Jun

IB: phospho-p38 → pp38

D. Kinase activation (fold increase)

H$_2$O$_2$ (mM)  0.01 0.1 1

ERK1/2, JNK, p38
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ROS and MAP kinase in cardiovascular disease

Angiotensin II, Endothelin, PDGF, TNF-α etc.

NADH/NADPH oxidase

Resting
Cell membrane

p22phox

Stimulation

Activated

O2
mox-1

p22phox

p47phox

Rac

GDP

p67phox

NADH/NADPH oxidase

O2•−
Calcium-dependent signal transduction by ROS

Phospholipid-dependent signal transduction by ROS
Tyrosine kinases as mediators of ROS-sensitive pathways

Small G proteins in ROS-sensitive signal transduction

ROS-induced activation of transcription factors: NF-κB and AP-1
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in vivo
ROS and MAP kinase in cardiovascular disease

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1. Introduction

In this section, we provide an overview of the role of ROS and MAP kinase in cardiovascular disease.

2. Methods

We describe the experimental methods used in our study.

3. Results

The results of our experiments are presented here.

4. Discussion

We discuss the implications of our findings and their relevance to cardiovascular disease.

5. Conclusion

In conclusion, we summarize the key points of our study and suggest areas for future research.