

**Is oxidative stress the pathogenic
mechanism underlying insulin resistance,
diabetes and cardiovascular disease?
The “Common Soil” hypothesis revisited.**

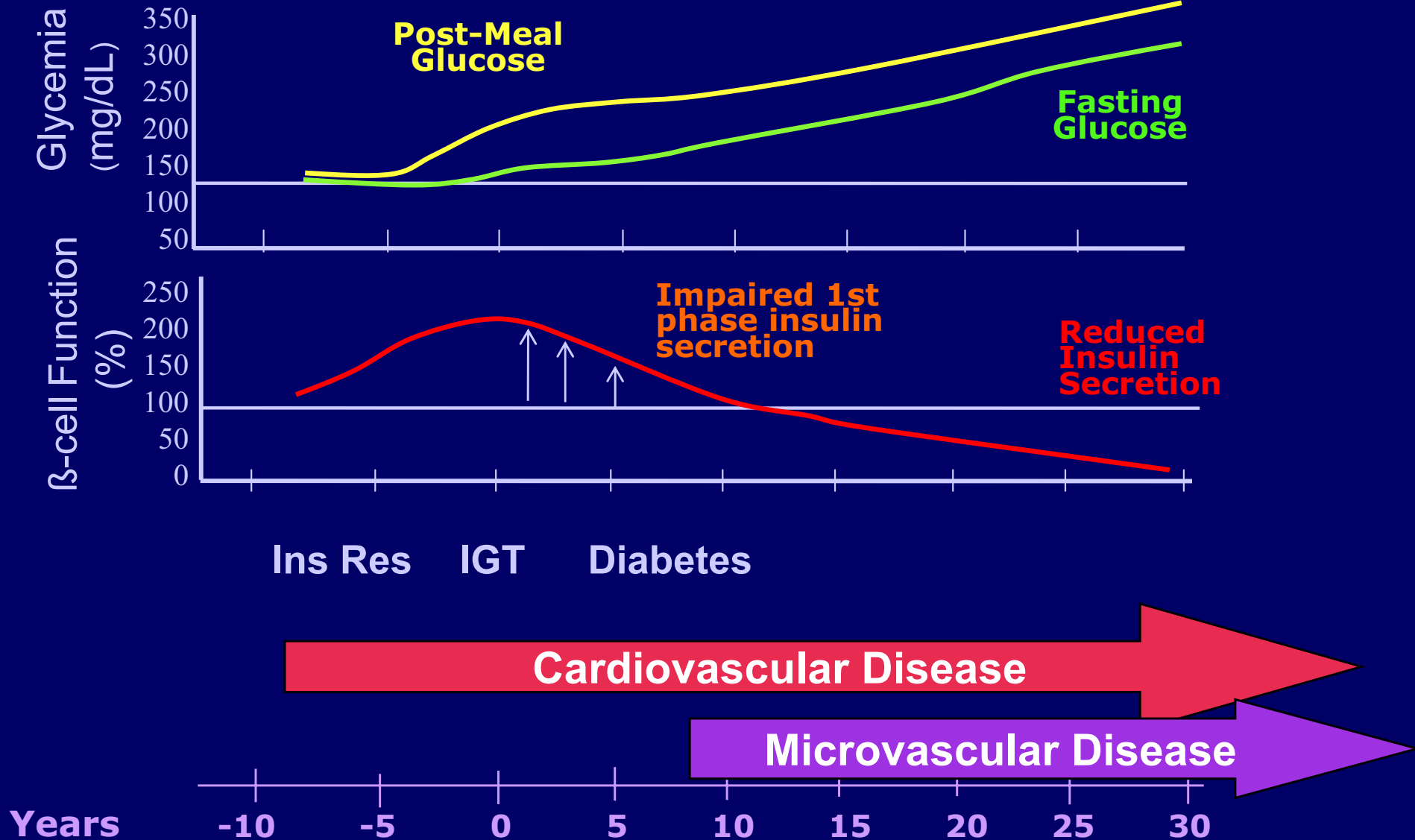
Antonio Ceriello

EASD 2004

Chair of Internal Medicine
University of Udine
Udine, Italy



From Insulin Resistance to Diabetes



Perspectives

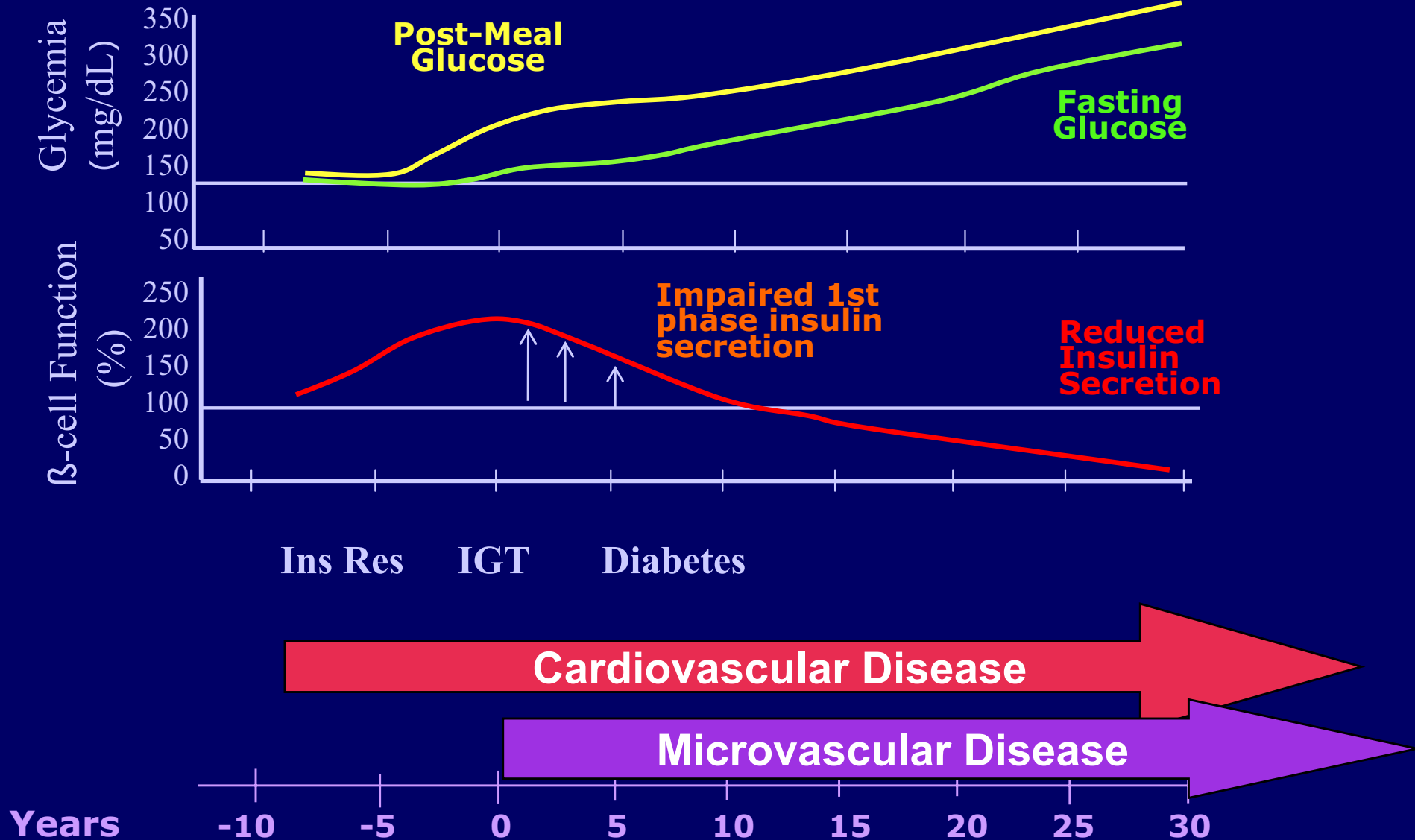
Microvascular complications of impaired glucose tolerance

Singleton JR et al.

“IGT is also independently associated with traditional microvascular complications of diabetes, including retinopathy, renal disease, and polyneuropathy”

Diabetes 2003

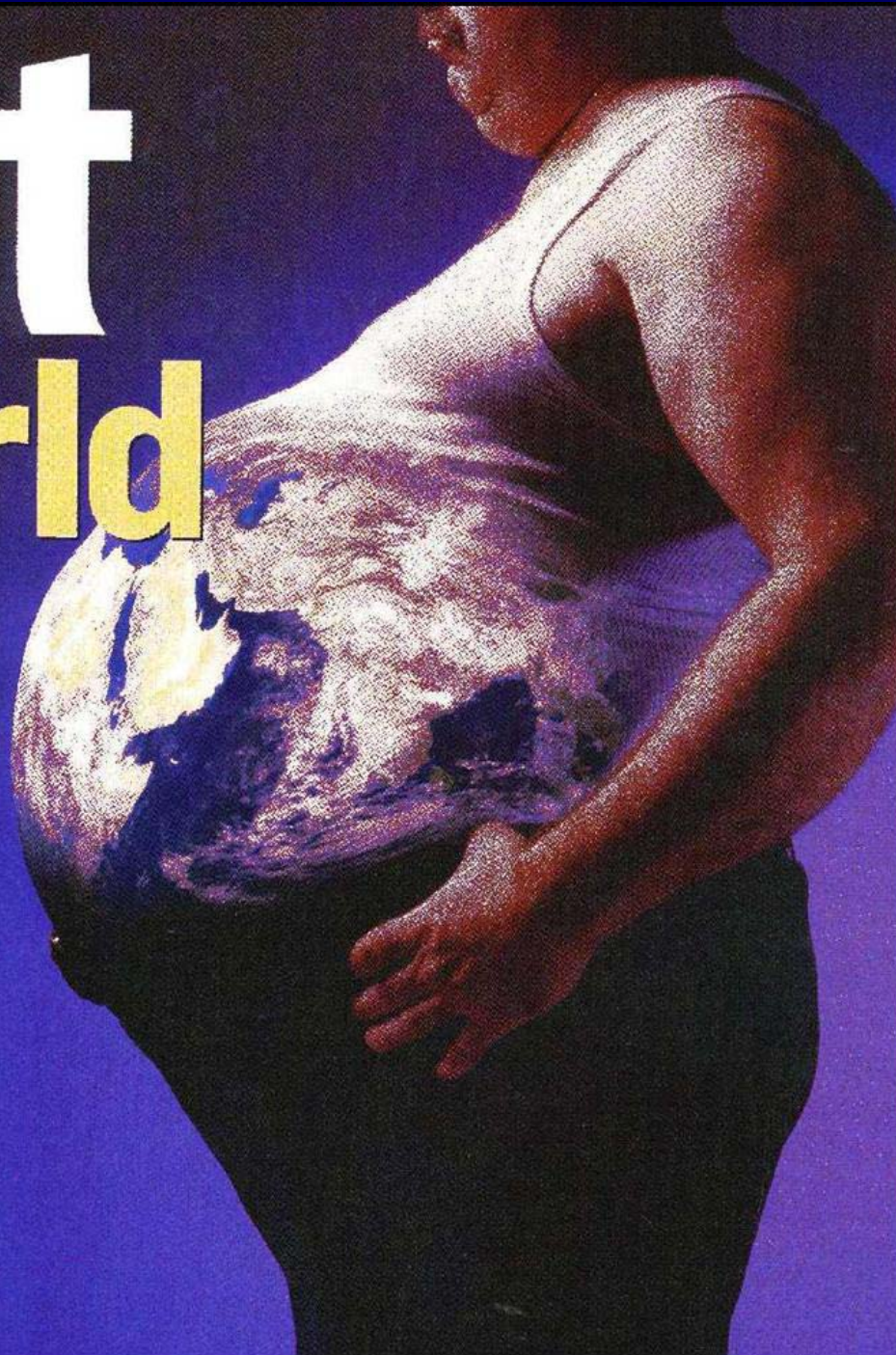
From Insulin Resistance to Diabetes

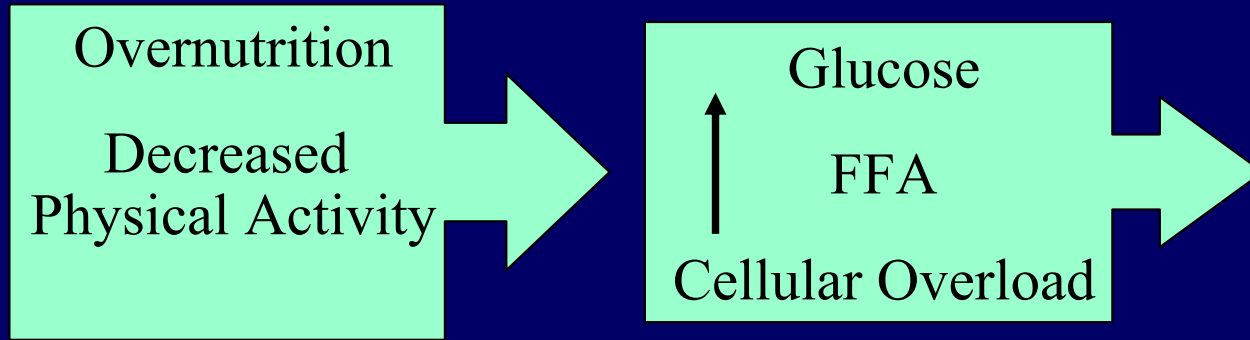


Fat World

We're Eating
More Junk
And Getting
Less Exercise.

Obesity Is
The Globe's
Newest
Epidemic.





Food



Glucose



glycolysis

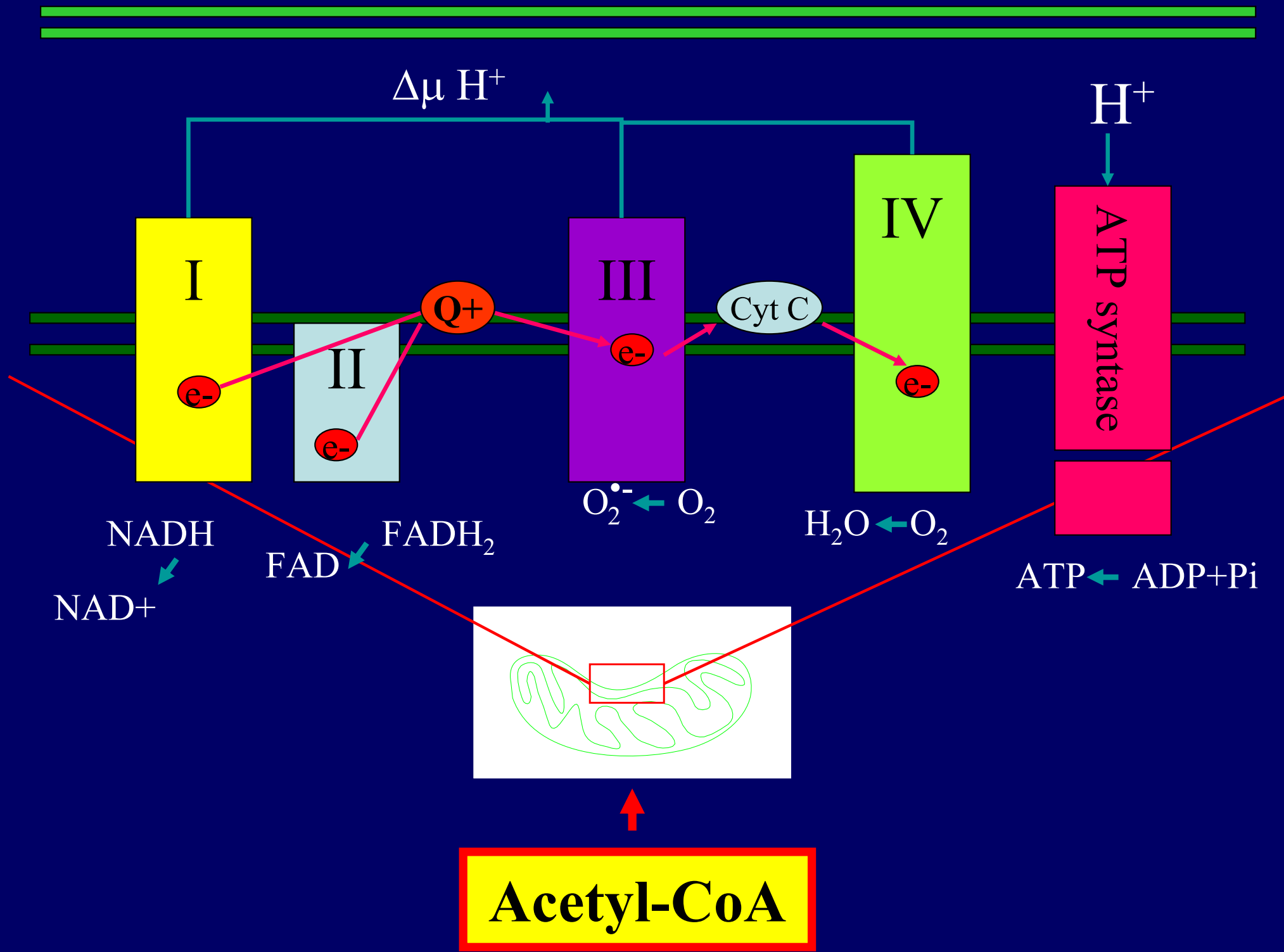
Acetyl-CoA

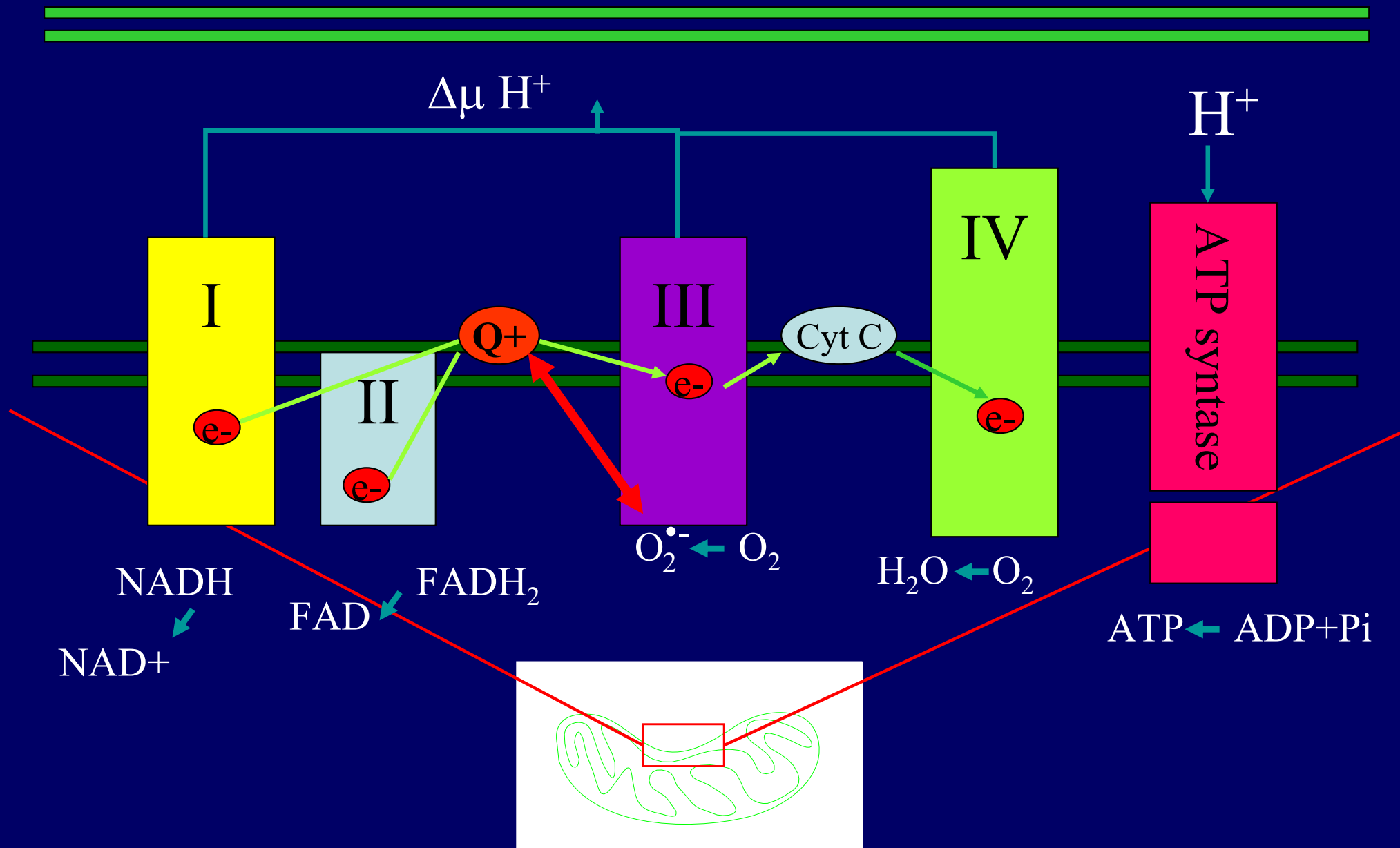
Fats



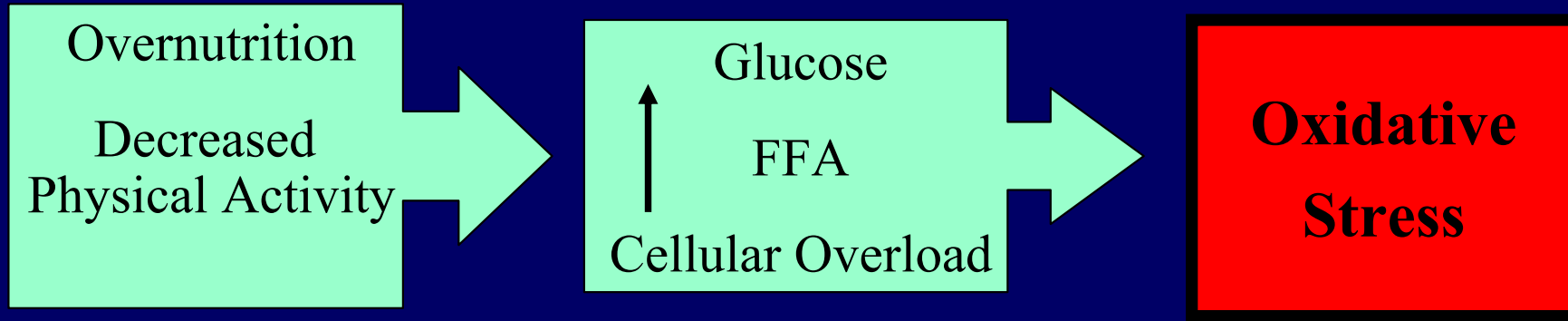
Beta-oxidation

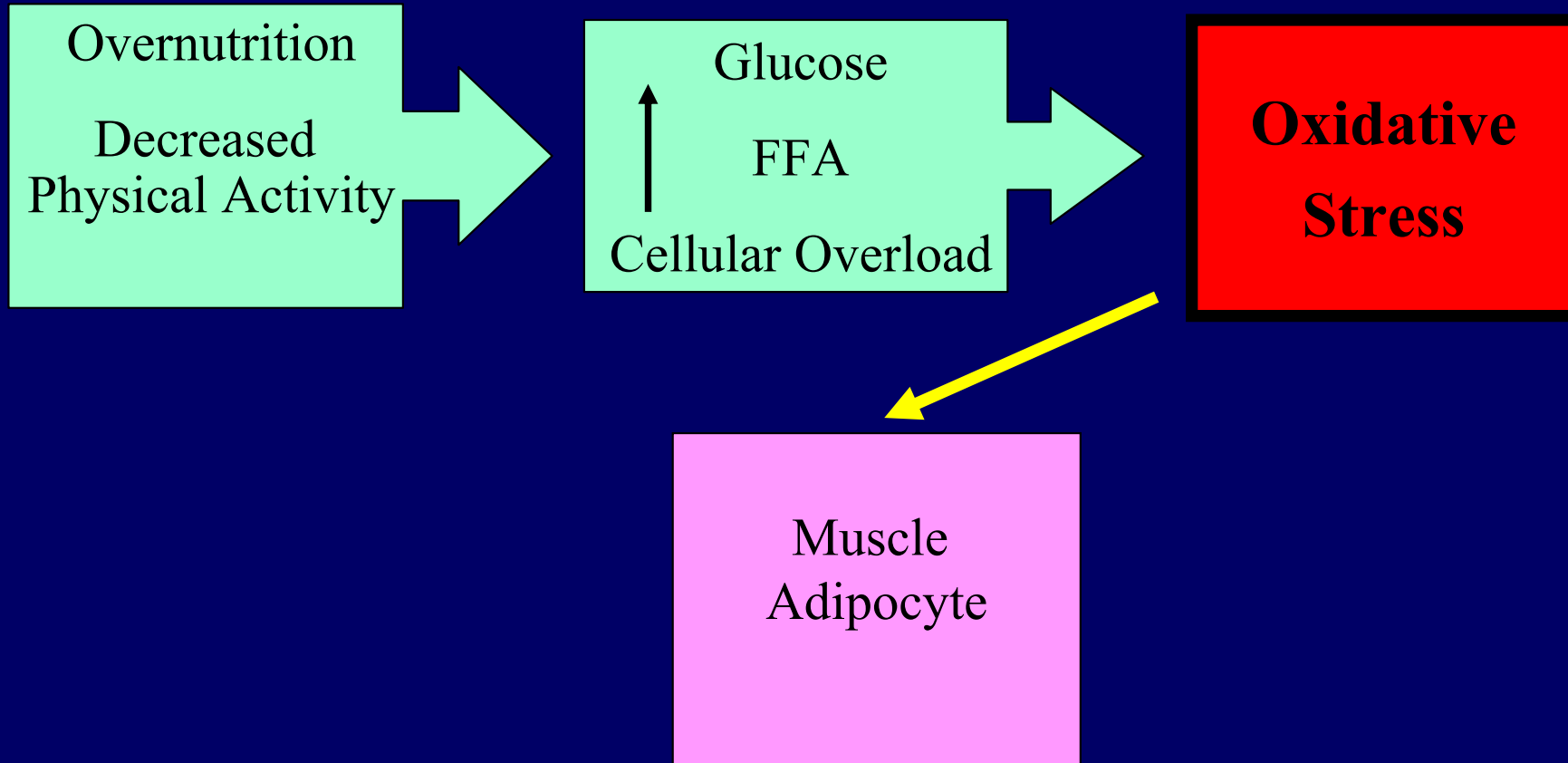
Acetyl-CoA





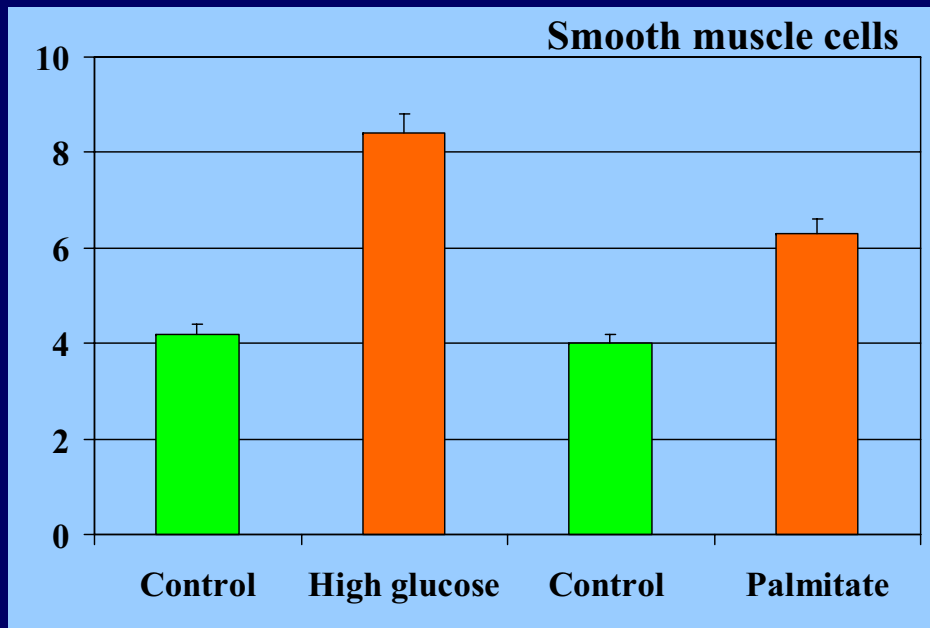
Acetyl-CoA Overload





High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C-dependent activation of NAD(P)H oxidase in cultured vascular cells.

Inoguchi T *et al.*



Ceriello A:

(insulin resistance associated with oxidative stress)

Metabolism 49: 27-29, 2000

Evans JL et al:

(oxidative stress induces insulin resistance)

Diabetes 52: 1-8, 2003

Maddux BA et al:

(FFA induce insulin resistance through oxidative stress)

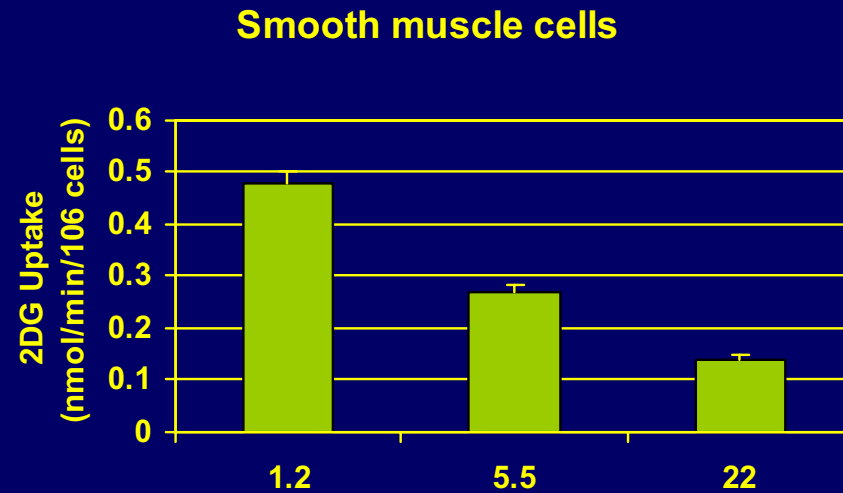
Diabetes 50: 404-410, 2001

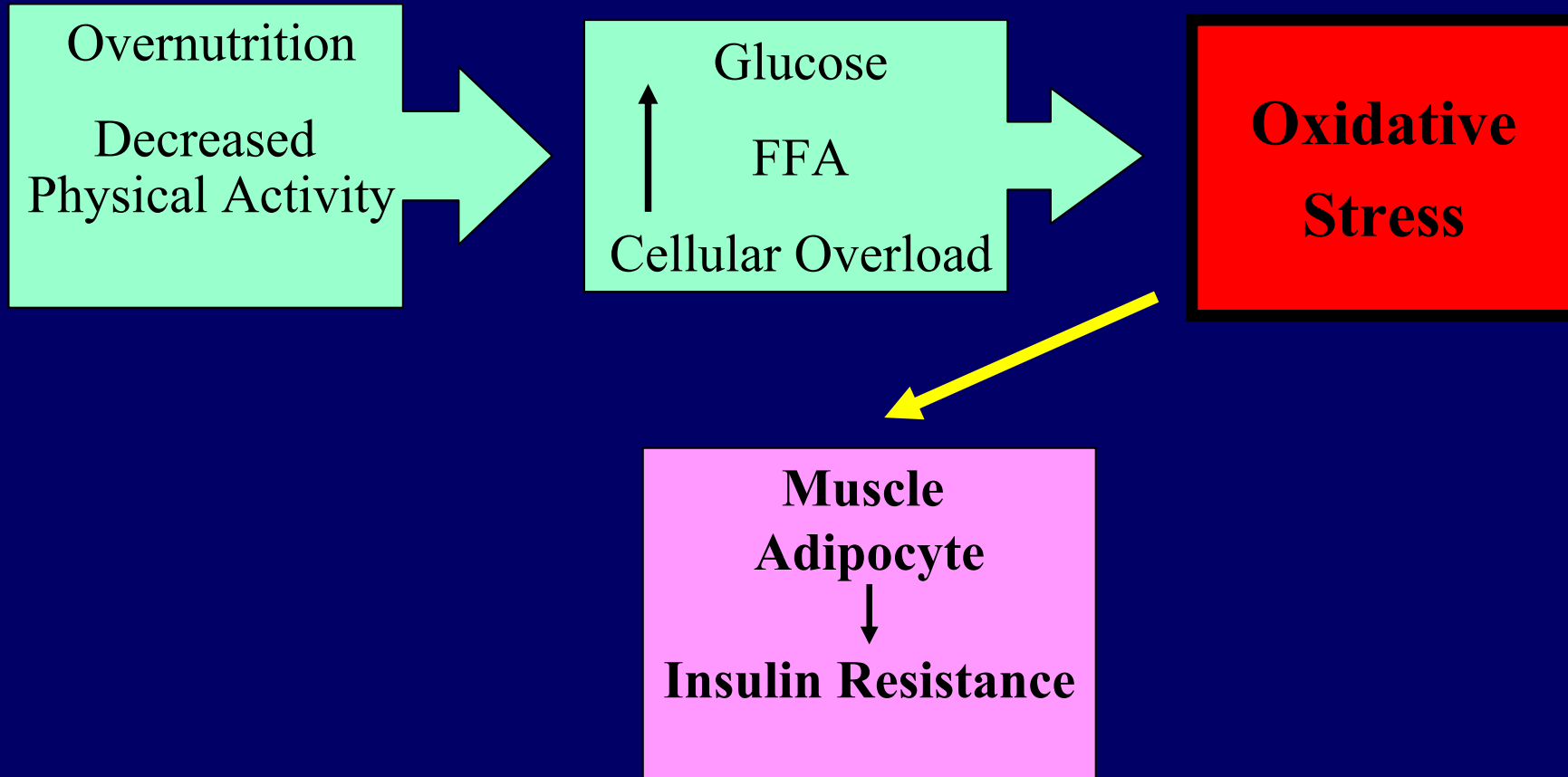
Maechler P et al:

(glucose induces insulin resistance through oxidative stress)

J Biol Chem 274: 27905-27913, 1999

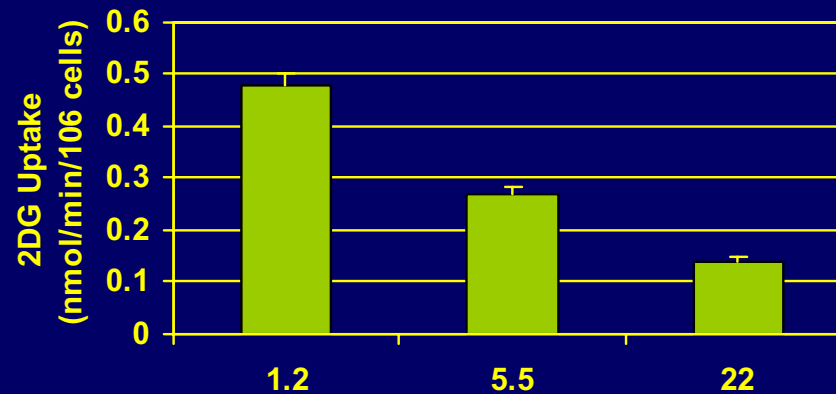
Glucose Transport is Downregulated by Hyperglycemia in Smooth Muscle Cells



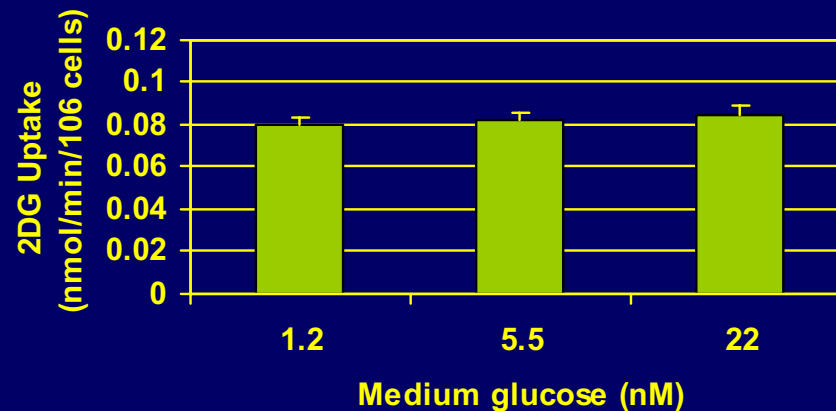


Glucose Transport is Downregulated by Hyperglycemia in Smooth Muscle Cells but not in Endothelial Cells

Smooth muscle cells

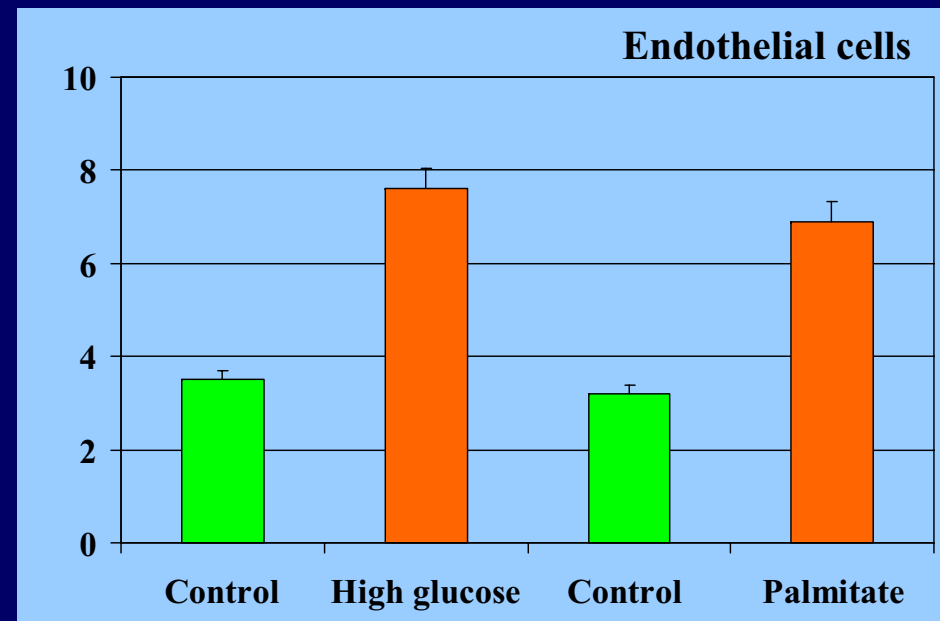
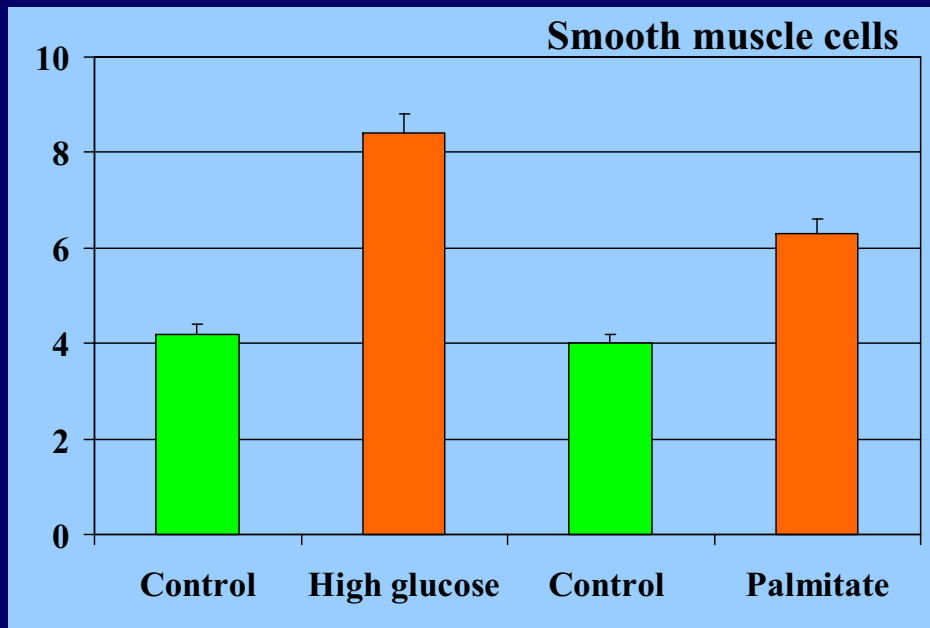


Endothelial cells

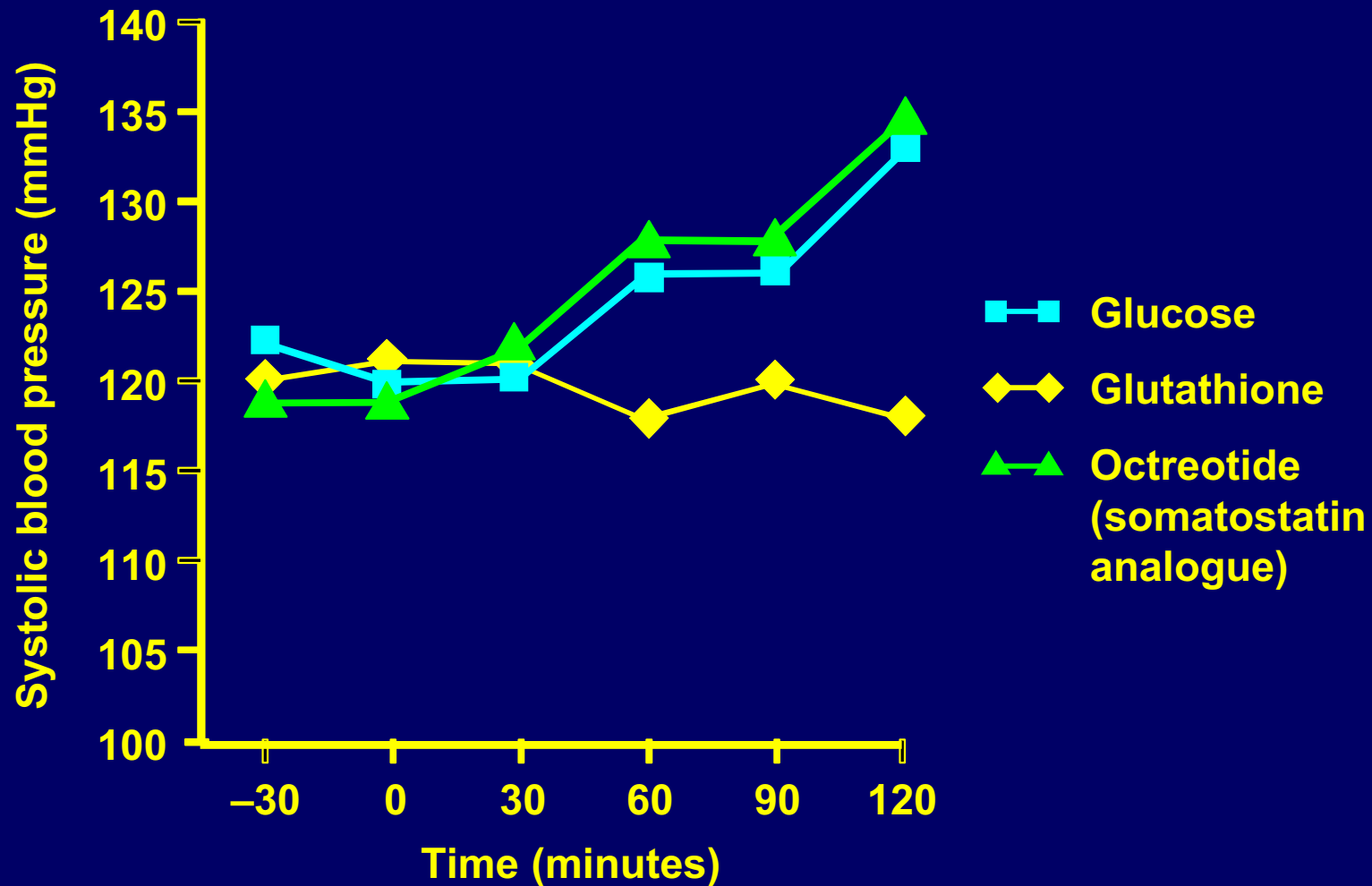


High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C-dependent activation of NAD(P)H oxidase in cultured vascular cells.

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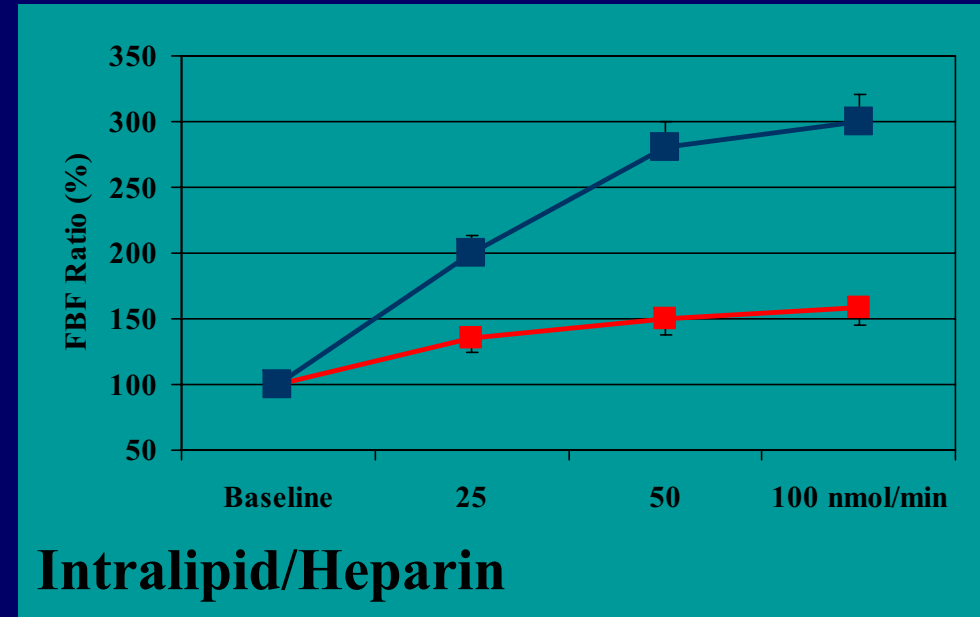
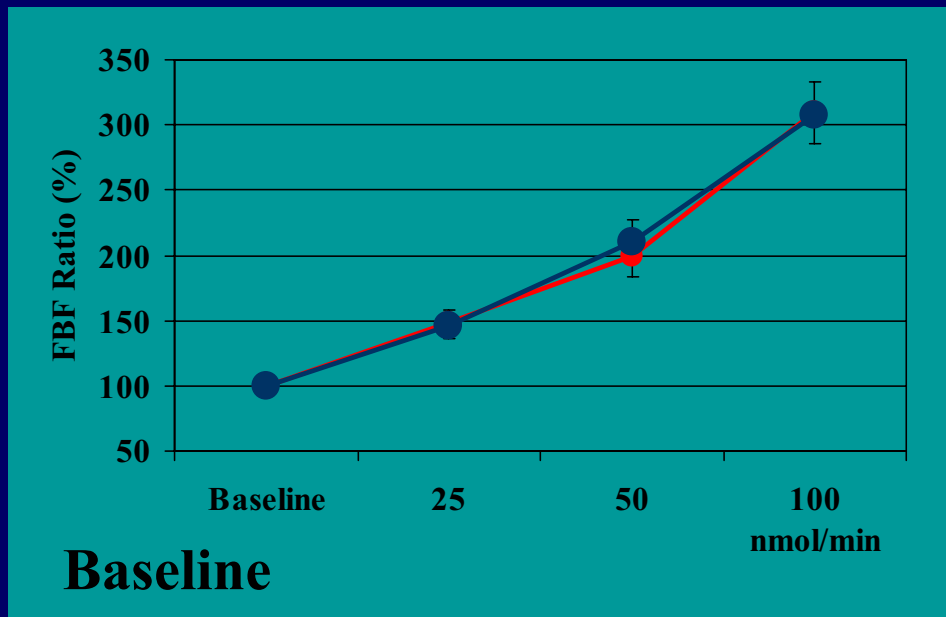


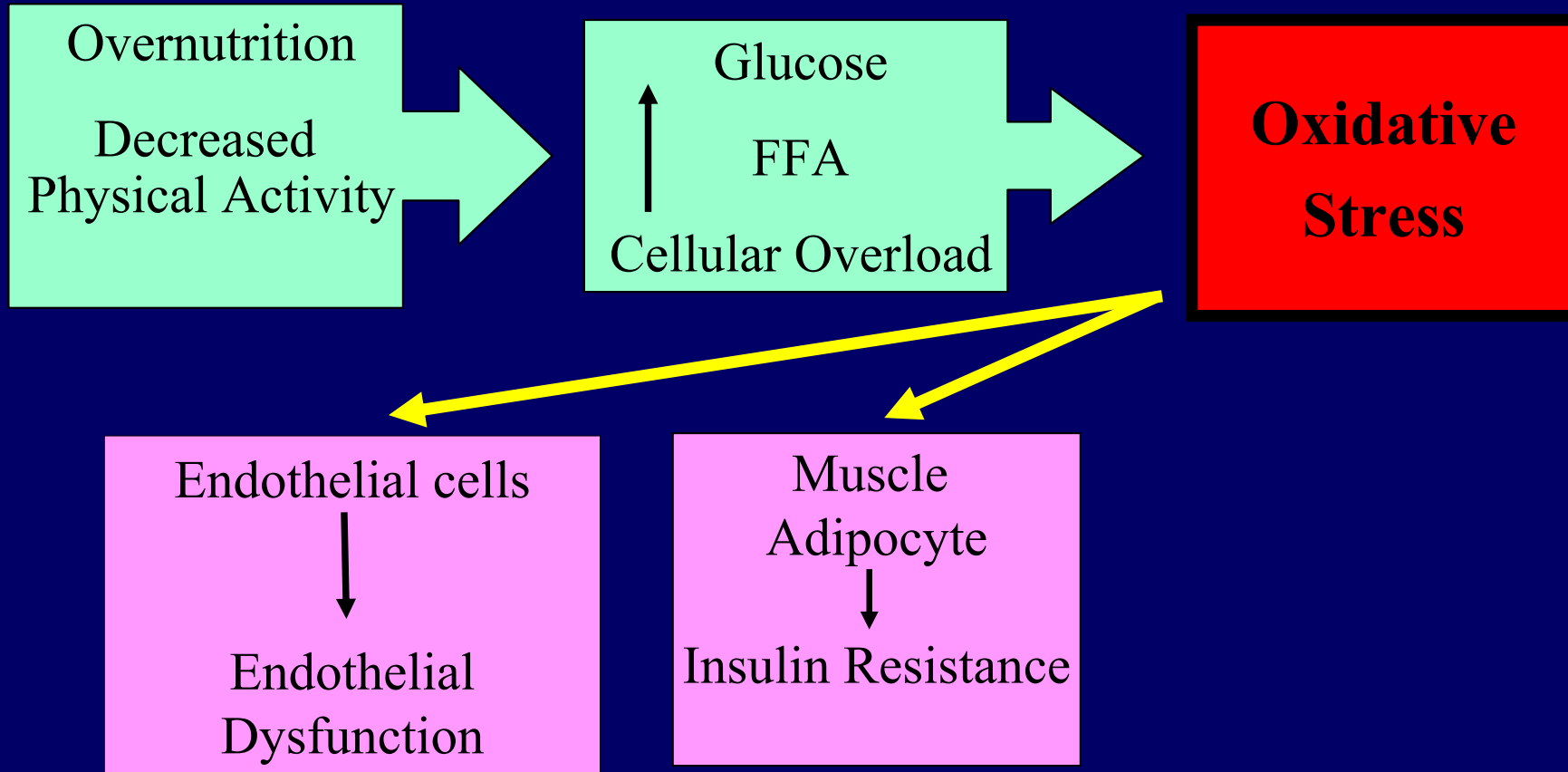
Glutathione reverses systemic haemodynamic changes induced by acute hyperglycaemia in healthy subjects

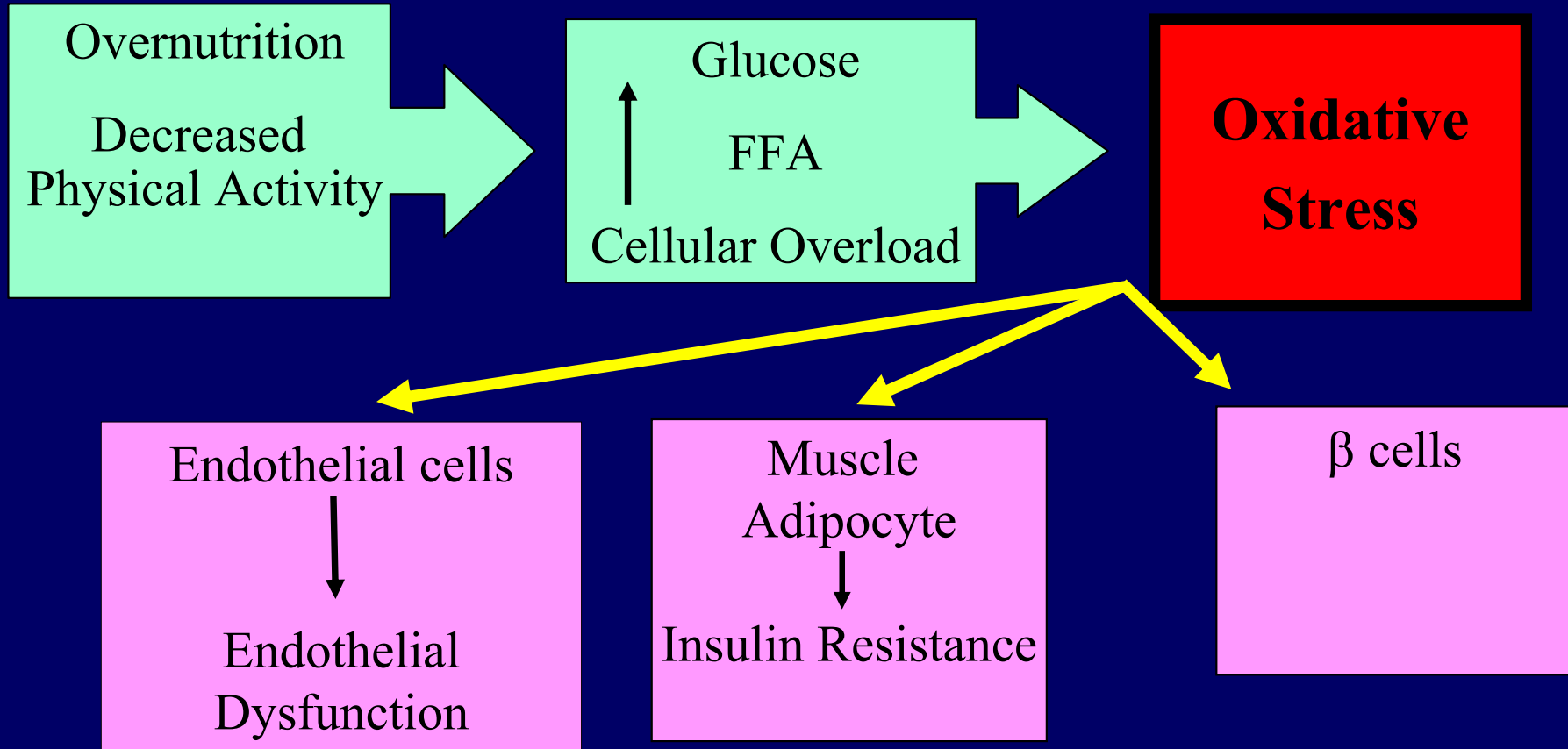


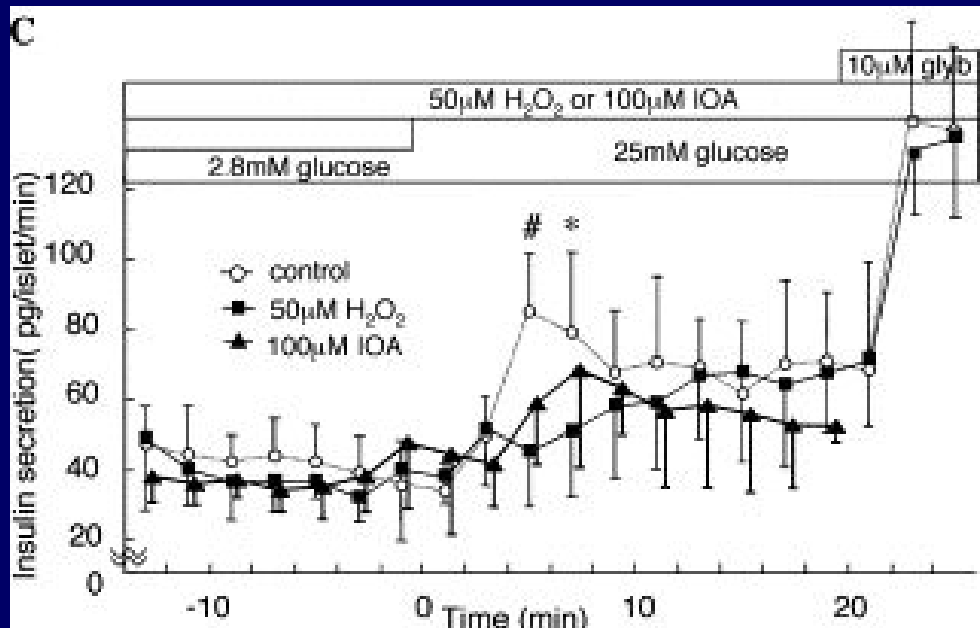
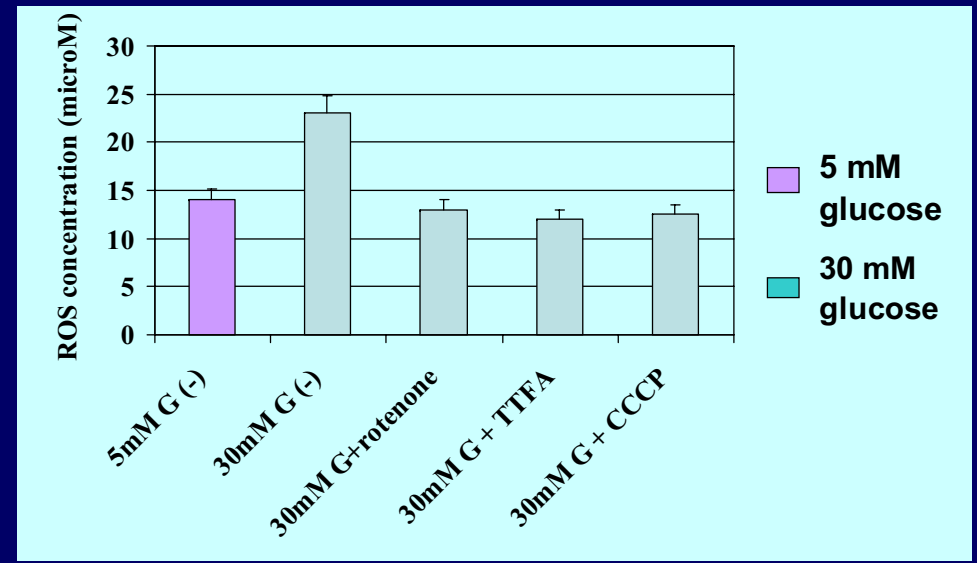
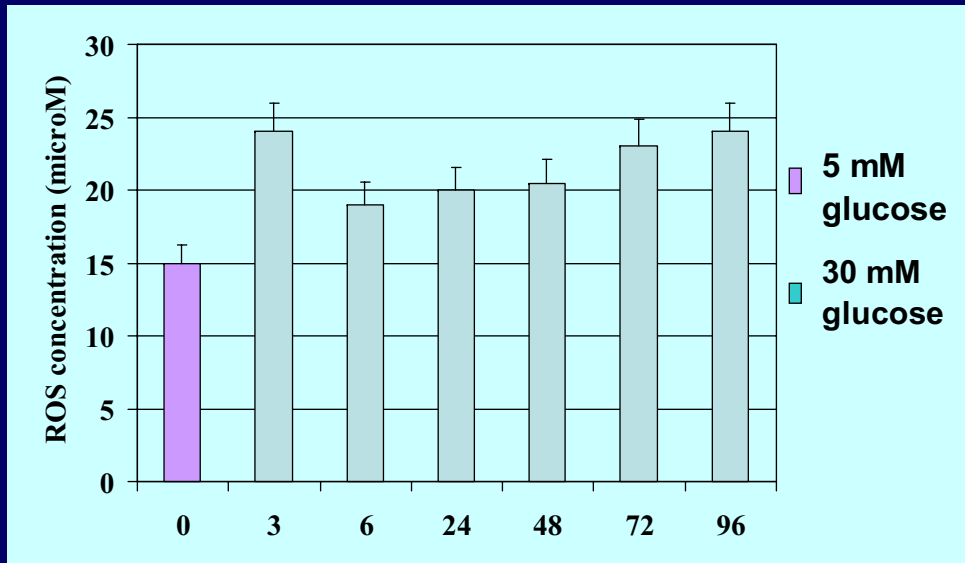
FFA-induced endothelial dysfunction can be corrected by vitamin C.

Pleiner J et al.



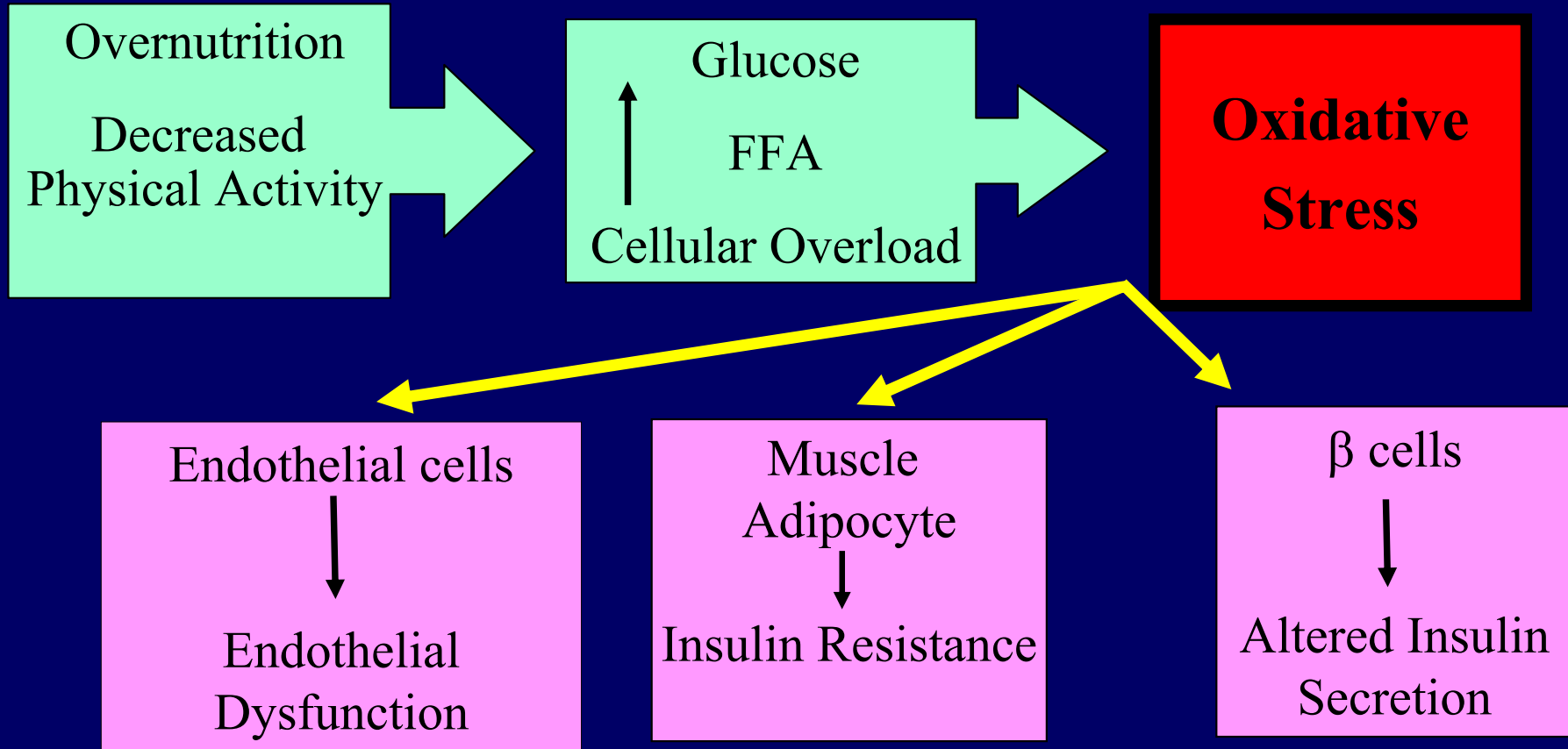


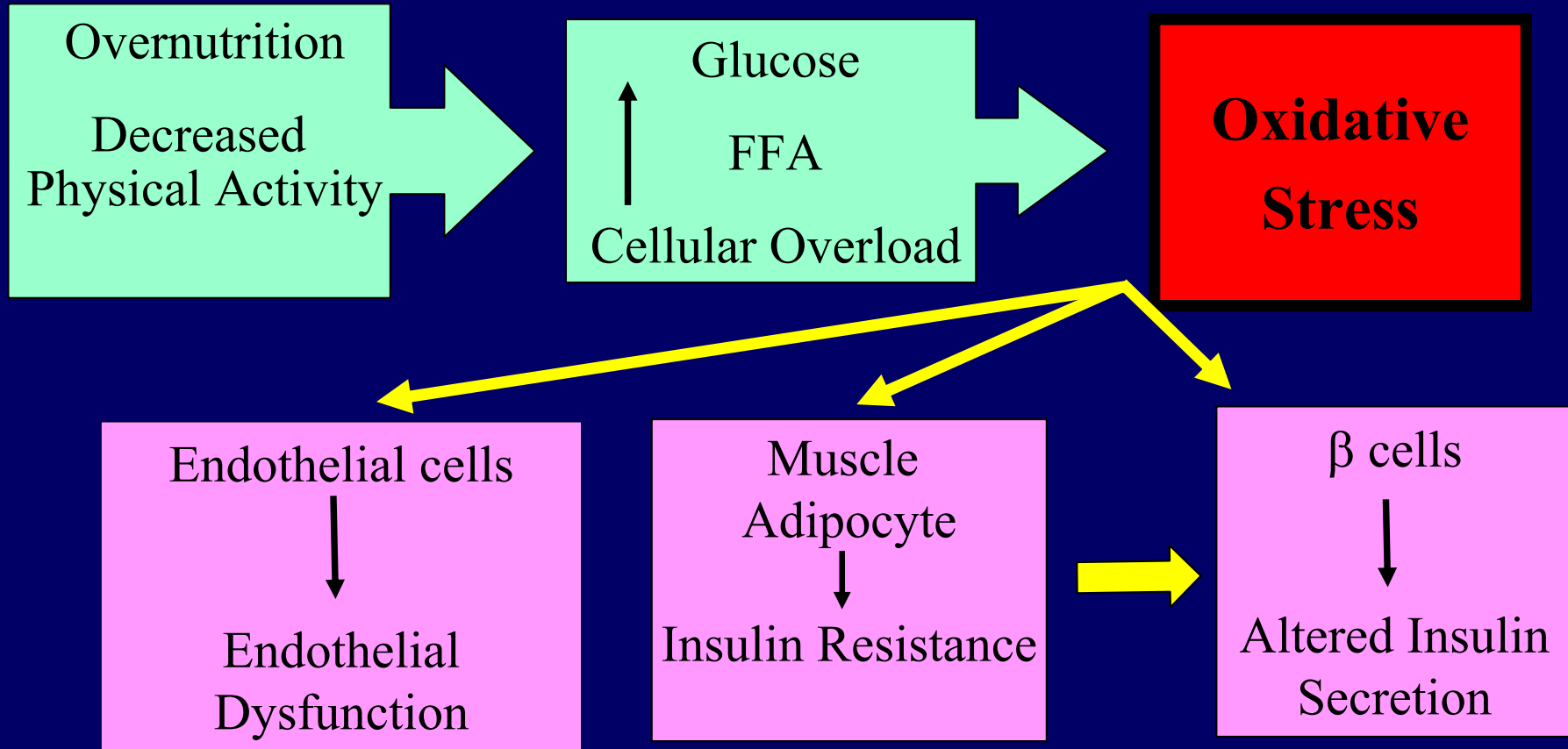




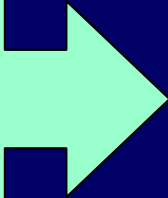
Mitochondrial reactive oxygen species reduce insulin secretion by pancreatic beta-cells.

Sakai K *et al*

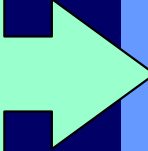




Overnutrition
Decreased
Physical Activity



↑
Glucose
FFA
Cellular Overload

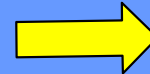


**Oxidative
Stress**

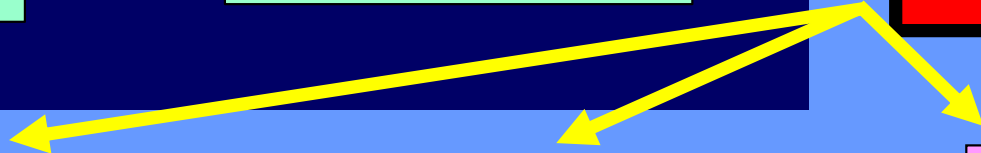
**Genetic
Predisposition**

Endothelial cells
↓
Endothelial
Dysfunction

Muscle
Adipocyte
↓
Insulin Resistance



β cells
↓
Altered Insulin
Secretion



Overnutrition
Decreased
Physical Activity

Glucose
↑
FFA
Cellular Overload

**Oxidative
Stress**

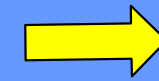
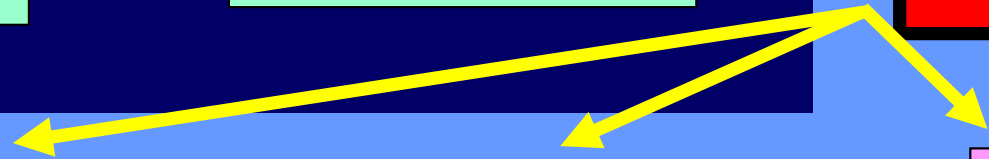
**Genetic
Predisposition**

Endothelial cells
↓
Endothelial
Dysfunction

Muscle
Adipocyte
↓
Insulin Resistance

β cells
↓
Altered Insulin
Secretion

CVD



ENDOTHELIAL DYSFUNCTION PREDICTS CARDIOVASCULAR DISEASE

**Endothelial dysfunction, oxidative stress, and
risk of cardiovascular events in patients with
coronary artery disease**

Heitzer T et al.

Patients number: 281

Follow-up: 4.5 years

Conclusion: Endothelial dysfunction and increased oxidative stress predict the risk of cardiovascular events in patients with coronary artery disease. These data support the concept that oxidative stress may contribute not only to endothelial dysfunction, but also to coronary artery disease activity.

Circulation 2001

Overnutrition
Decreased
Physical Activity

Glucose
FFA
Cellular Overload

**Oxidative
Stress**

**Genetic
Predisposition**

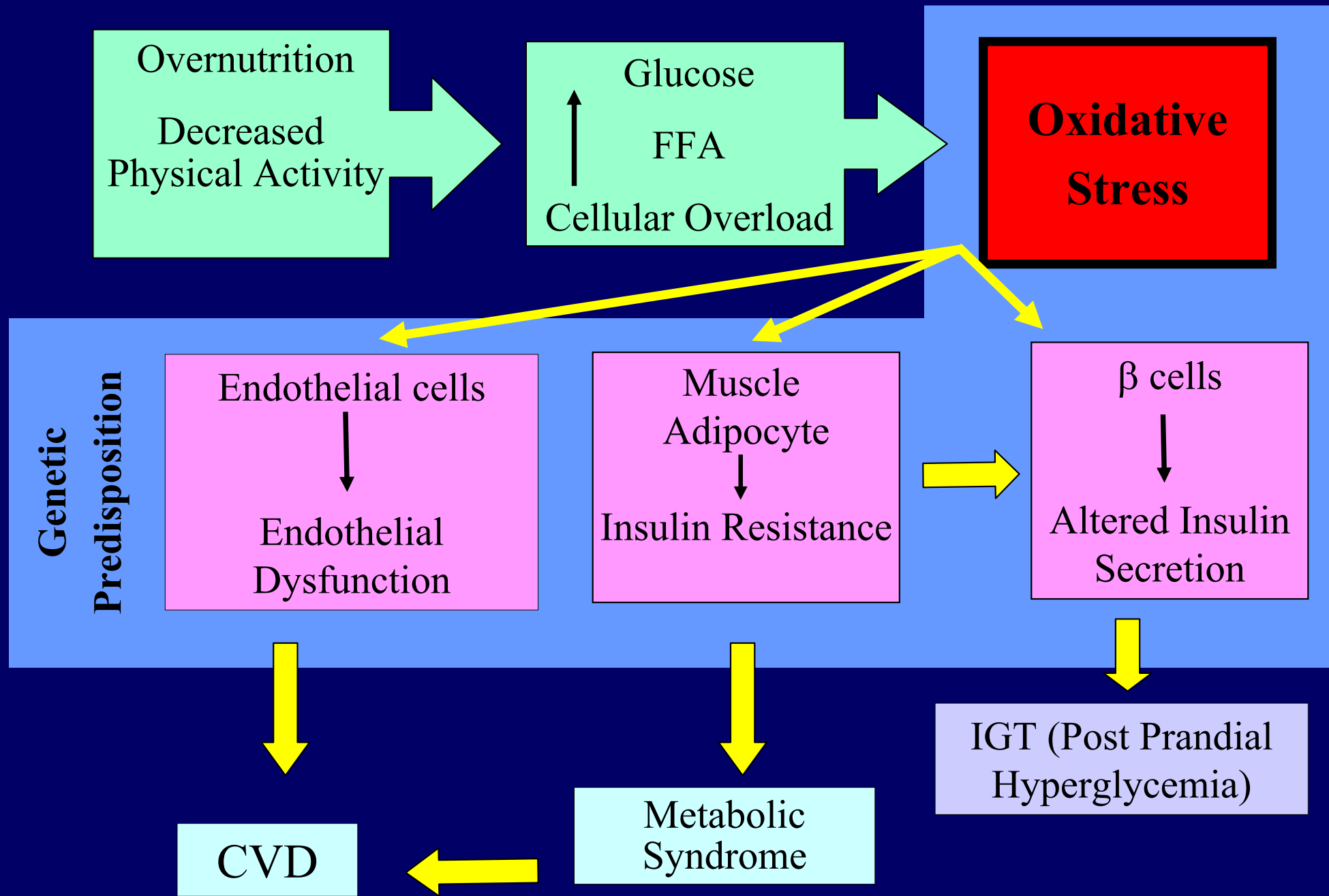
Endothelial cells
↓
Endothelial
Dysfunction

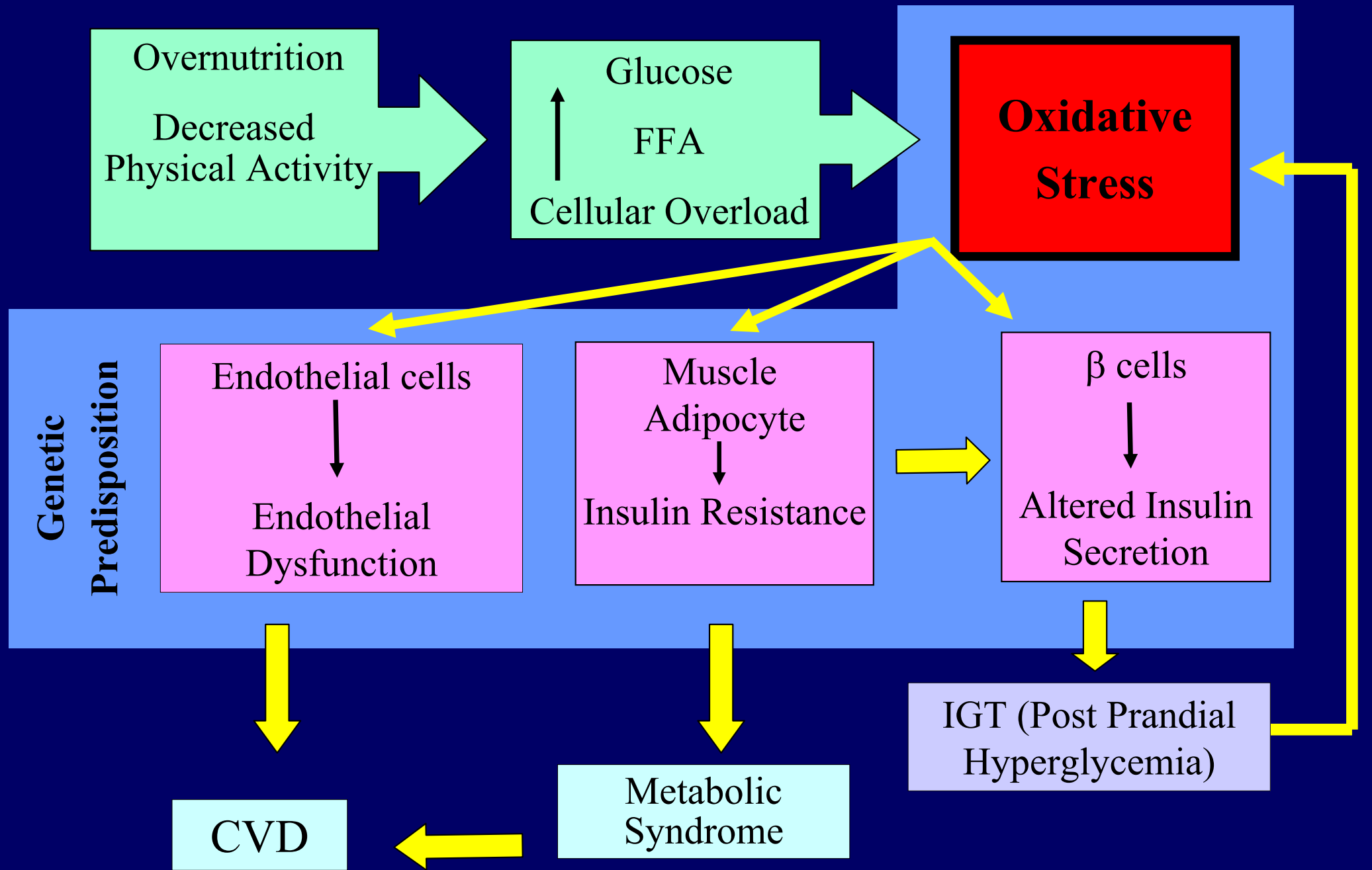
Muscle
Adipocyte
↓
Insulin Resistance

β cells
↓
Altered Insulin
Secretion

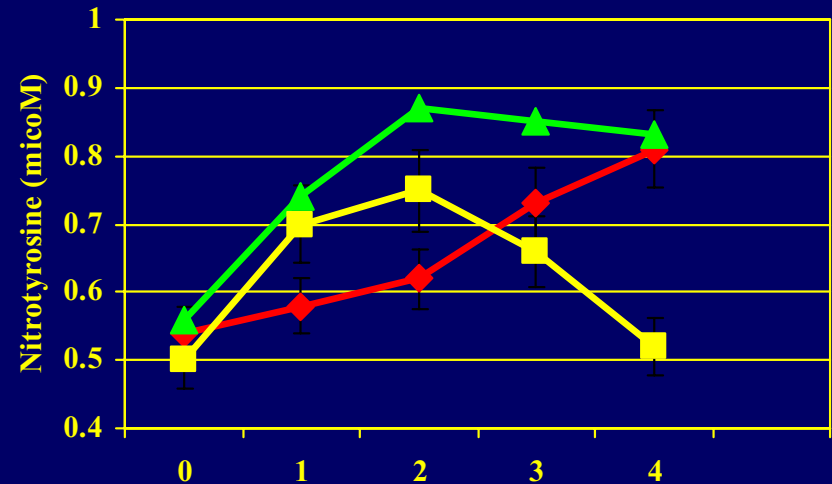
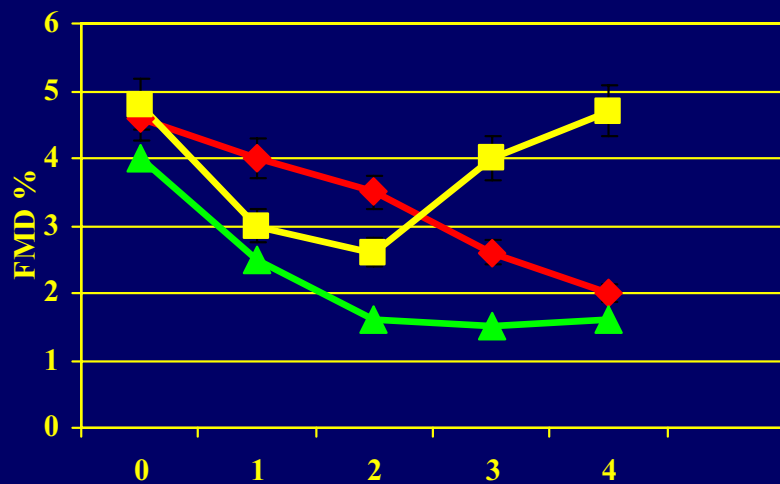
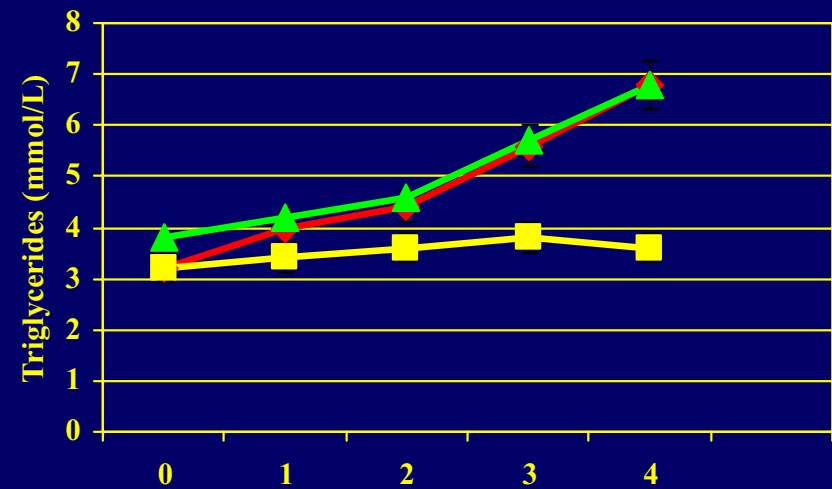
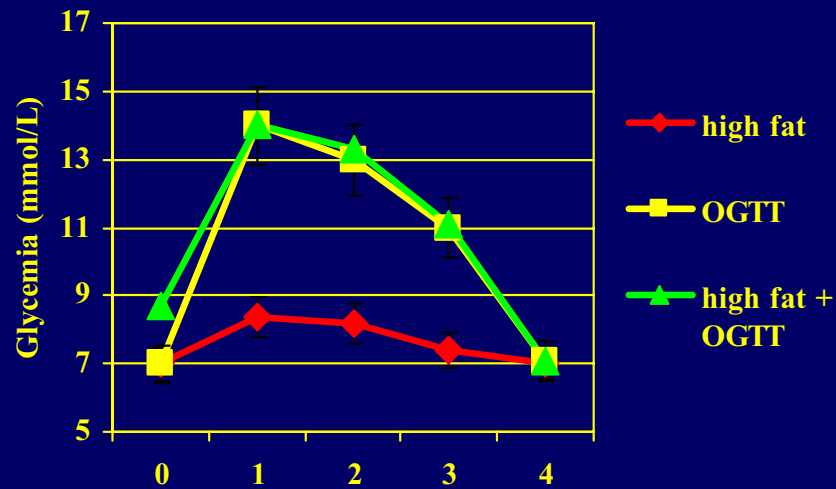
CVD

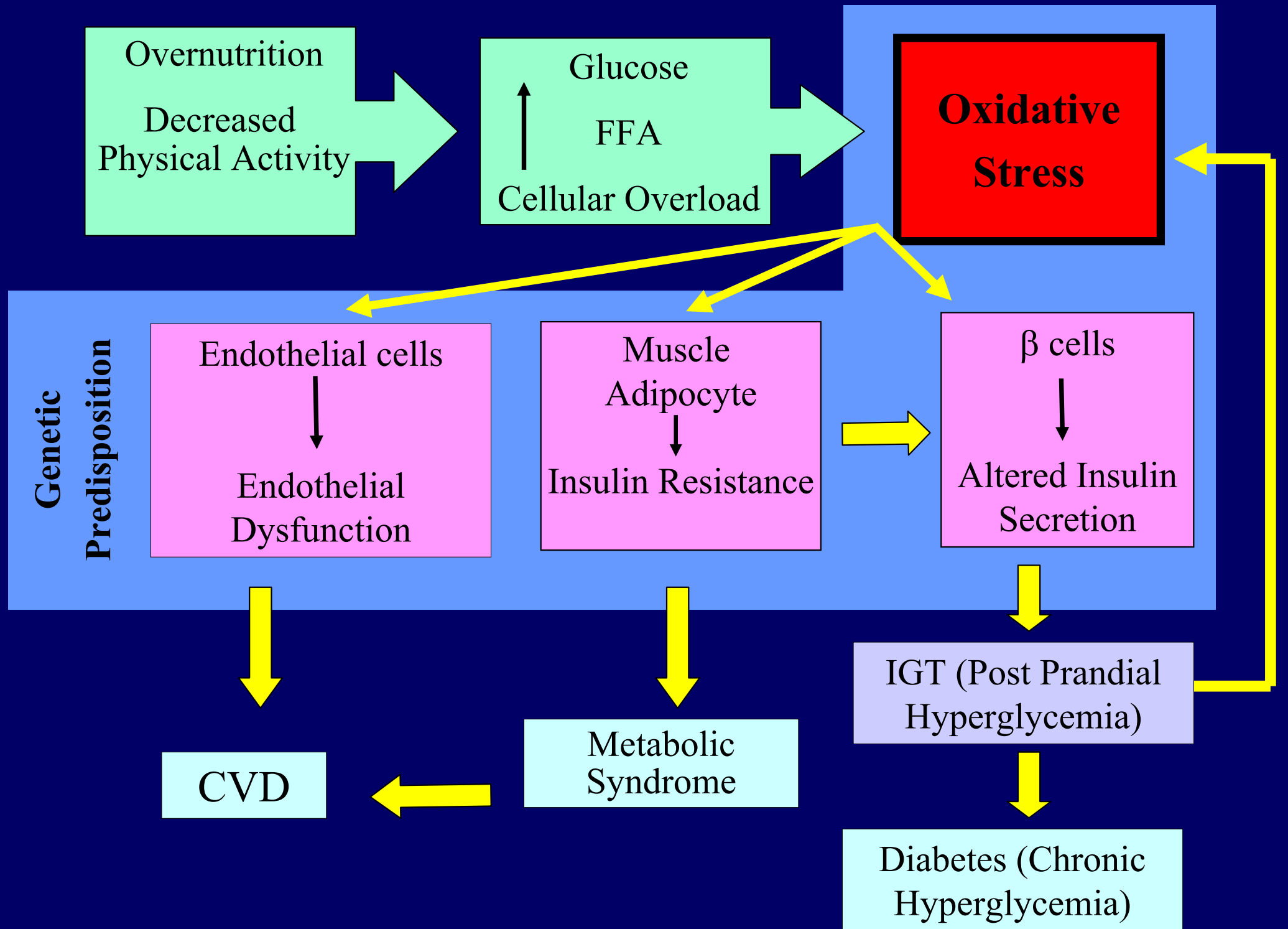
Metabolic
Syndrome

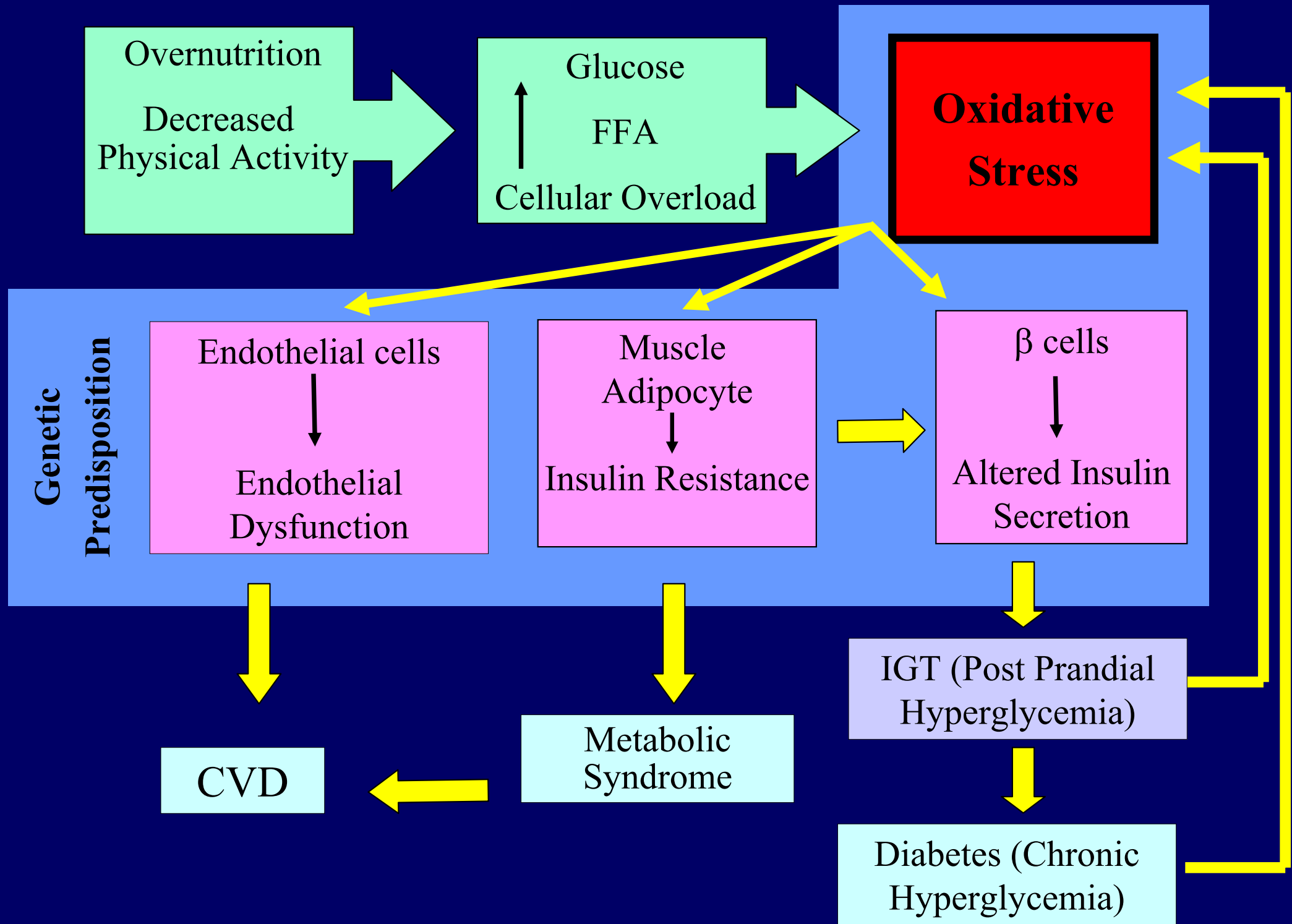




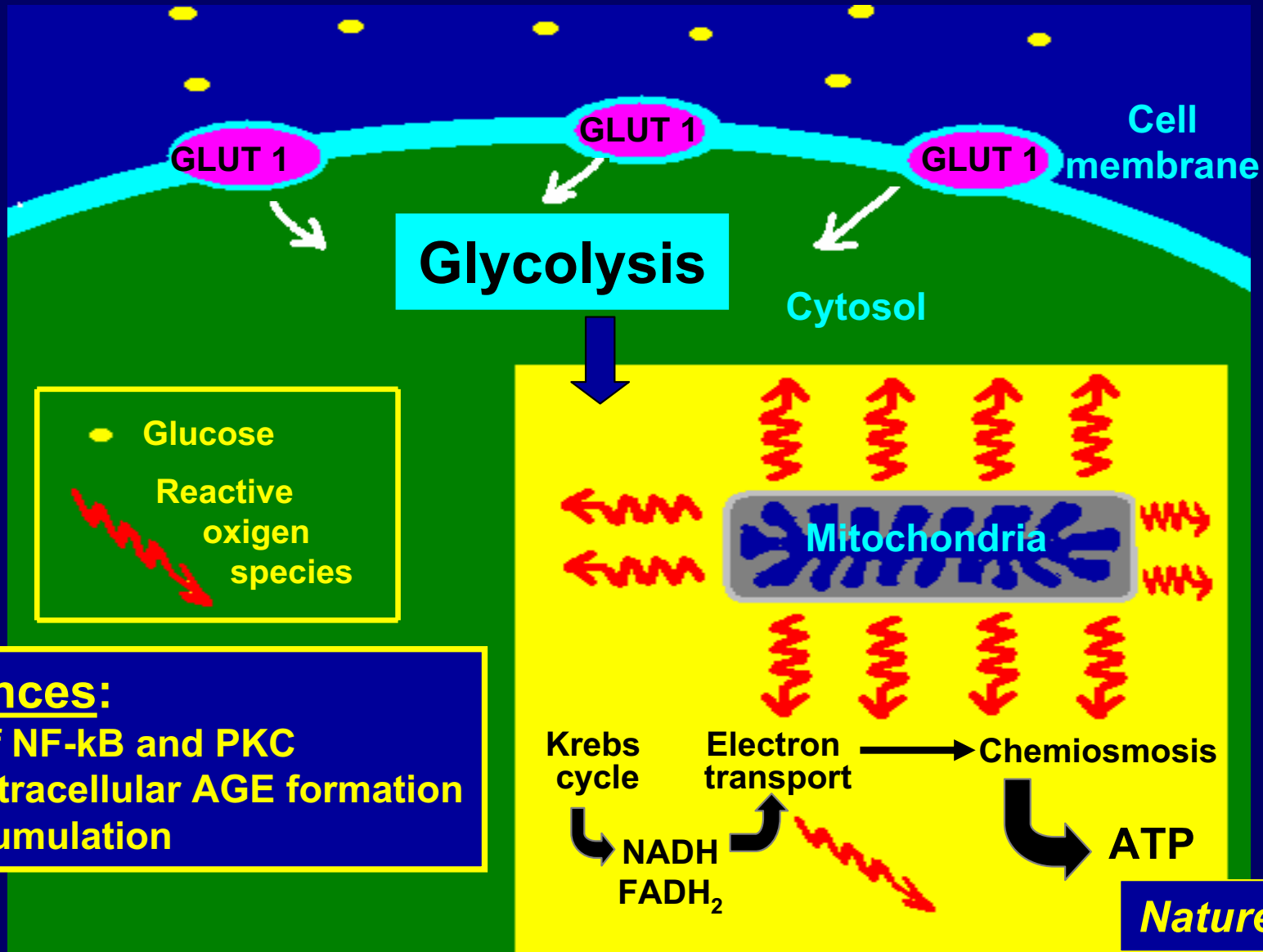
The Role of Hyperglycemia and Hypertriglyceridemia in Postprandial Oxidative Stress Generation in Diabetic Patients







ENDOTHELIAL CELL GLUCOSE UTILIZATION AND GENERATION OF OXIDANTS



Conclusion 1

Evidences suggest that **oxidative stress** may be the **underlying** pathogenetic mechanism linking insulin resistance and dysfunction of both beta cells as well as endothelium, which leads to overt **diabetes** and **cardiovascular disease**, respectively.

Conclusion 2

Since evidences are cumulating about the possibility of a “specific” and “causal” antioxidant interventions, this hypothesis suggests that oxidative stress may be, in a near future, a therapeutic target to prevent both diabetes and cardiovascular complications.

Prevention of Diabetes Mellitus and Cardiovascular Disease

WOSCOPS: Pravastatin

HOPE: Ramipril

INSIGHT: Nifedipine

LIFE: Losartan

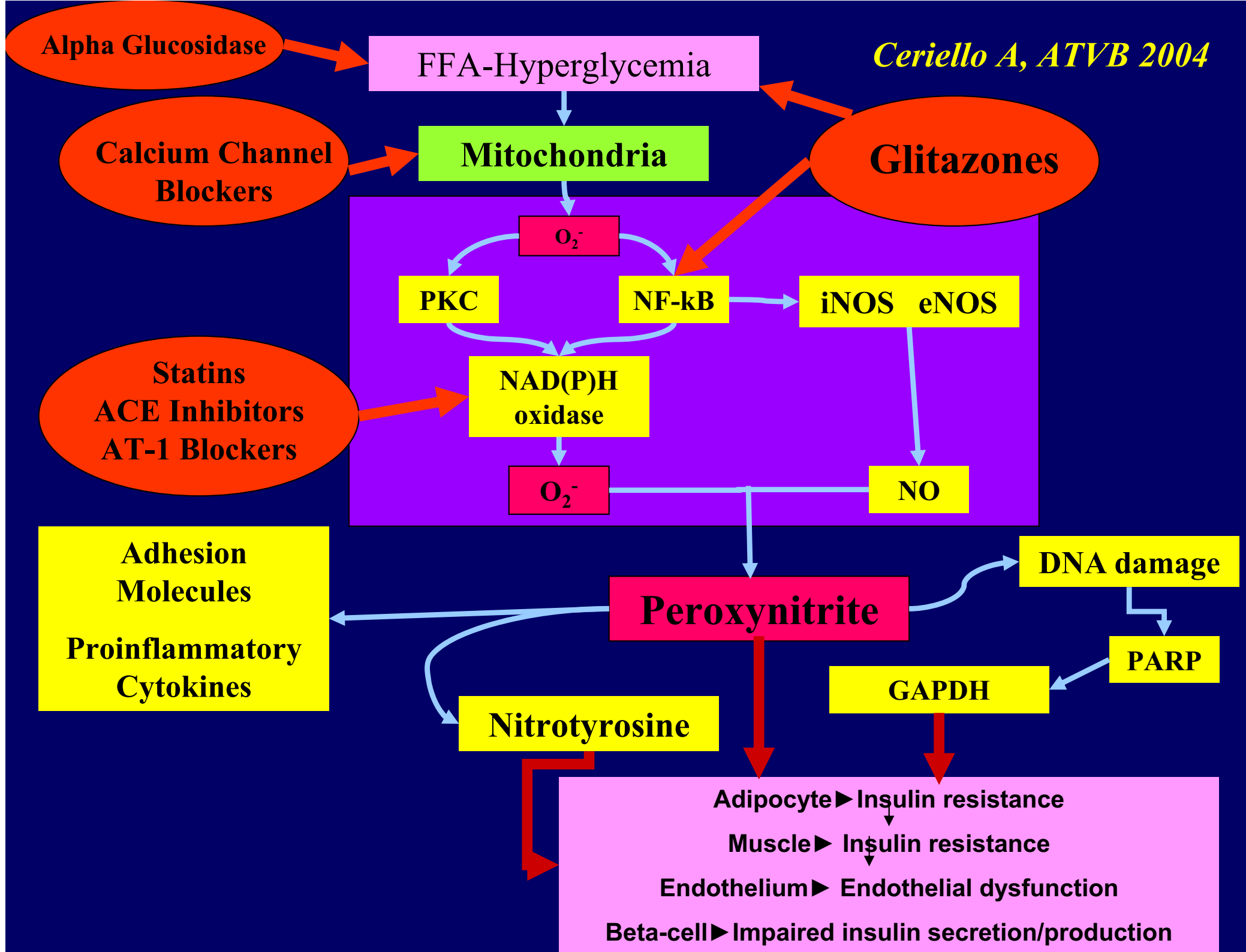
SOLVD: Enalapril

STOP-NIDDM: Acarbose – Post-prandial Hyperglycemia

TRIPOD: Troglitazone

**The anti-oxidant effect is the only
known property that all of these drugs
have in common.**

Ceriello A, ATVB 2004





α -tocopherol

γ -tocopherol



Lipid-peroxydes

Nitrosilation

3-Nitrotyrosine

γ -tocopherol

5-Nitro- γ -tocopherol



Nitrotyrosine

Risk
factor for
CVD

Shishebor MH et al. JAMA 2003

5-Nitro- γ -tocopherol

Increased in
CVD

Morton LW et al. Biochem J 2002

α -tocopherol
with diet

Prevention
of CVD

α -tocopherol
 γ -tocopherol
 δ -tocopherol

Supplementation
 α -tocopherol

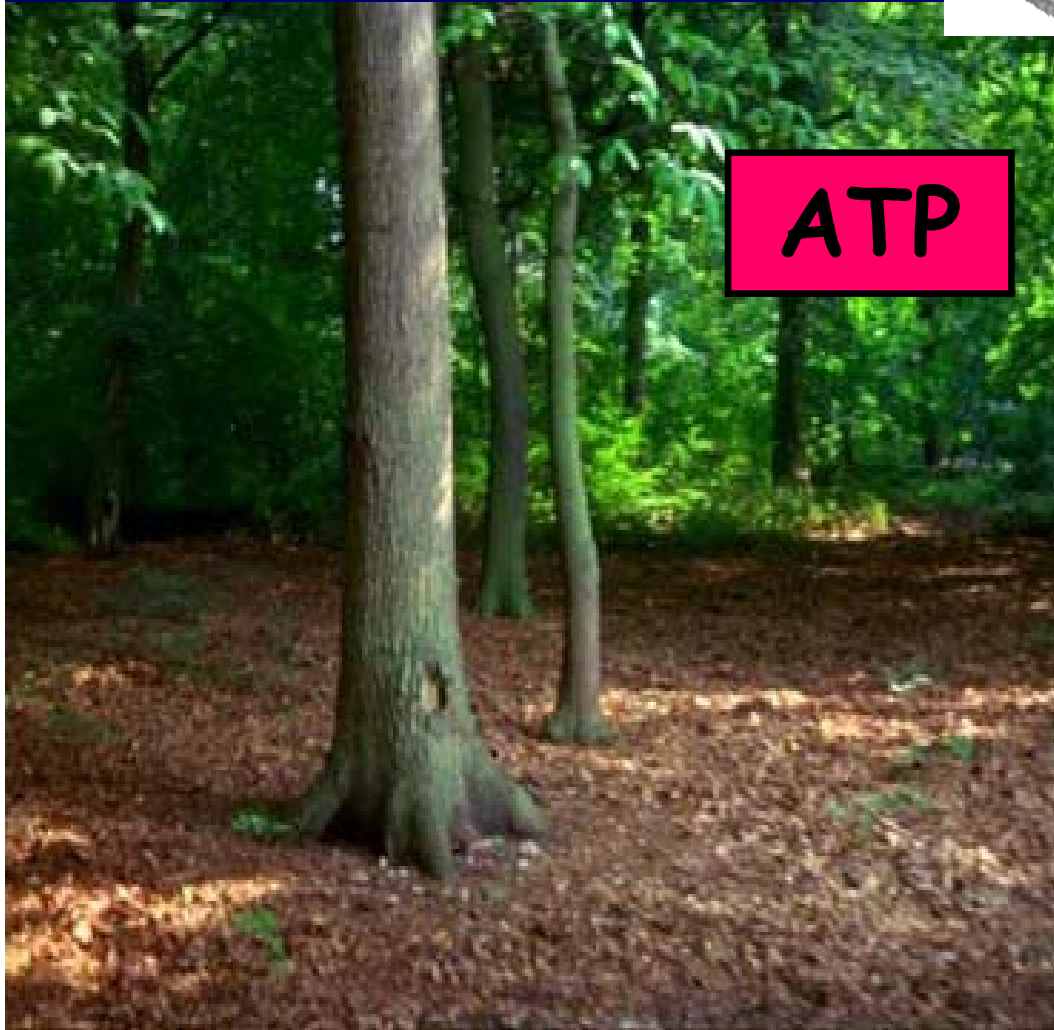
No effect
on CVD

Reduces the absorption
and therefore the plasma
levels of γ -tocopherol

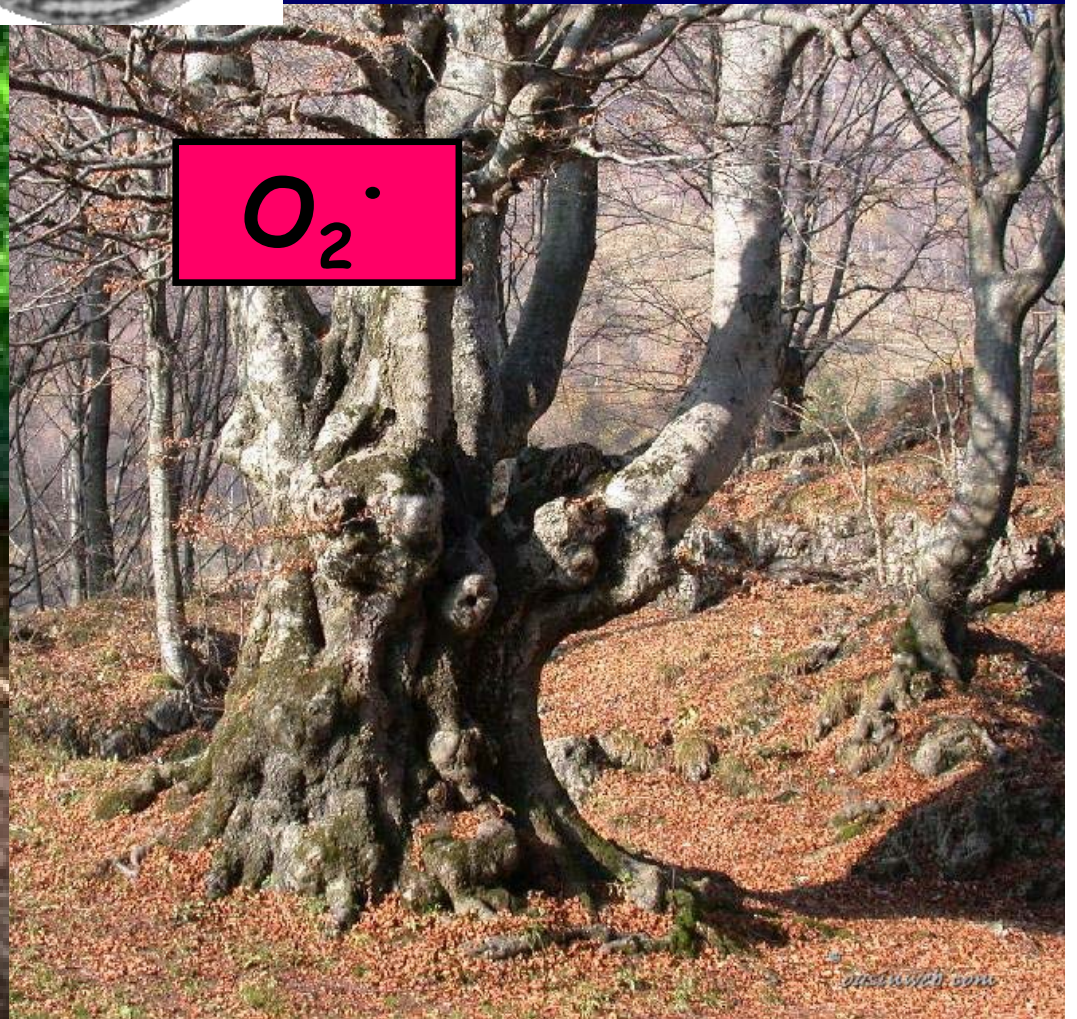
Conclusions:

- ✓ A-tocopherol with diet means increased amounts of g-tocopherol, which can contrast nitrosative stress
- ✓ A-tocopherol supplementation reduces plasma levels of g-tocopherol, therefore favouring nitrosative stress and may be CVD

Glucose-FFA



ATP



O_2



TRY ONE OF OUR PRIME
DRY-AGED MEAT PACKAGES TODAY!



SPICE UP YOUR SALADS
WITH OUR HOME MADE
DRESSINGS!



TRY ONE OF OUR
ALL NATURAL
ITALIAN SAUCES



In Manhattan
you'll find....