

**The Role of
Advanced Lipoxidation End-Products
(ALEs) in Diabetic Complications**

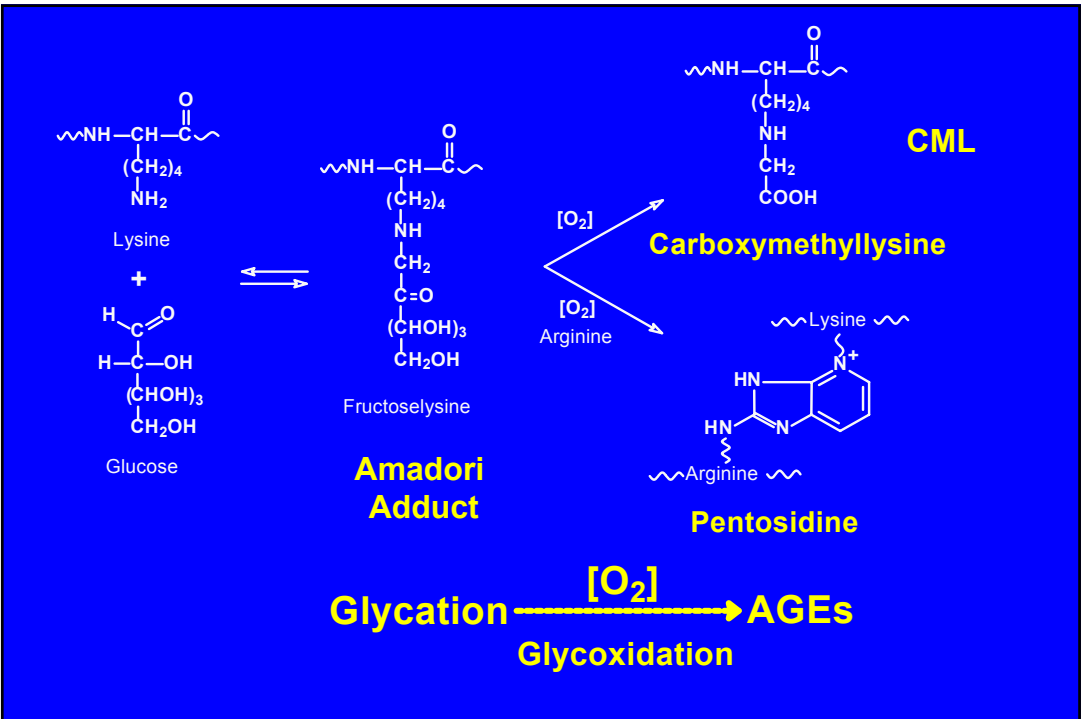
**John W. Baynes
University of South Carolina**

Two Topics

- **The role of lipids in chemical modification of proteins and development of diabetic complications**
- **The mechanism by which metabolic memory or imprinting affects the risk for diabetic complications**

Part I

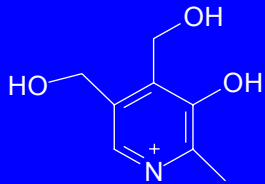
LIPIDS



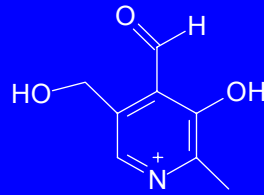
The Vitamin B₆ Family



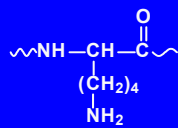
Pyridoxamine



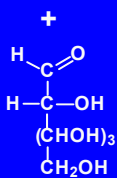
Pyridoxine



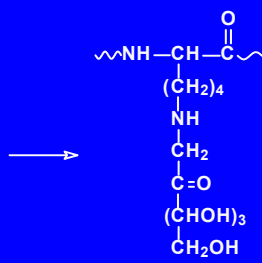
Pyridoxal



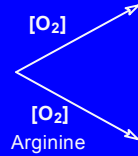
Lysine



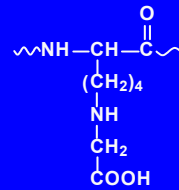
Glucose



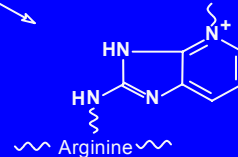
Fructoselysine



Arginine



~Lysine~

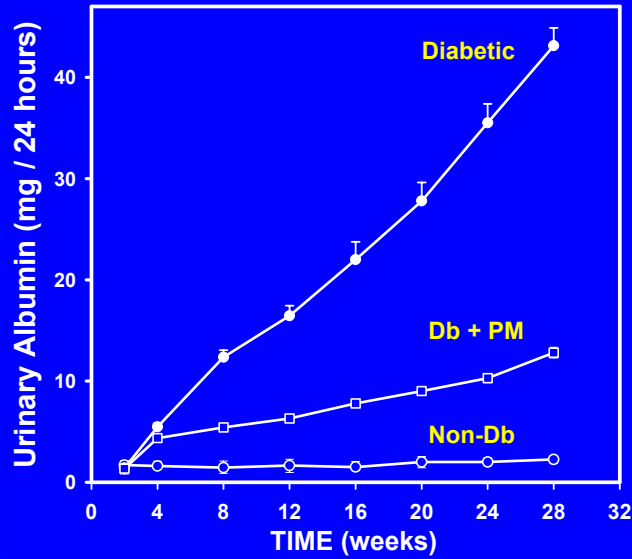


~Arginine~

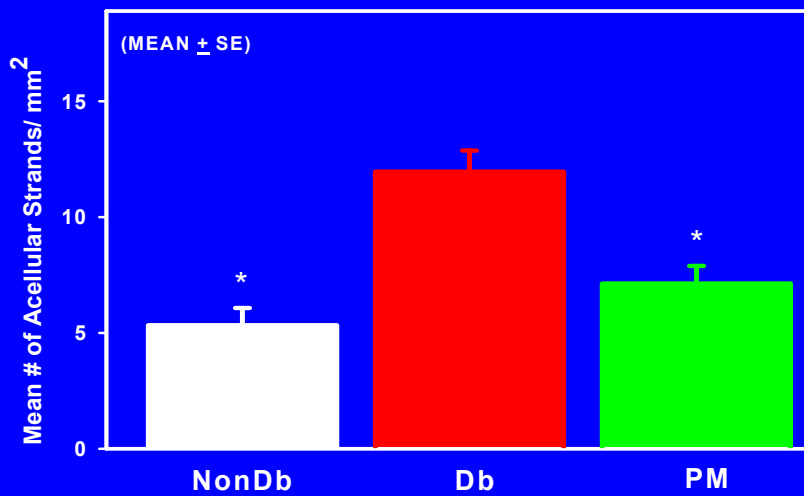
Glycation ~~→~~ AGEs

Pyridoxamine

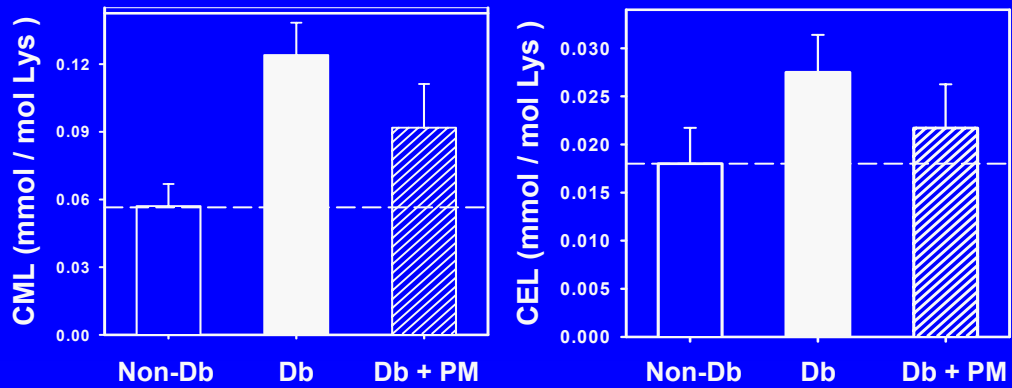
PM inhibits the development of kidney disease in the STZ-diabetic rat.



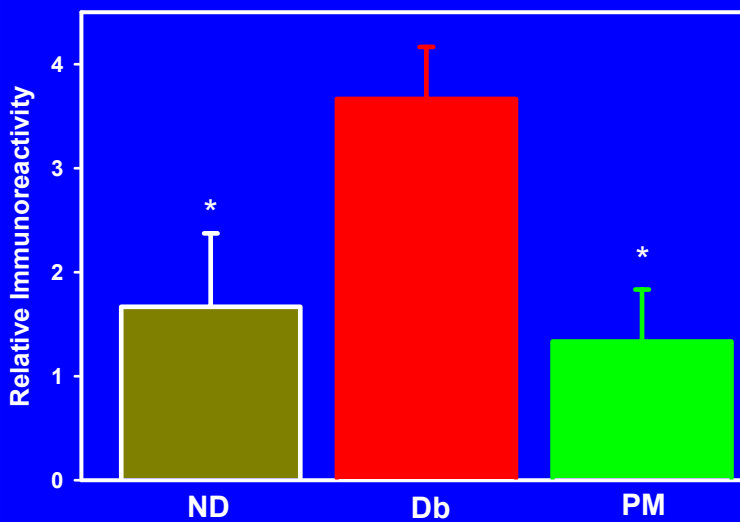
PM Limits Acellular Capillary Formation In Diabetic Rat Retina

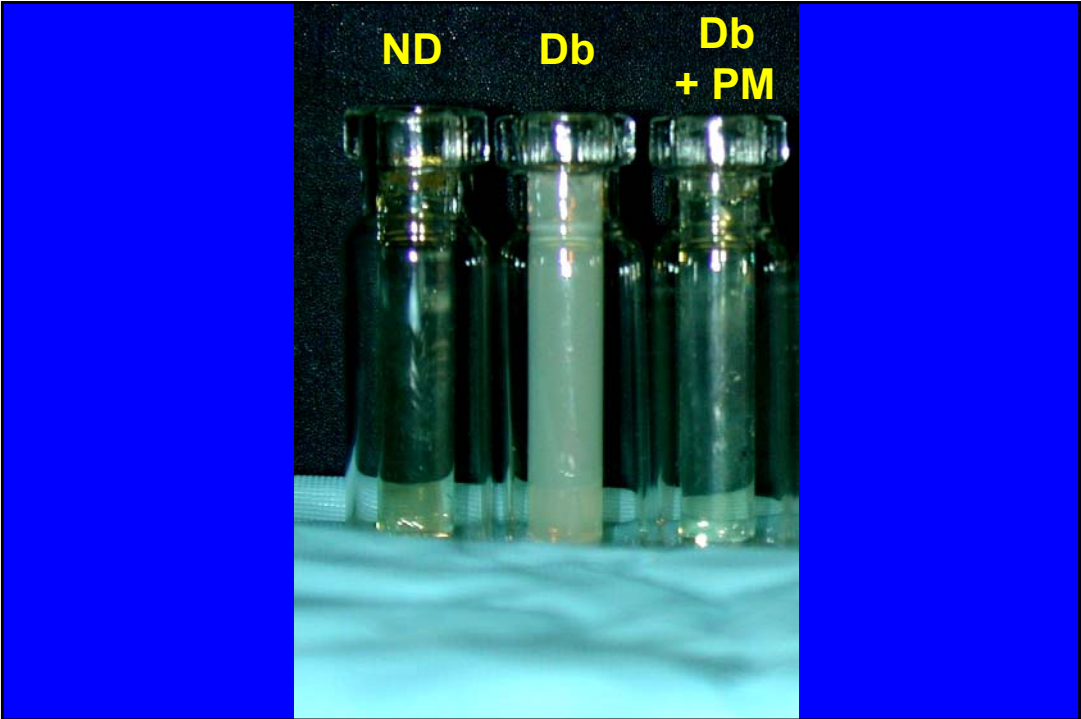


PM inhibits the increase in CML and CEL in skin collagen of STZ-diabetic rats.

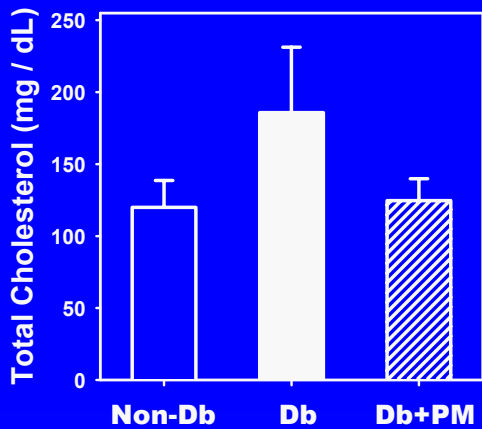
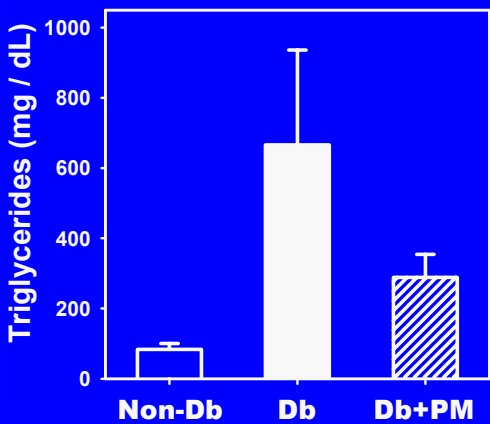


CML IMMUNOREACTIVITY IN RAT RETINA

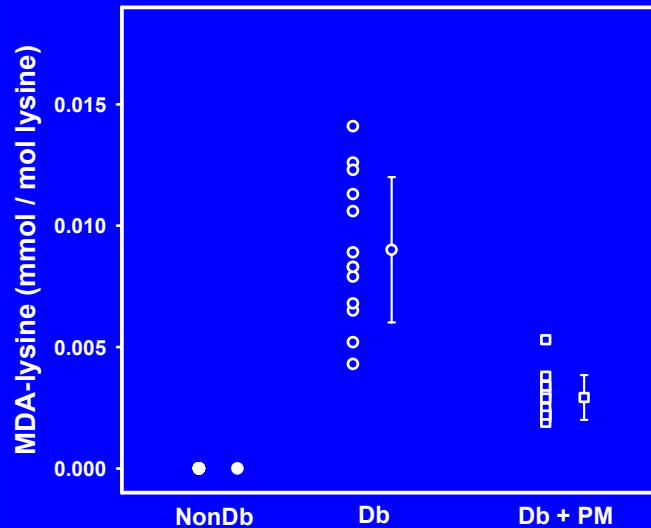




PM inhibits the increase in triglycerides and cholesterol in plasma of STZ-diabetic rats.



PM Limited the Formation of the ALE MDA-lysine in Skin Collagen of Diabetic Rats

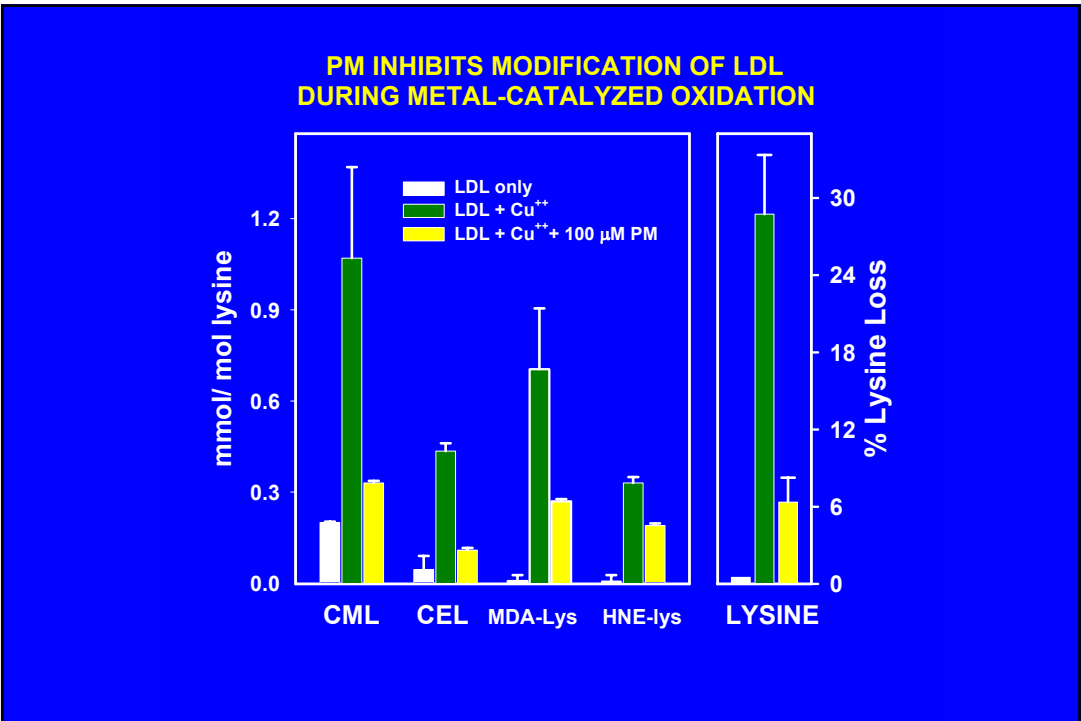
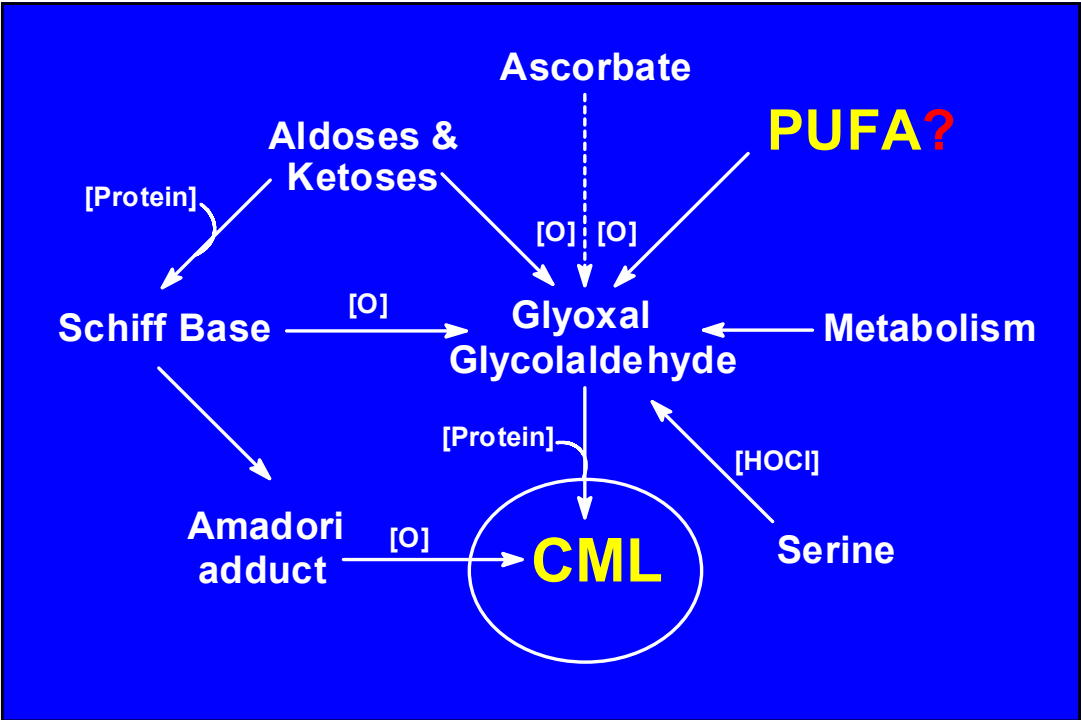


BENEFITS of PM in STZ-diabetic rats

- Retarded development of renal and retinal disease
- Decreased chemical modification of tissue proteins

BUT

- PM did not decrease levels of the AGE pentosidine
- PM inhibited hyperlipidemia and ALE formation
- Strong correlation between plasma triglycerides & CML
- Strong correlation between triglycerides & albuminuria

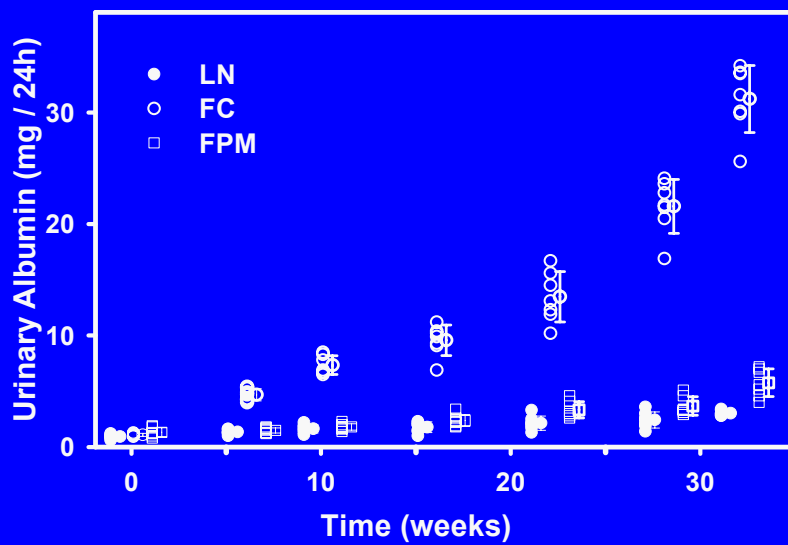




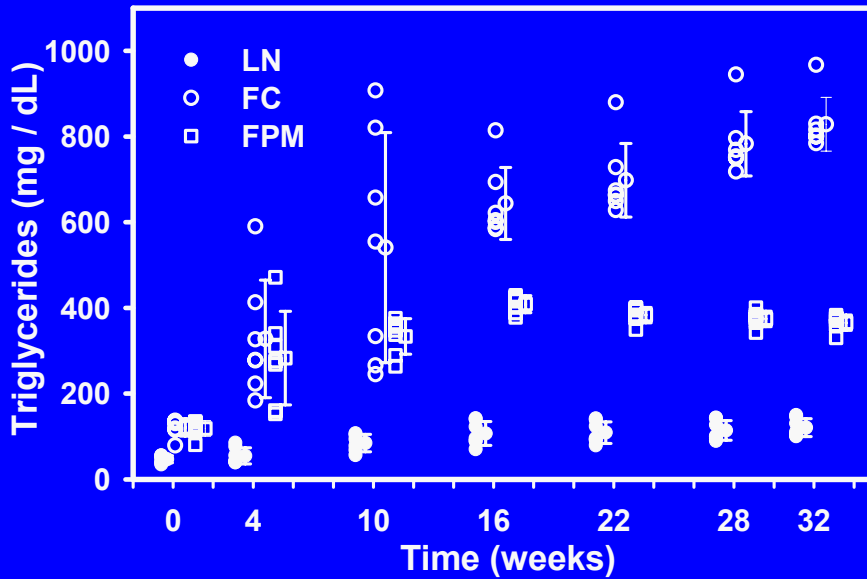
**Zucker *fa/fa* rat
(Model of
Syndrome X)**

**Obese
Hyperlipidemic
Hypertensive
Insulin Resistant**

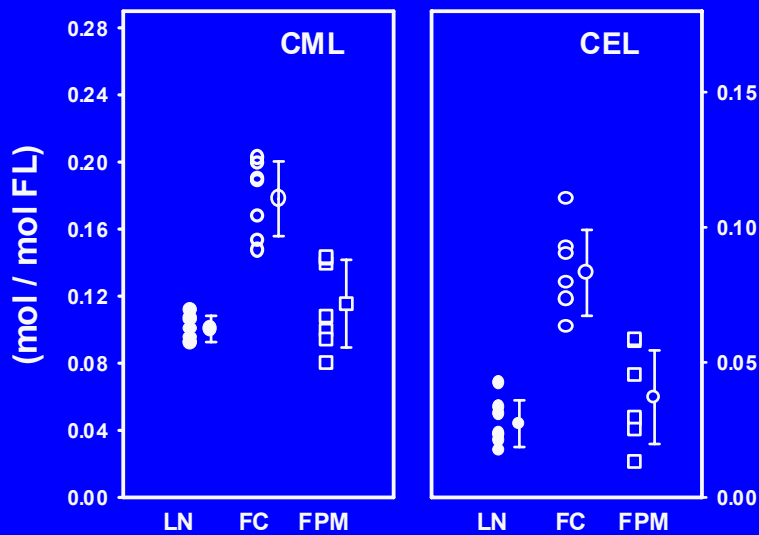
**PM inhibits microalbuminuria
in Zucker *fa/fa* rats**



PM inhibits increase in triglycerides in Zucker *fa/fa* rats



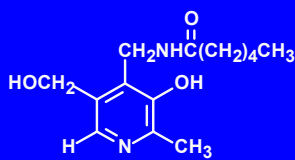
AGE/ALEs are increased in skin collagen of Zucker *fa/fa* rats; PM inhibits this increase.



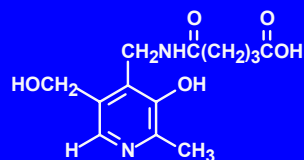
PM-adducts formed during inhibition of lipoxidation reactions *in vitro*



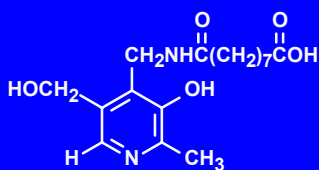
FAPM, $m/z = 197$



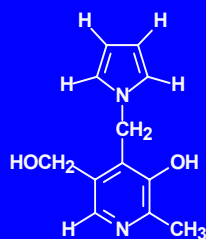
HAPM, $m/z = 267$



PDAPM, $m/z = 283$



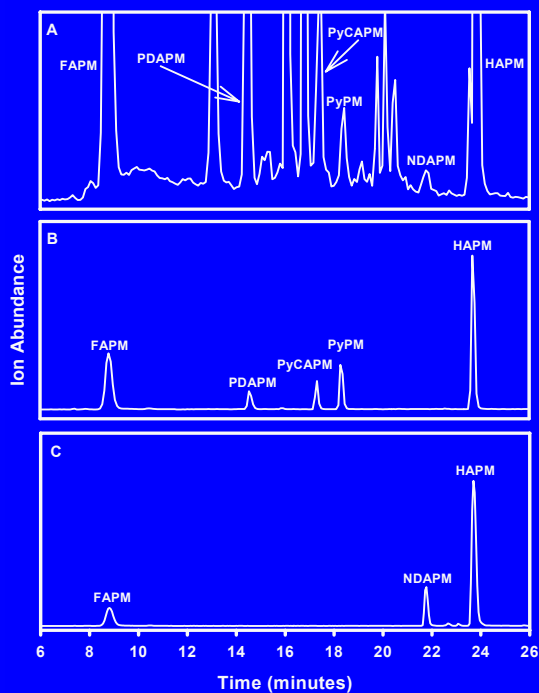
NDAPM, $m/z = 339$



PyPM, $m/z = 219$



PyCAPM, $m/z = 247$

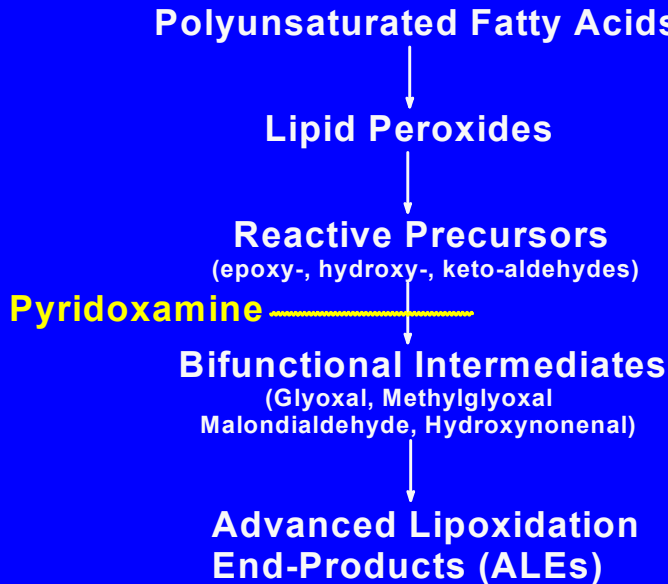


Urine

Arachidonate

Linoleate

Proposed Site of Action of Pyridoxamine



Summary

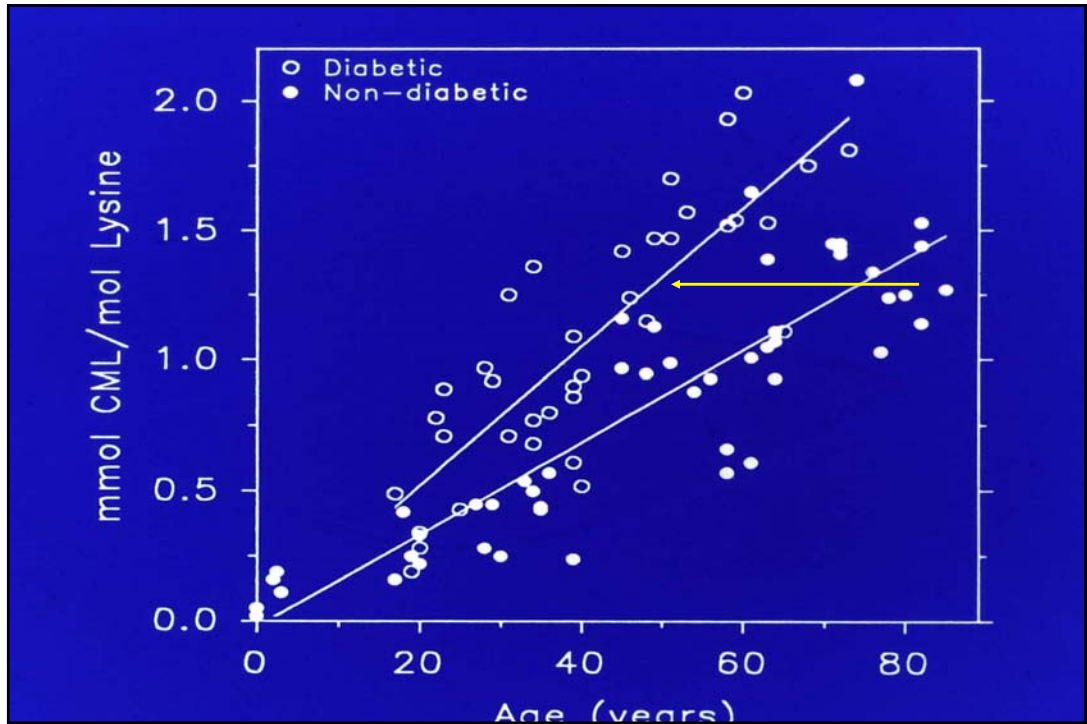
- Pyridoxamine inhibits the progression of nephropathy in diabetic and obese rats.
- Pyridoxamine inhibits AGE/ALE formation in diabetic and obese rats.
- Pyridoxamine inhibits development of hyperlipidemia in diabetic and obese rats.
- PM inhibits lipoxidative chemical modification of protein, trapping similar intermediates *in vitro* & *in vivo*.

CONCLUSION

Lipids are an important source of chemical modification of proteins in diabetes and hyperlipidemia.

Part II

**The Mechanism of
Metabolic Memory
or
Metabolic Imprinting
in Diabetes**



Assumptions

- Most significant damage is oxidative in nature.
- Protein is a useful sensor, but relevant damage is to genetic material.
- Genetic damage is silent.

Proposal

Damage to genome of target tissues leads to:

- 1) loss of cell replicative capacity
and/or
- 2) loss of cellularity.

Origin of Metabolic Memory

- Cell damage is propagated by cell division.
- Younger cells have greater replicative capacity.
- Early damage will be amplified, even after initiation of more rigorous control.
- Early protection (rigorous control) will have a long-term effect.

Analogy

Irradiation → Oxidative Stress

Irradiation of animal lenses *in vivo*

**Cataracts develop more rapidly
in younger animals^{1,2}**

1. O Hockwin (1962) *Exp Eye Res* 1:422-426.
2. DG Cogan and DD Donaldson (1951) *Invest Ophthalmol* 45: 508 ff.
3. AV Desjardins (1931) *Am J Roentgenol* 26: 643 ff.2.

Conclusions

- **The earlier and more severe the period of poor control, the more severe the long-term consequences.**
- **Rigorous metabolic control at an early age yields (apparent) protection during later periods of poorer control.**
- ***Memories may be good or bad.***