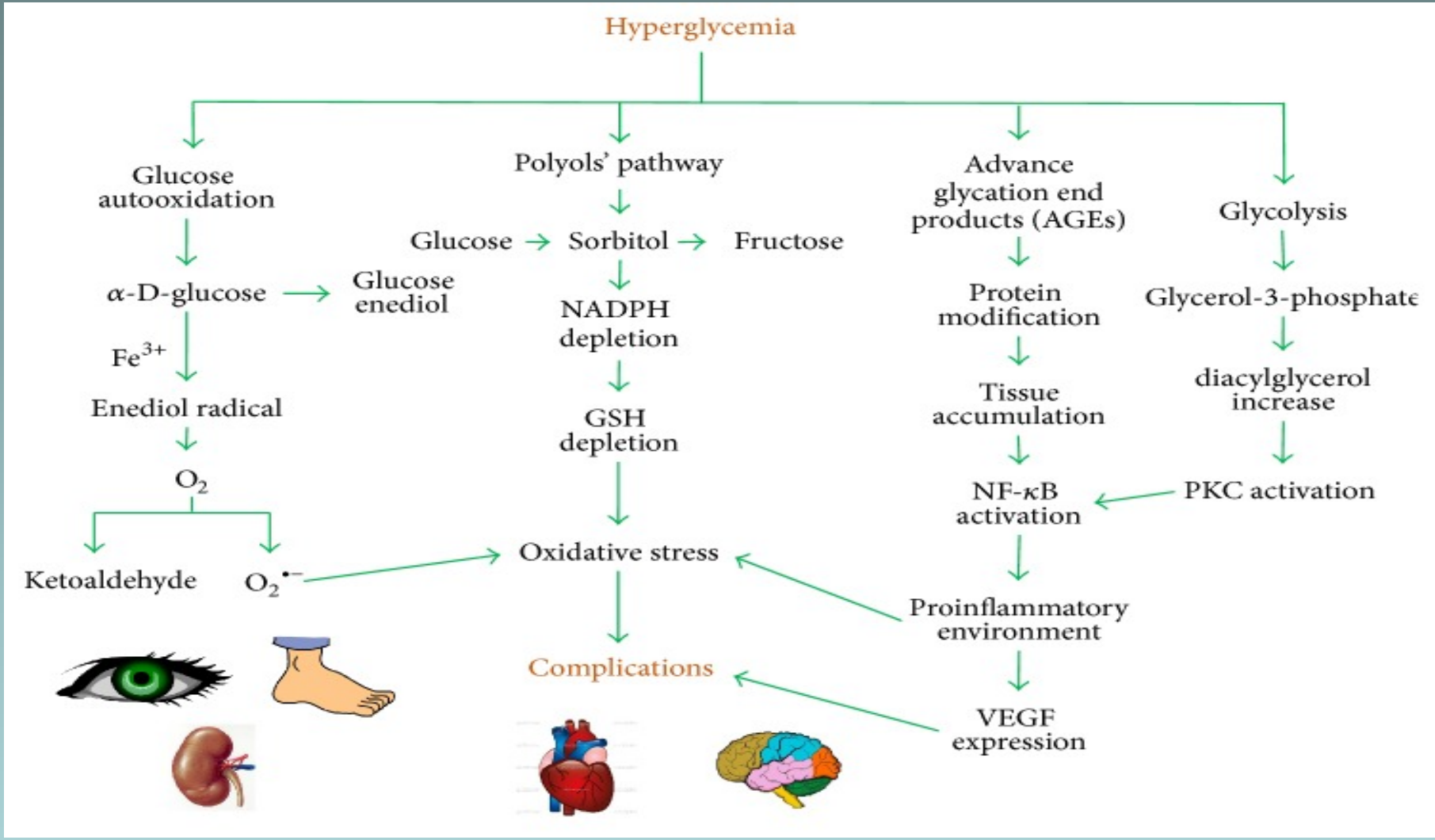
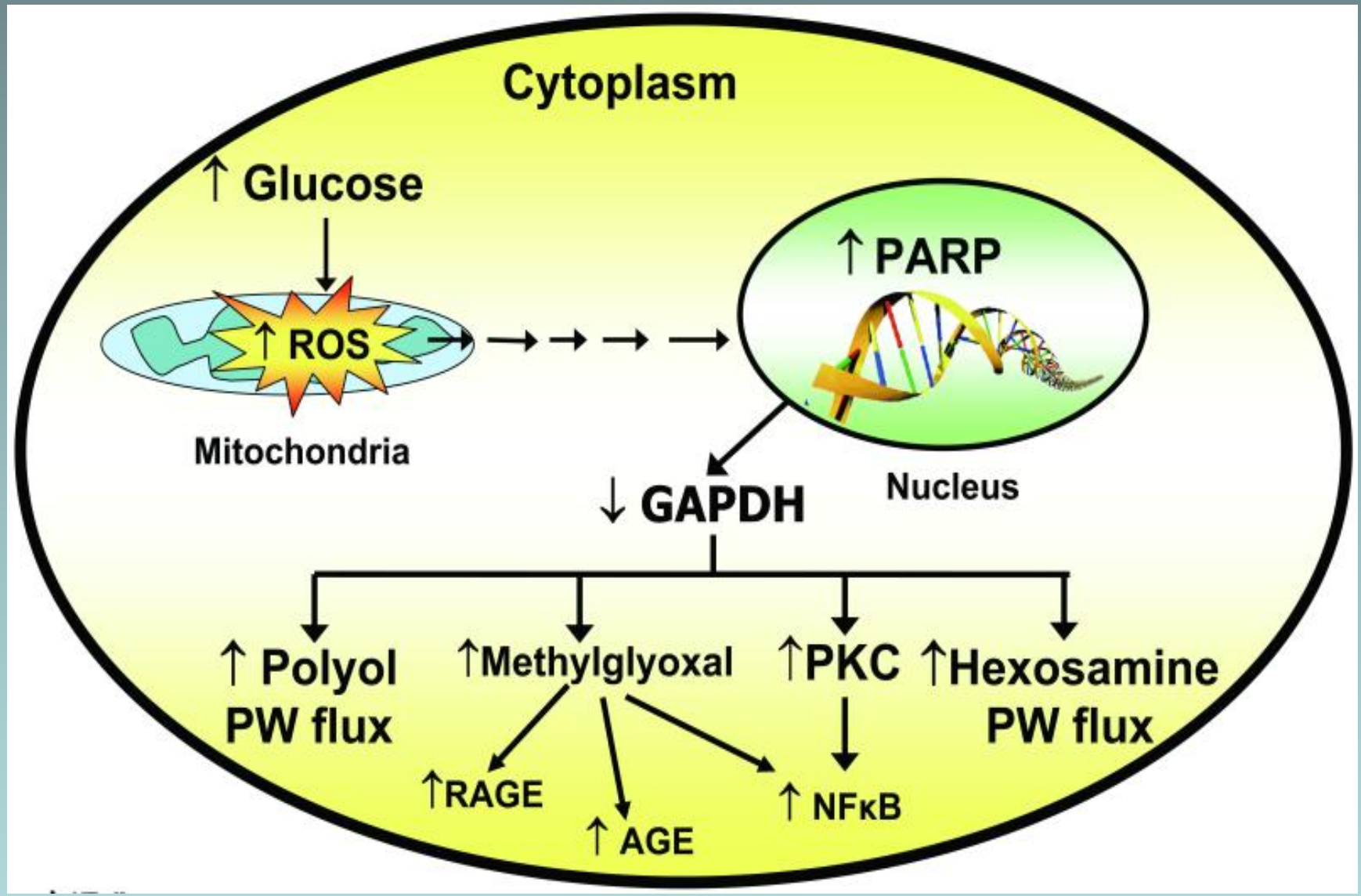
Oxidative stress/Diabetes

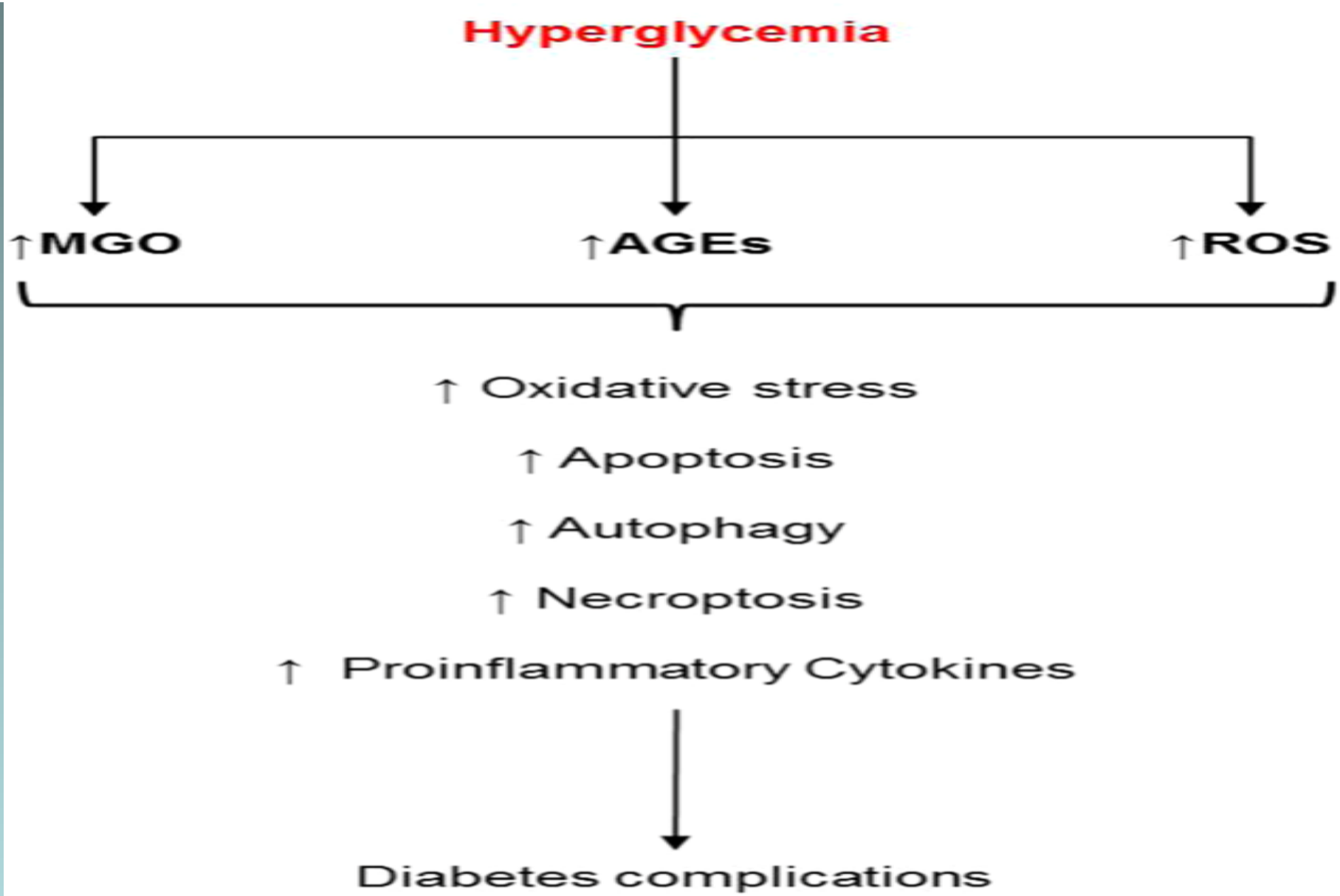
Prof.Dr.Nuray ARI



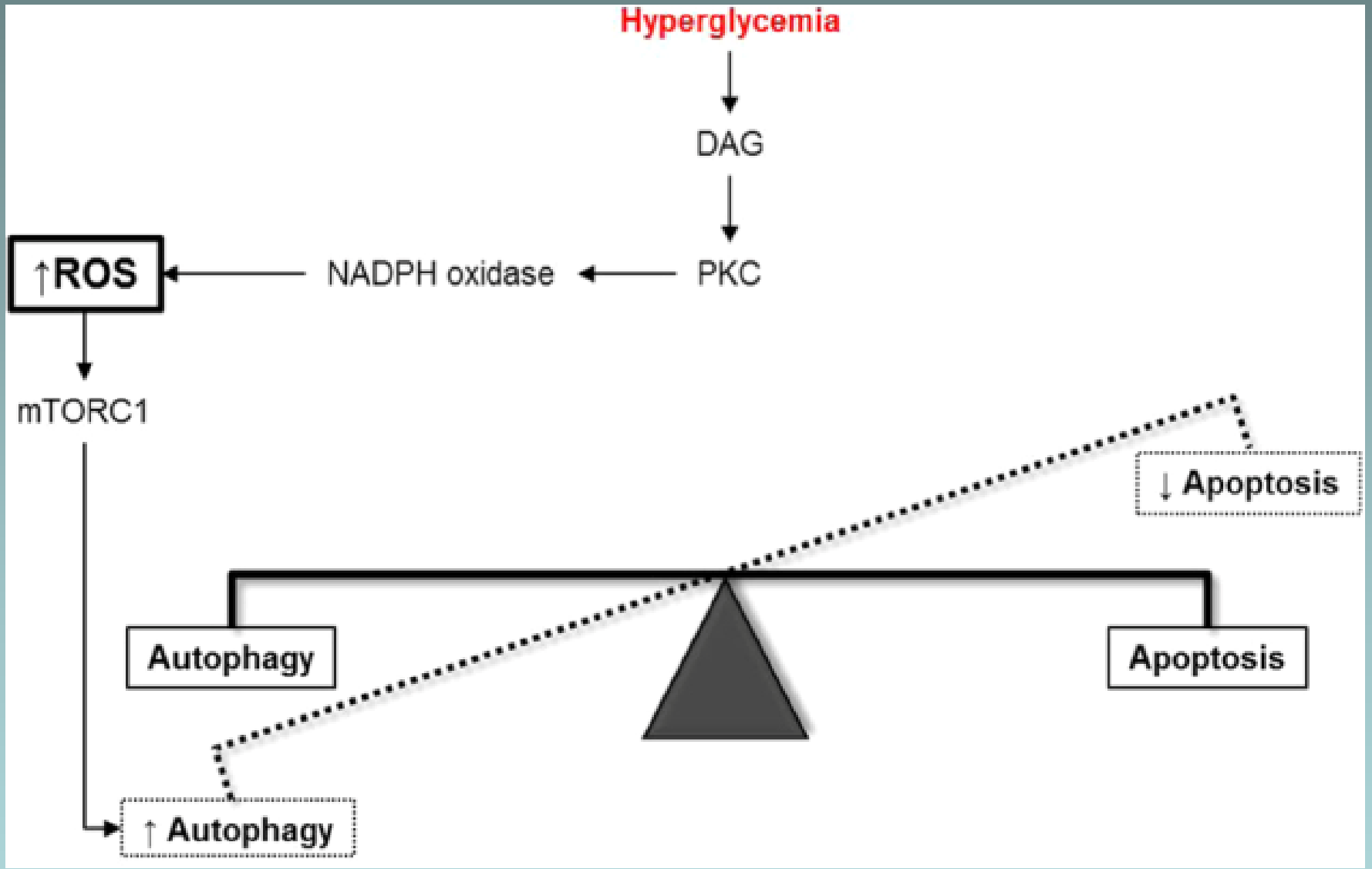
The main pathways triggered by hyperglycemia include glucose autooxidation and constant activation of polyols' pathway and formation of advance glycation end products (AGEs) and excessive glycolysis.
With the constant activation of these pathways, living cells and tissues are damaged, mainly by impairment of target protein function, increase in oxidative stress, and activation of signal transduction pathways, leading to the imbalance of normal physiological functions and therefore the development of diabetic complications. ***Current Advances in the Biochemical and Physiological Aspects of the Treatment of Type 2 Diabetes Mellitus with TZDS.*** ***Alemán-González-Duhart D et al.***



Schematic showing elements of the unifying mechanism of hyperglycemia-induced cellular damage. Circ Res. 2010.107(9):1058–1070. **Oxidative stress and diabetic complications** Giacco F and Brownlee M.

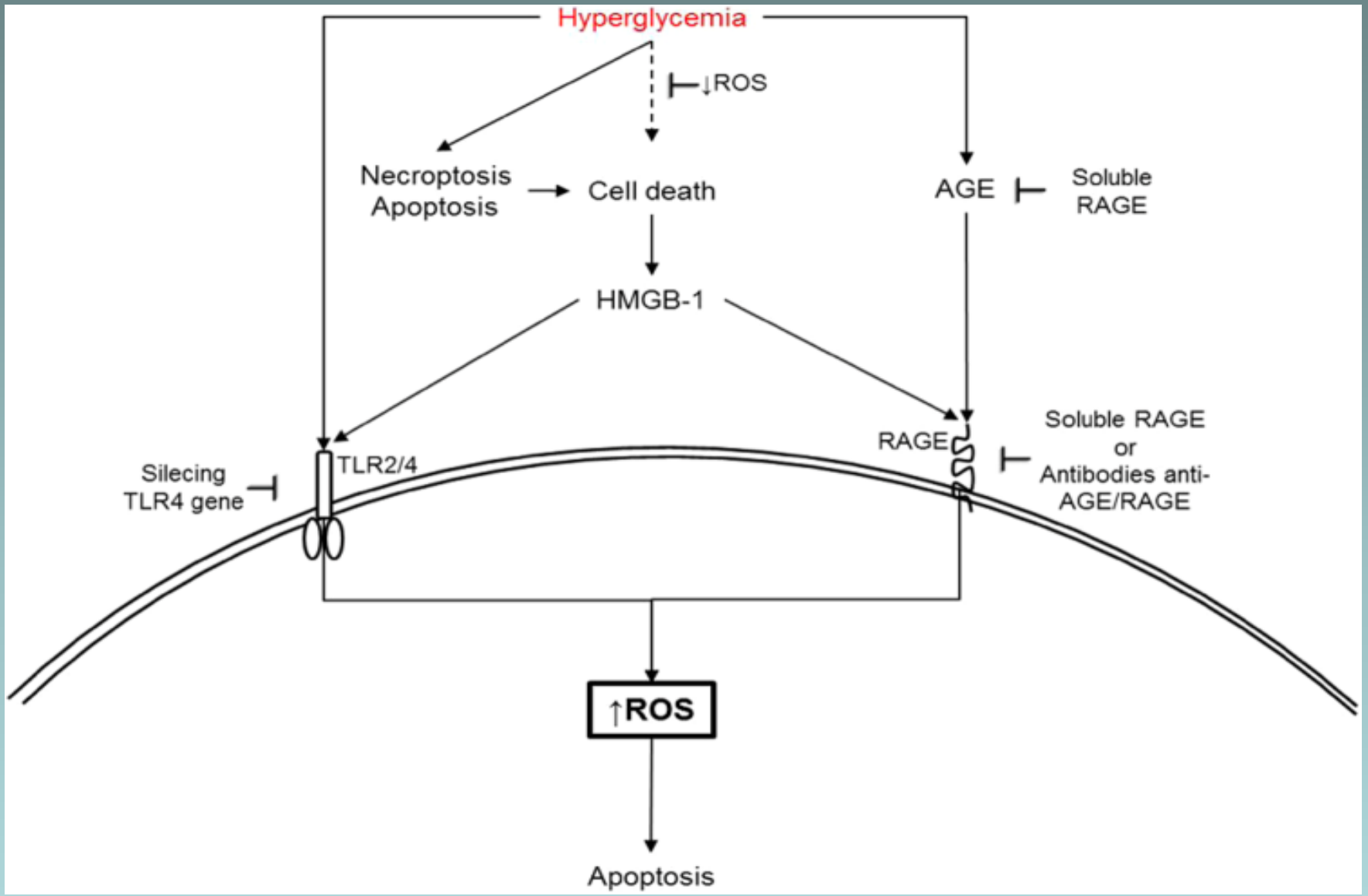


Oxidative stress and cell death: necroptosis, a programmed necrosis of inflammatory cell, and apoptosis can be induced in diabetes by AGEs, ROS, and MGO, leading to diabetes complications (retinopathy, age-related macular etc)MGO = methylglyoxal, AGEs = advanced glycation end products, ROS = reactive oxygen species. *Cell Death Dis. 2018 25;9(2):119. Volpe CMO et al.*

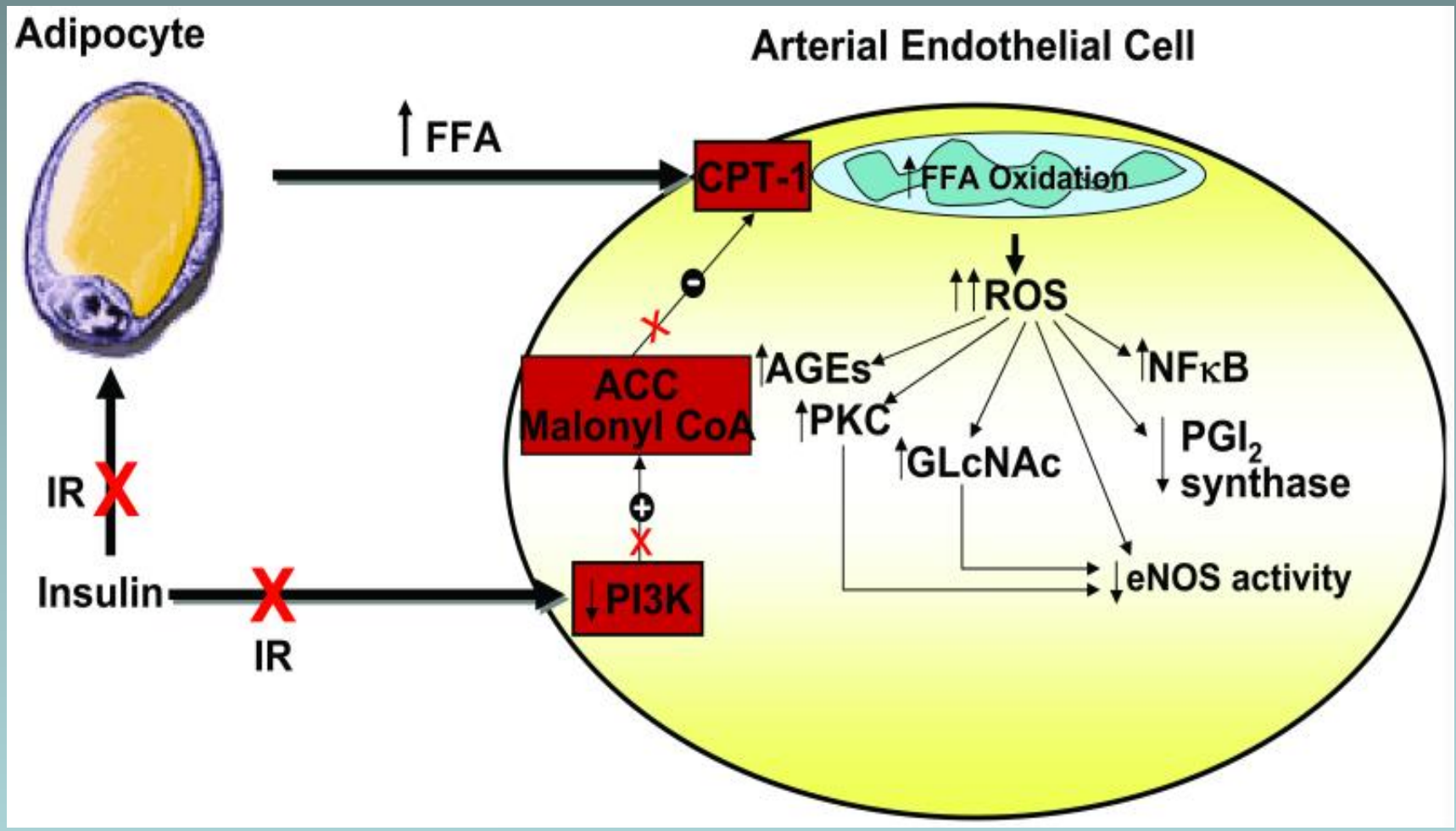


Balance between autophagy and apoptosis: apoptosis is downregulated by autophagy

The activation of mTORC1 depends on PKC, which is activated by DAG. Thus, PKC in conjunction with ROS and mTORC1 pathway are associated in the control of cellular autophagy. Akt/mammalian target of rapamycin complex 1 = mTORC1, ROS reactive oxygen species, PKC = protein kinase C, DAG = diacylglycerol. *Cell Death Dis. 2018 25;9(2):119.* Volpe CMO et al.



Targets for modulation of cell death: some points may act as modulators of cell death depending on the kind of activation
Apoptosis induced by TLR activation has been suggested to be downregulated by silencing of TLR4 gene in experimental model or using soluble RAGE and/or specific antibodies against RAGE. Cell death is a source of HMGB-1, an activator of RAGE. TLR TLR-Toll-like receptors, RAGE receptor for advanced glycation end products. *Cell Death Dis. 2018 25;9(2):119. Volpe CMO et al.*



Role of insulin resistance and free fatty acids in macrovascular endothelial cell ROS formation and atherogenesis.

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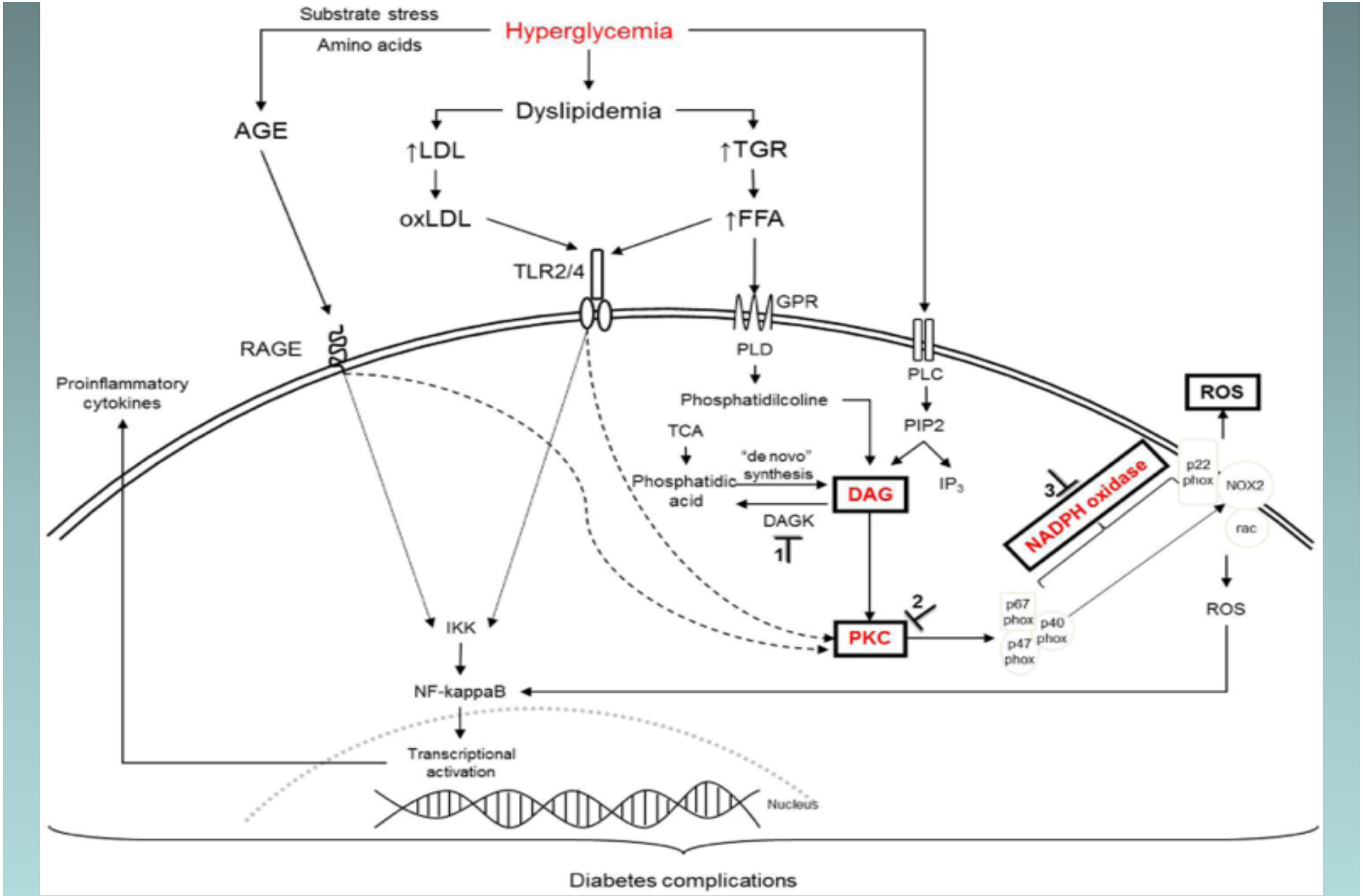
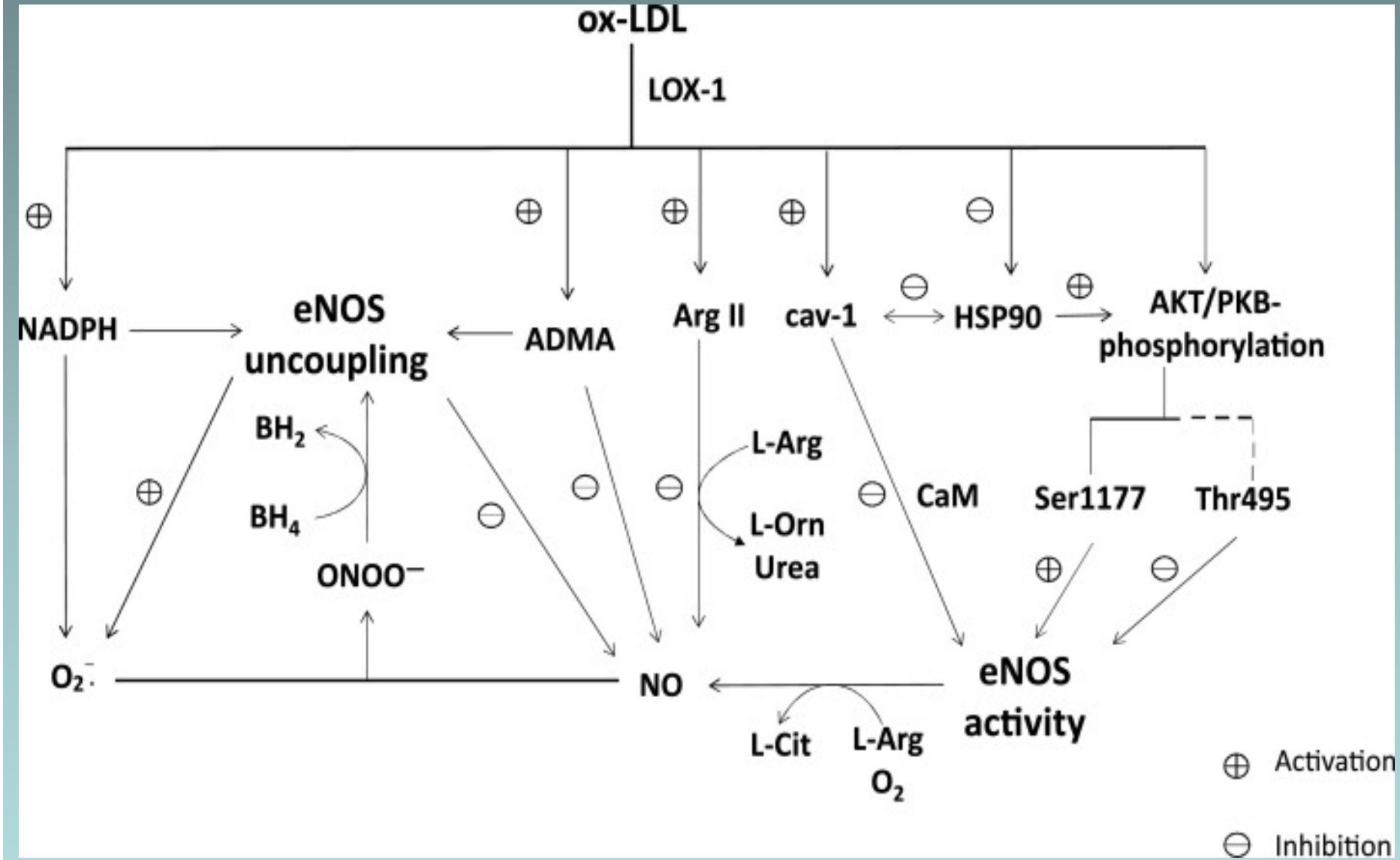
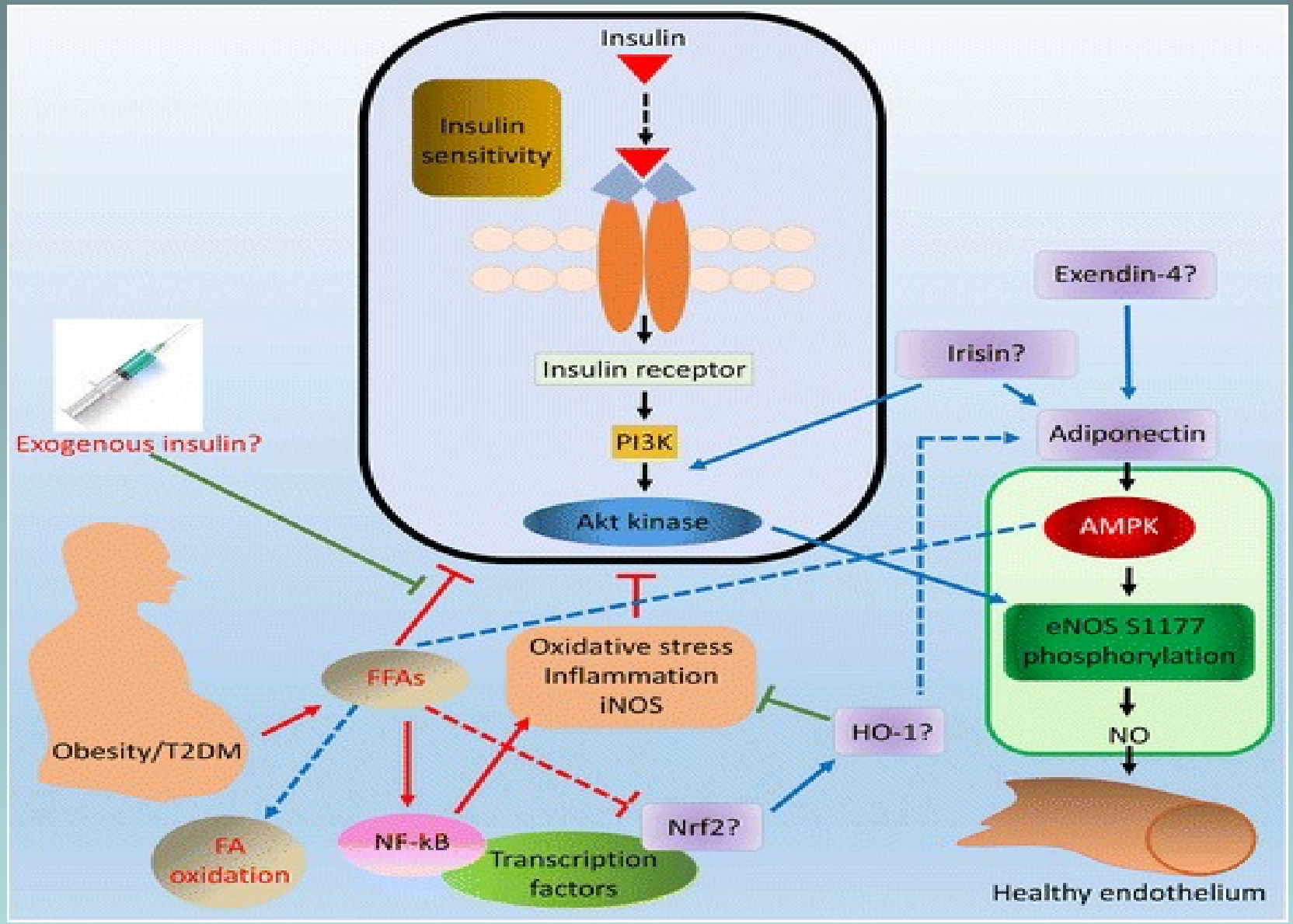


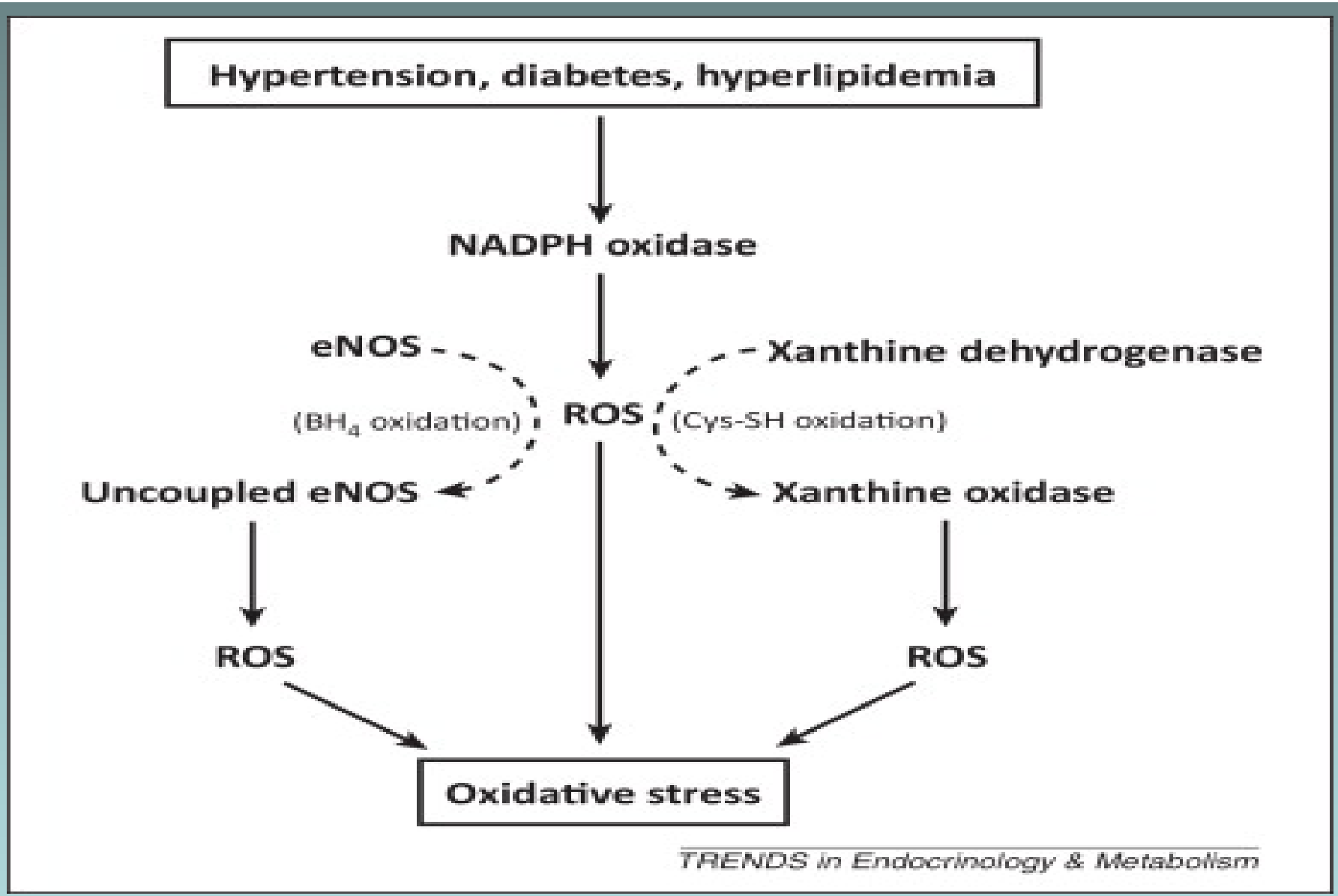
Proposed signaling pathways from hyperglycemia to ROS production and cytokine release leading to diabetes complications *Cell Death Dis. 2018 25;9(2):119. Volpe CMO et al.*



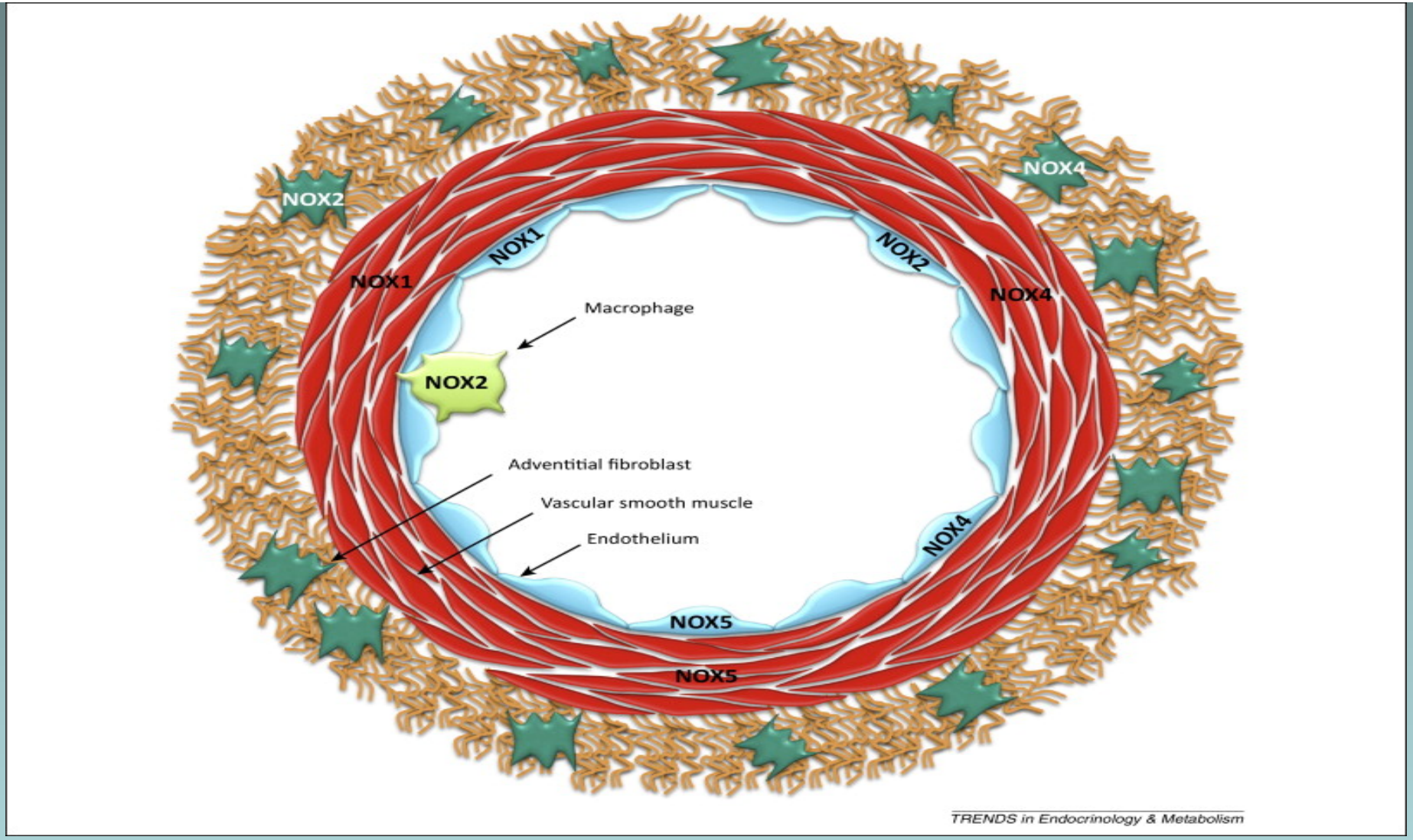
Biomed Pharmacother. 2018 Jan;97:423-428. Chen JY et al



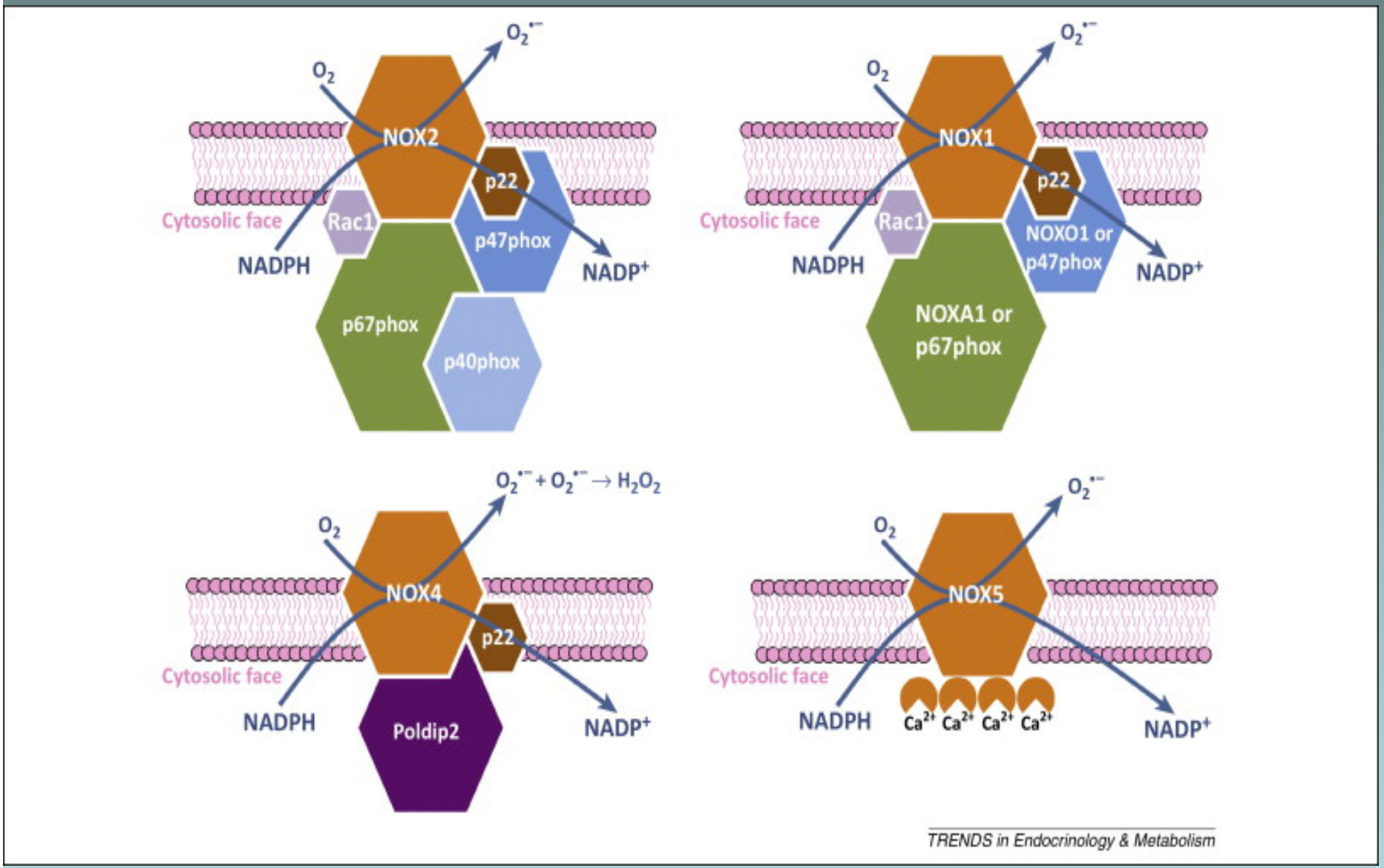
J Biomed Sci. 2017; 24(1):50. **Role of free fatty acids in endothelial dysfunction.** Ghosh A et. al.



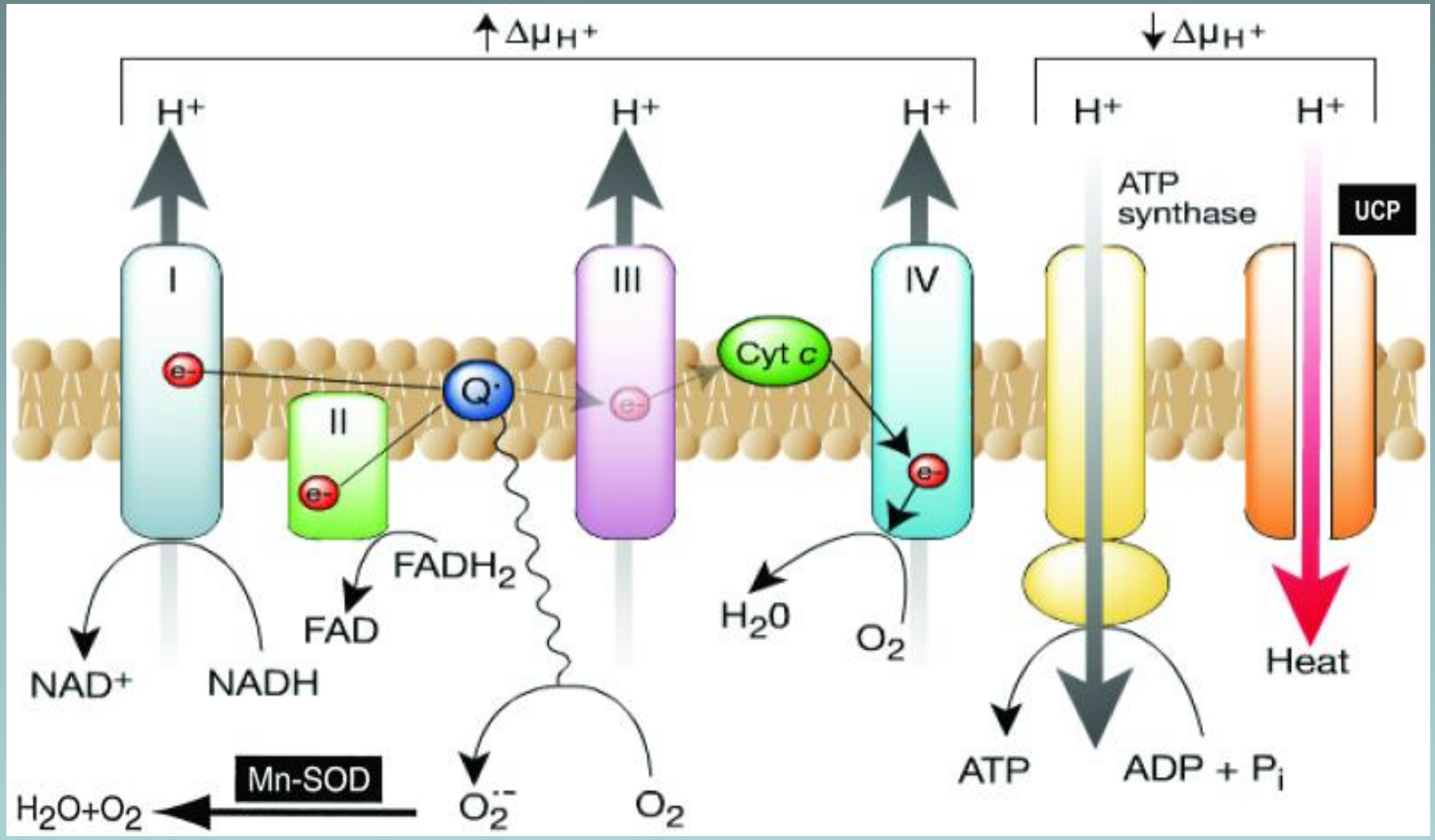
NADPH oxidase (NOX)-derived reactive oxygen species (ROS) elicit ROS production from other enzyme sources. Trends Endocrinol Metab. 2014 25(9):452-63. **Endothelial NADPH oxidases: which NOX to target in vascular disease?** Drummond GR, and Sobey CG.



NADPH oxidase (NOX) isoform expression in the various cell types of the blood vessel wall.
Four NOX isoforms are expressed in the vascular wall, including NOX1 (in endothelial cells and VSMCs) NOX2 (in endothelial cells, adventitial fibroblasts, and leukocytes such as monocytes, macrophages, and platelets), NOX4 (in endothelial cells, VSMCs, and adventitial fibroblasts), and NOX5 (in endothelial and VSMCs – not expressed in rodents). Trends Endocrinol Metab. 2014 25(9):452-63. **Endothelial NADPH oxidases: which NOX to target in vascular disease?** Drummond GR, and Sobey CG.

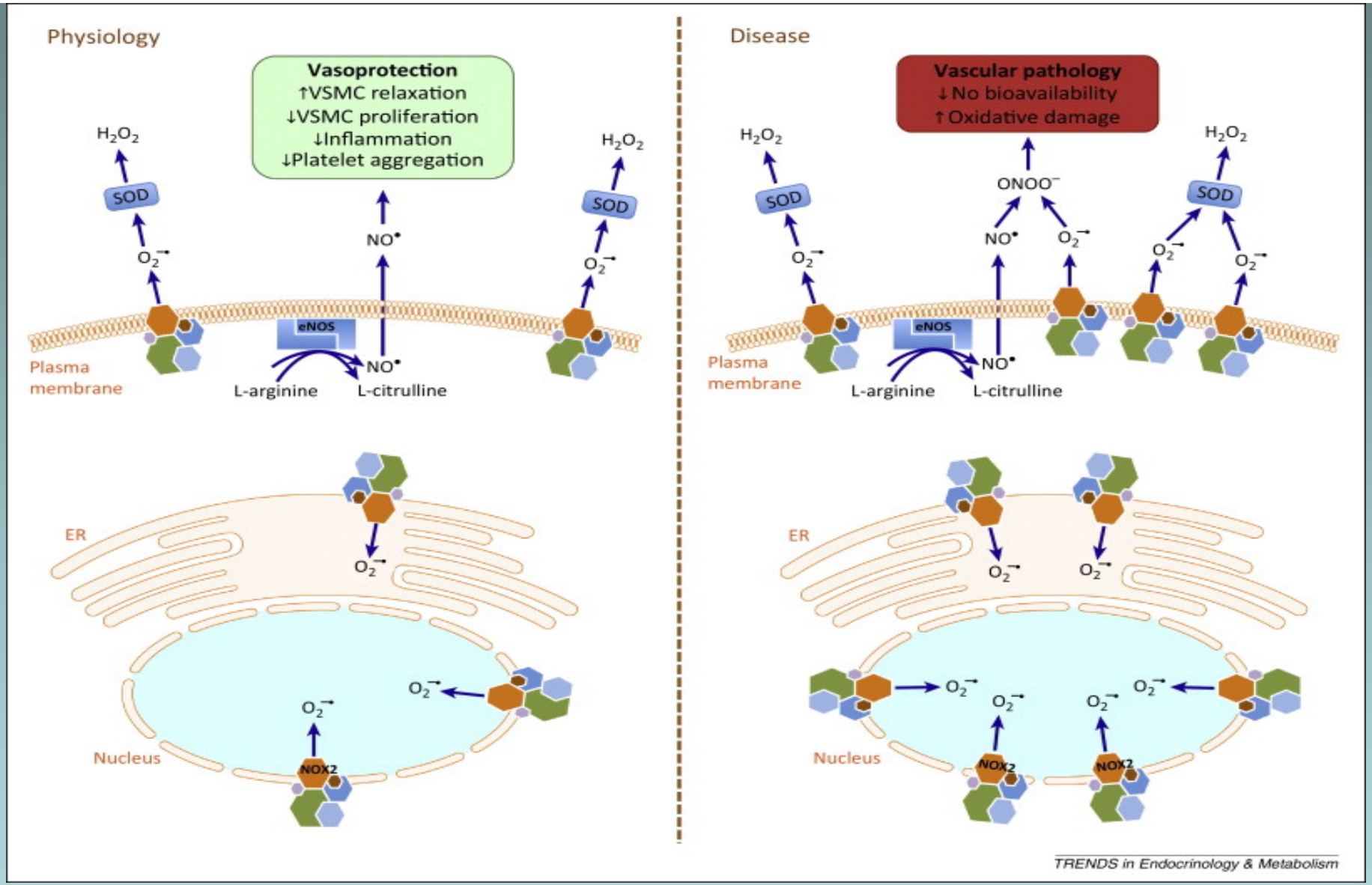


Molecular composition of the endothelial NADPH oxidases ('NOXs') Trends Endocrinol Metab. 2014 25(9):452-63. ***Endothelial NADPH oxidases: which NOX to target in vascular disease?*** Drummond GR, and Sobey CG.

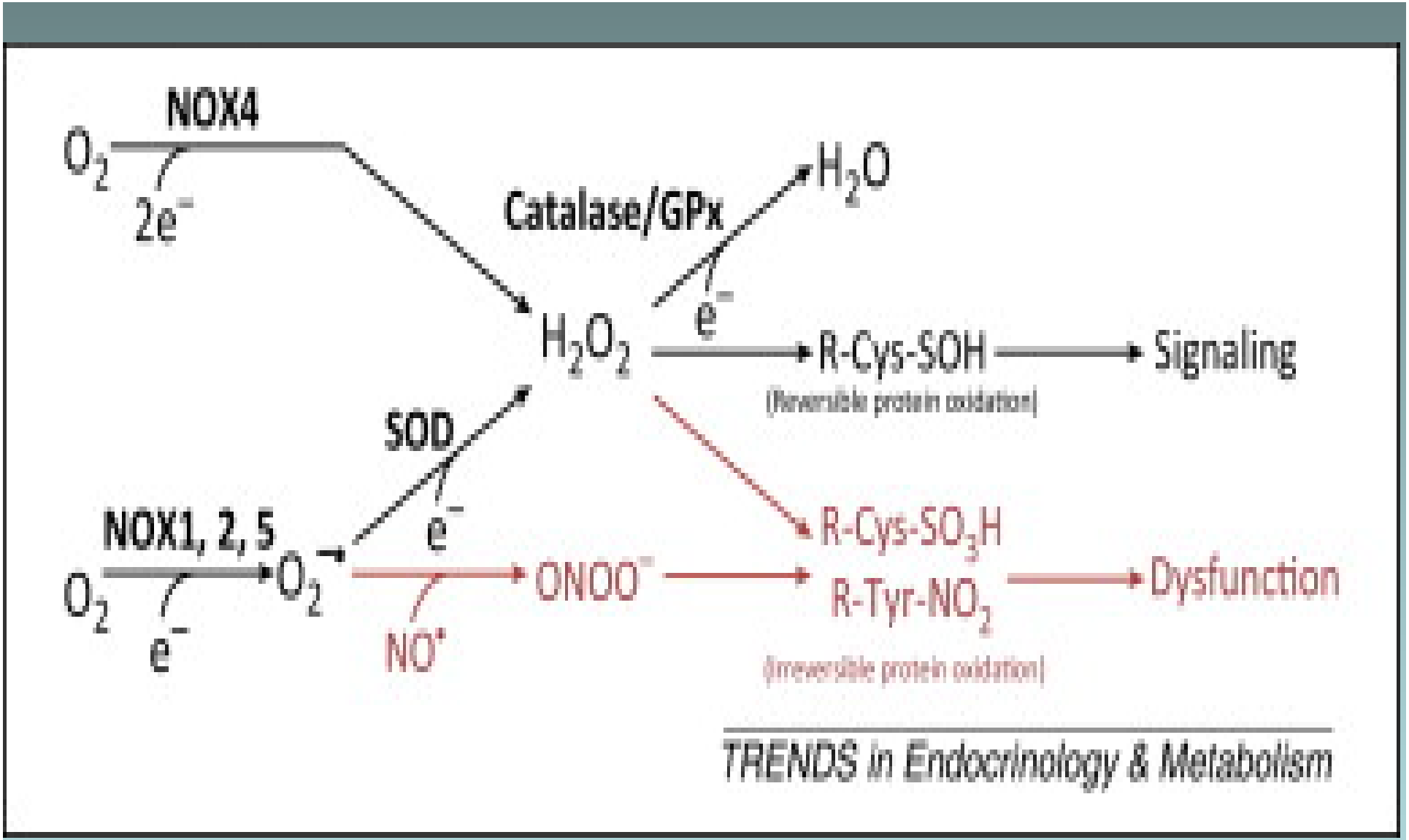


Production of ROS by the mitochondrial electron transport chain.

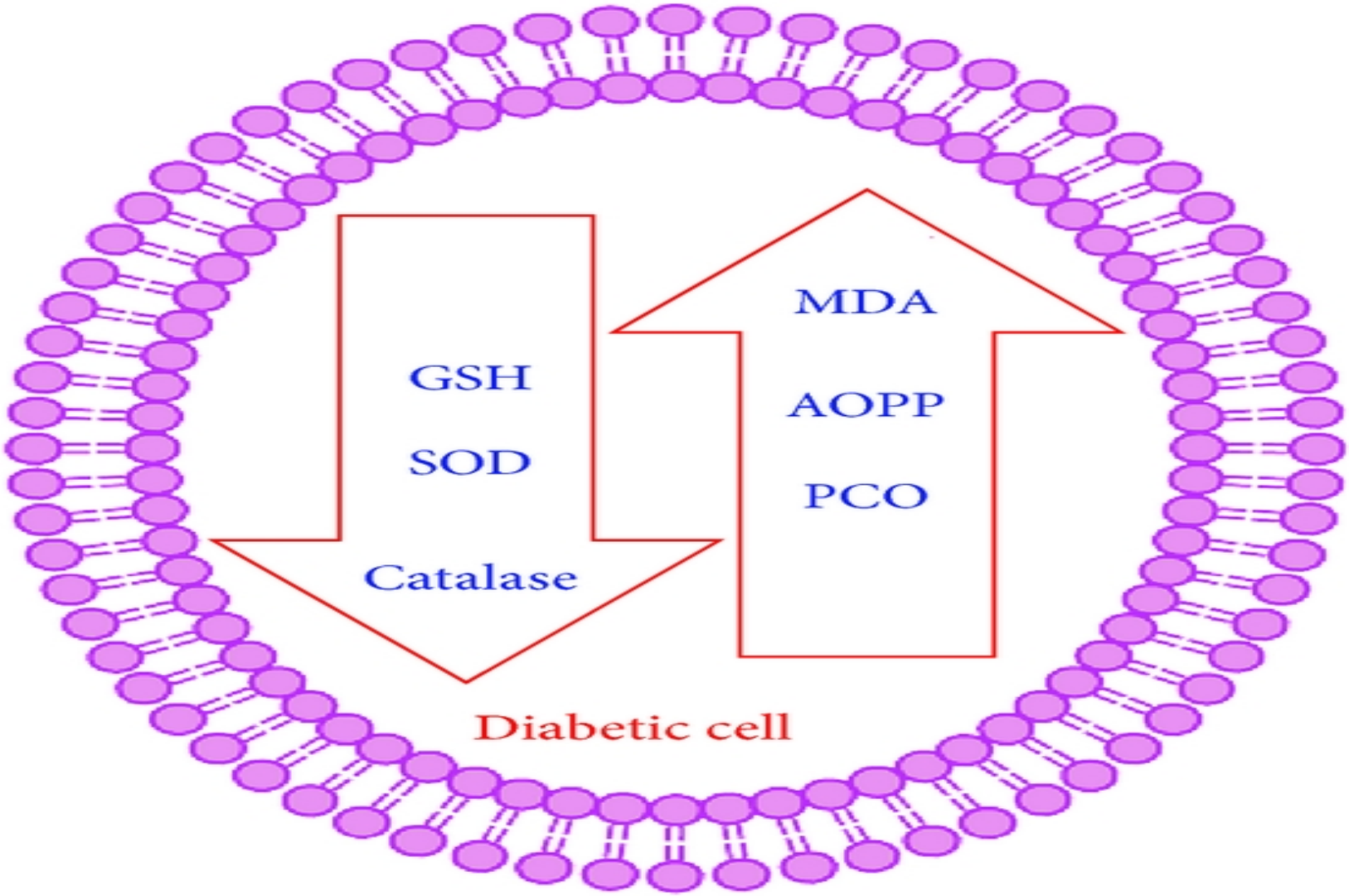
Circ Res. 2010, 107(9):1058–1070. **Oxidative stress and diabetic complications** Giacco F and Brownlee M.



Subcellular compartments into which NADPH oxidase NOX2 generates superoxide in the endothelium in physiology and disease, and the impact on nitric oxide (NO) bioavailability. Trends Endocrinol Metab. 2014 25(9):452-63. **Endothelial NADPH oxidases: which NOX to target in vascular disease?** Drummond GR, and Sobey CG.



The chemistries of redox signaling and endothelial dysfunction in endothelial cells. Trends Endocrinol Metab. 2014 25(9):452-63. **Endothelial NADPH oxidases: which NOX to target in vascular disease?** Drummond GR, and Sobey CG.



Schematic representation of the status of oxidative stress markers during diabetes. MDA: malondialdehyde, AOPP: Advanced oxidation protein products, PCO: protein carbonyls, GSH: reduced glutathione, and SOD: superoxide dismutase. Markers of Oxidative Stress during Diabetes Mellitus.Tiwari BT. J. Biomark. Vol 2013 (2013), Article ID 378790, 8 pages

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Circ Res. 2010, 107(9):1058-70..
Oxidative stress and diabetic complications. Giacco F, Brownlee M.
Abstract
Oxidative stress plays a pivotal role in the development of diabetes complications, both microvascular and cardiovascular. The metabolic abnormalities of diabetes cause mitochondrial superoxide overproduction in endothelial cells of both large and small vessels, as well as in the myocardium. This increased superoxide production causes the activation of 5 major pathways involved in the pathogenesis of complications: polyol pathway flux, increased formation of AGEs (advanced glycation end products), increased expression of the receptor for AGEs and its activating ligands, activation of protein kinase C isoforms, and overactivity of the hexosamine pathway. It also directly inactivates 2 critical antiatherosclerotic enzymes, endothelial nitric oxide synthase and prostacyclin synthase. Through these pathways, increased intracellular reactive oxygen species (ROS) cause defective angiogenesis in response to ischemia, activate a number of proinflammatory pathways, and cause long-lasting epigenetic changes that drive persistent expression of proinflammatory genes after glycemia is normalized ("hyperglycemic memory"). Atherosclerosis and cardiomyopathy in type 2 diabetes are caused in part by pathway-selective insulin resistance, which increases mitochondrial ROS production from free fatty acids and by inactivation of antiatherosclerosis enzymes by ROS. Overexpression of superoxide dismutase in transgenic diabetic mice prevents diabetic retinopathy, nephropathy, and cardiomyopathy. The aim of this review is to highlight advances in understanding the role of metabolite-generated ROS in the development of diabetic complications.