

Mechanisms of Obesity Nephropathy: A tale from two genetic mice models of obesity



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Overview

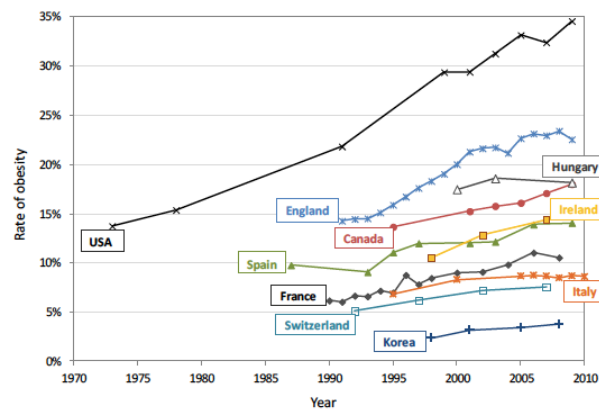
- Obesity & Renal Failure
 - Epidemiology
 - Risk Factor for Renal Failure
- Lipotoxicity & Renal Failure
- Hypothesis
- Experimental Design & Methods
- Results
- Summary & Conclusions



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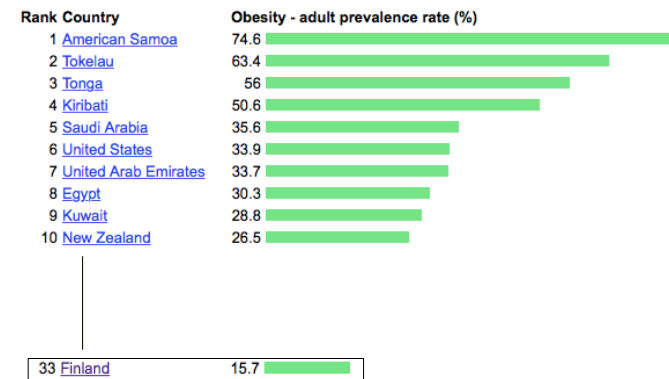
Global Obesity Prevalence, 2010



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www.oecd.org/health/49716427.pdf

Global Obesity Prevalence, 2012



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<http://www.indexmundi.com/g/r.aspx?v=2228>

Obesity in Qatar

The New York Times
GLOBAL EDITION
WITH THE International Herald Tribune
Tuesday, April 27, 2010 - Last Update: 2:18 AM ET (06:18 GMT)

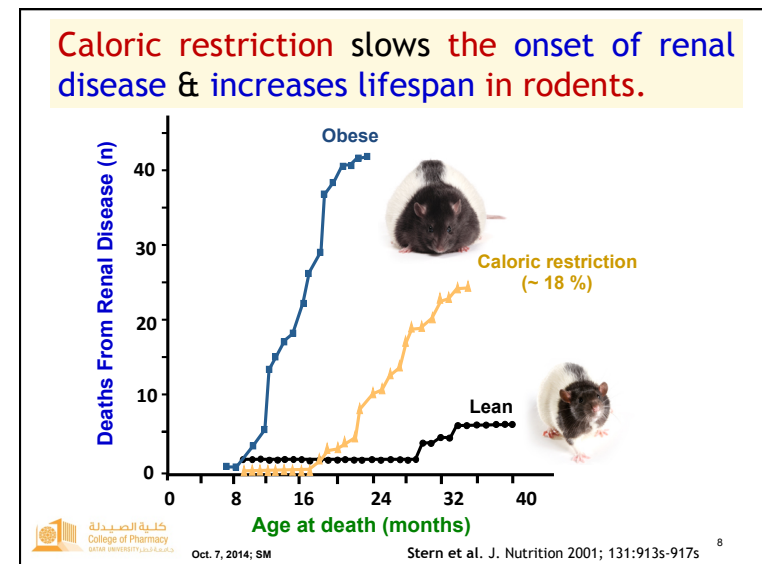
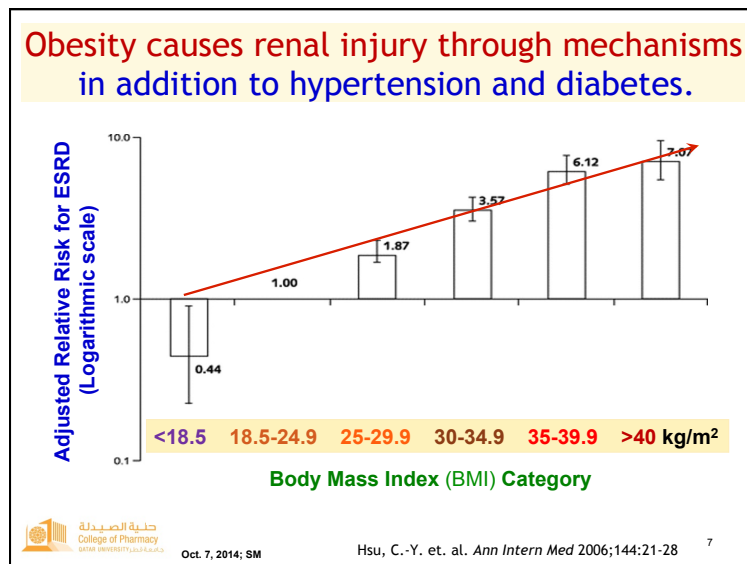
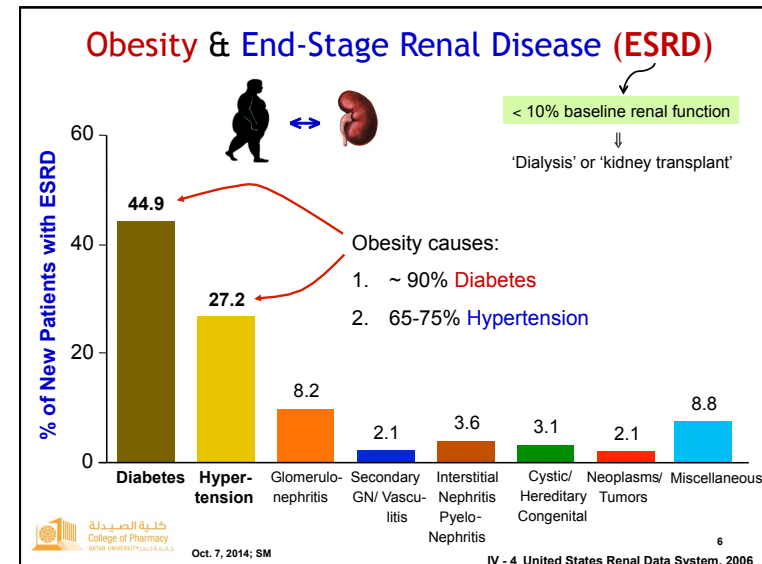
Qatar Moves Toward Unhealthy Choices
By MICHAEL SLACKMAN
DOHA, Qatar — Qataris are suffering health problems that relate to a privileged lifestyle paid for with the nation's oil wealth.

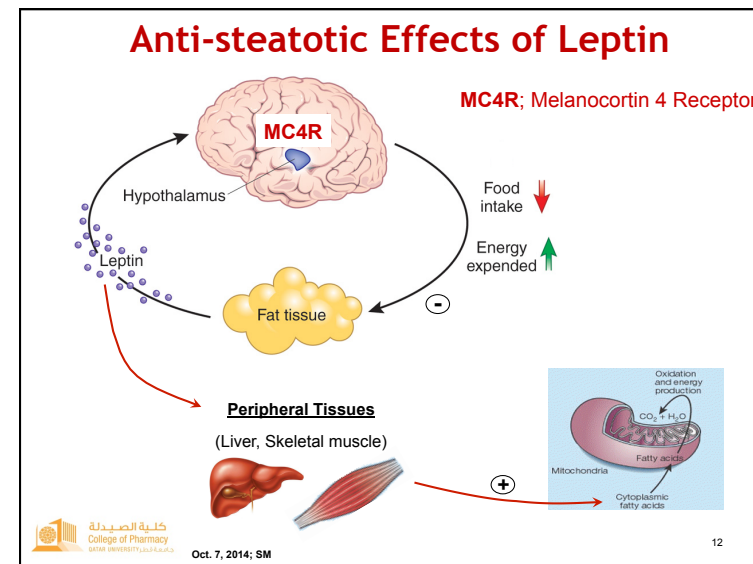
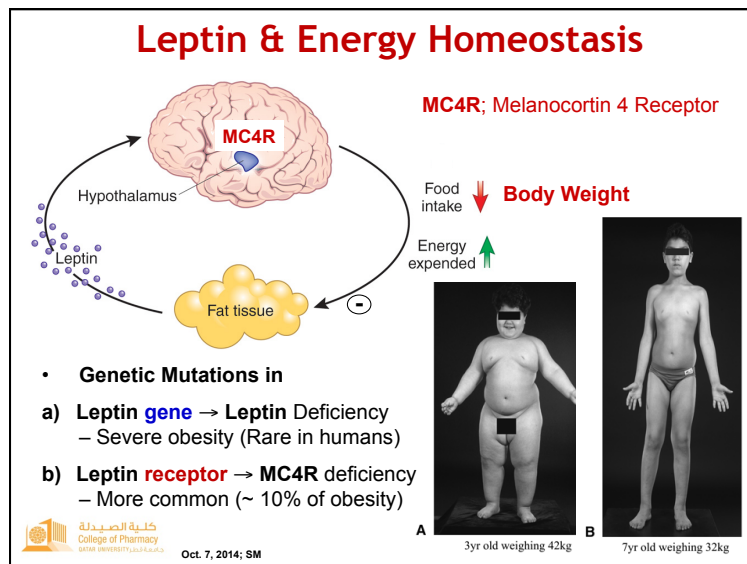
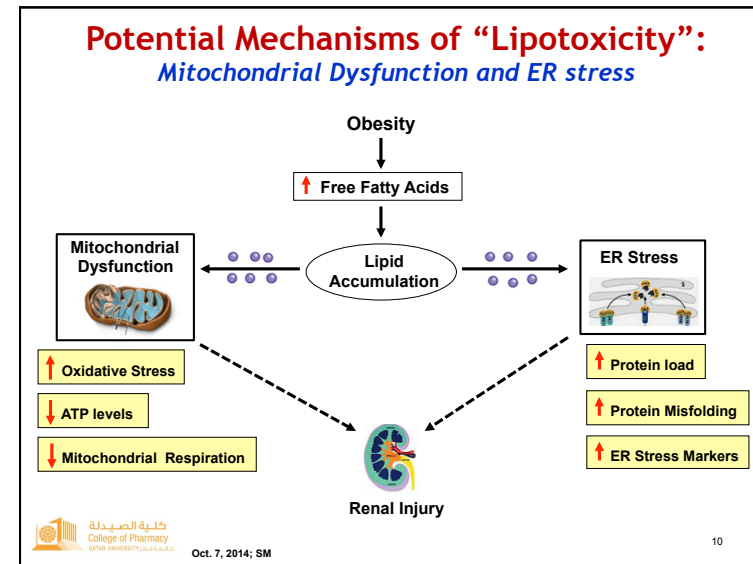
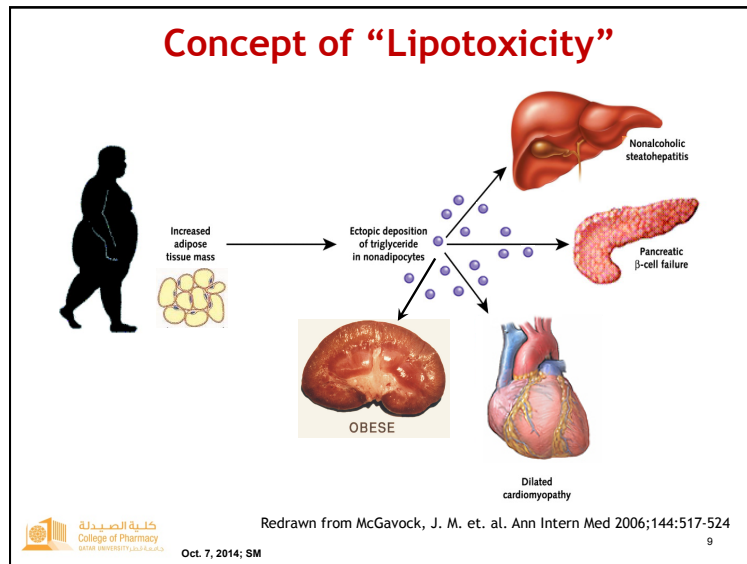
71%	Overweight
32%	Obese
28%	Childhood Obesity
17%	Diabetes (# 4 in the world)

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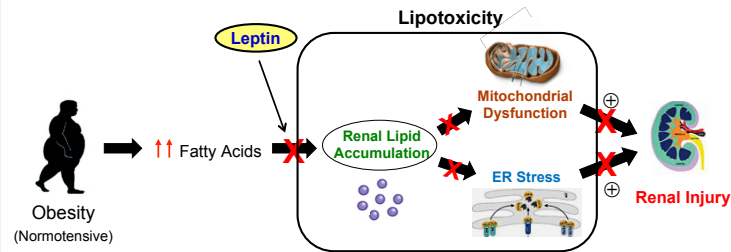
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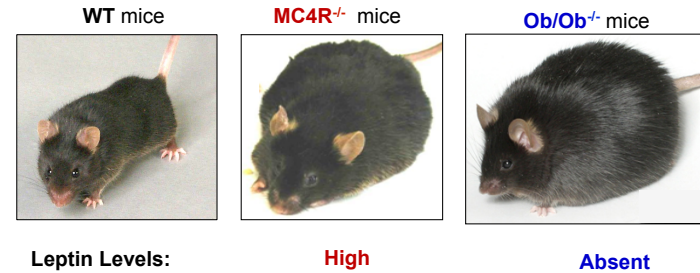


Hypothesis

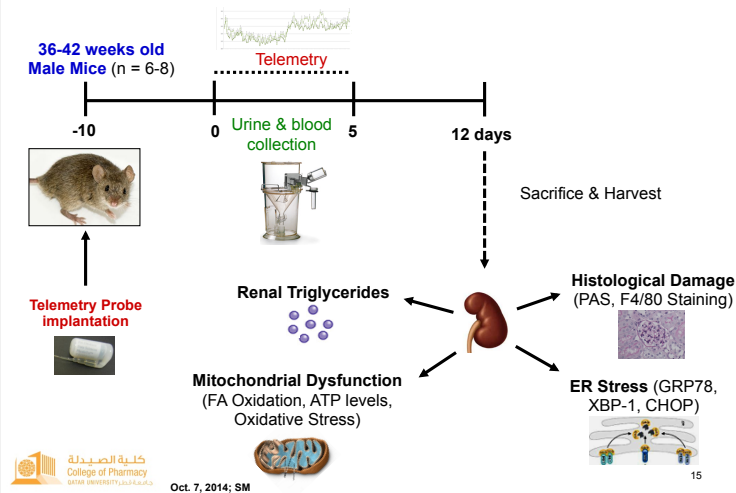
- Obesity-induced dyslipidemia → Lipid accumulation in kidney → Mitochondrial dysfunction & ER stress ⇒ Renal injury.
- Leptin protects against lipid accumulation & renal injury in obesity.



Transgenic Mouse Models of Obesity



Experimental Design & Methods

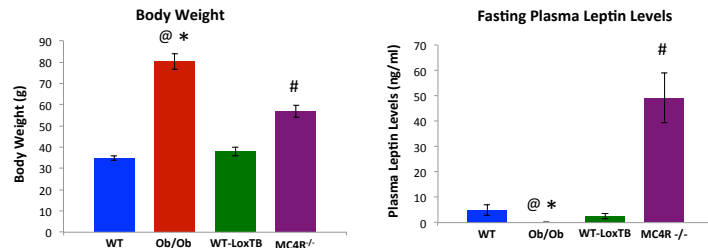


Characterization of Mouse Models



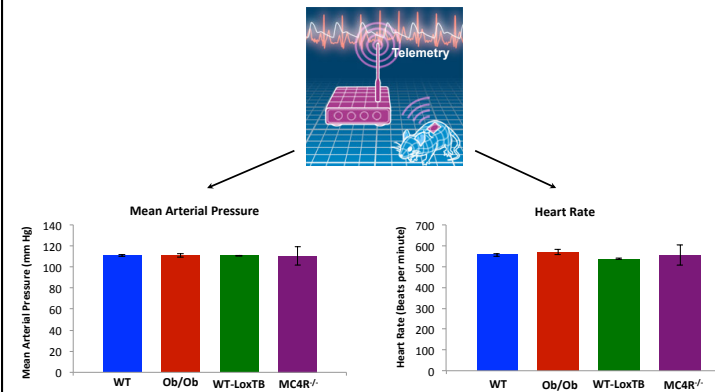
- MC4R^{-/-} & Ob/Ob^{-/-} mice → Obese

- MC4R^{-/-} → Hyperleptinemic mice
- Ob/Ob^{-/-} → Leptin deficient



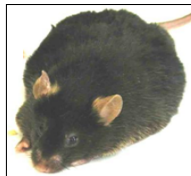
*P < 0.05 as compared to WT; # P < 0.05 as compared to WT-LoxTB; @ P < 0.05 as compared to MC4R^{-/-}

- MC4R^{-/-} & Ob/Ob^{-/-} mice → “Normotensive”

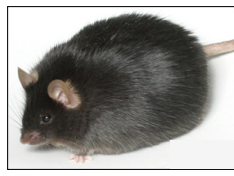


Validation of Mouse Models

MC4R^{-/-} mice



Ob/Ob mice



Vs.

Body Weight: Obese

Leptin Levels: High

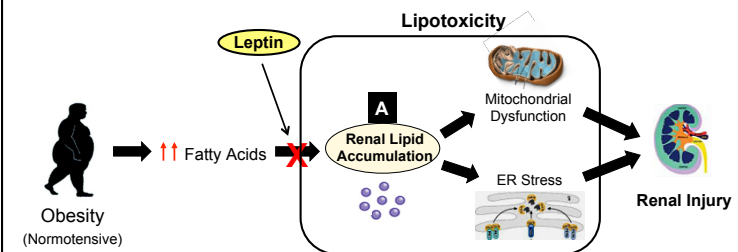
Blood Pressure: Normotensive

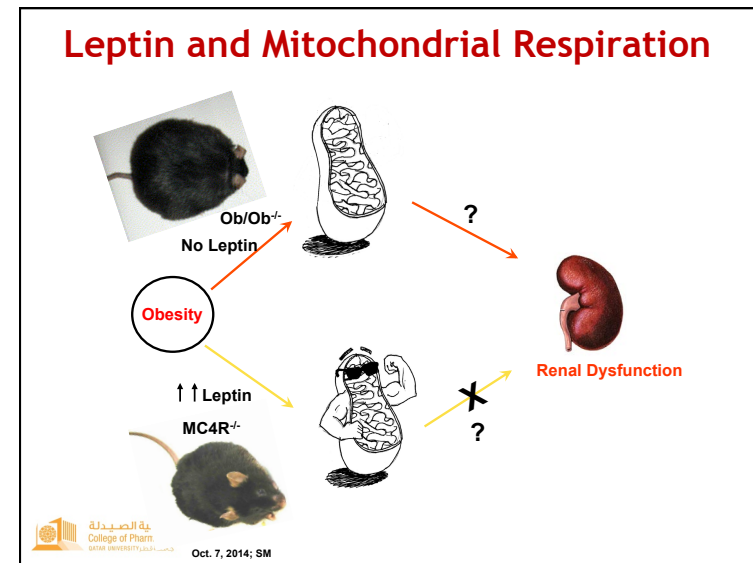
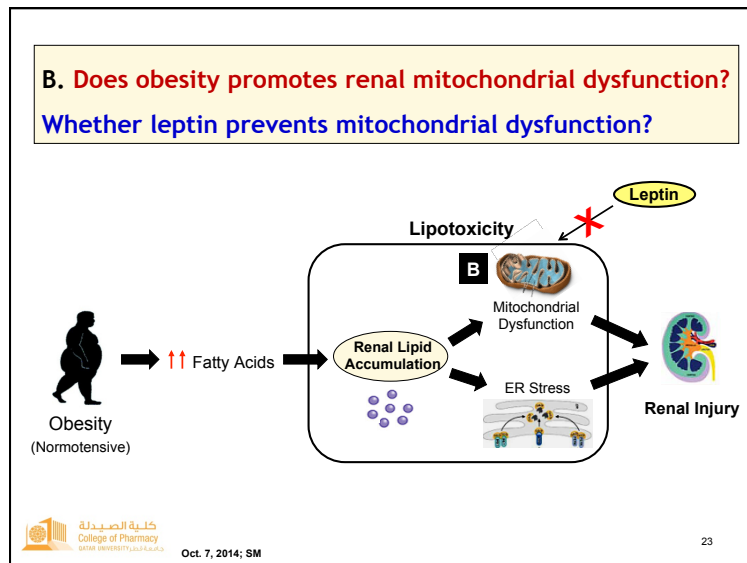
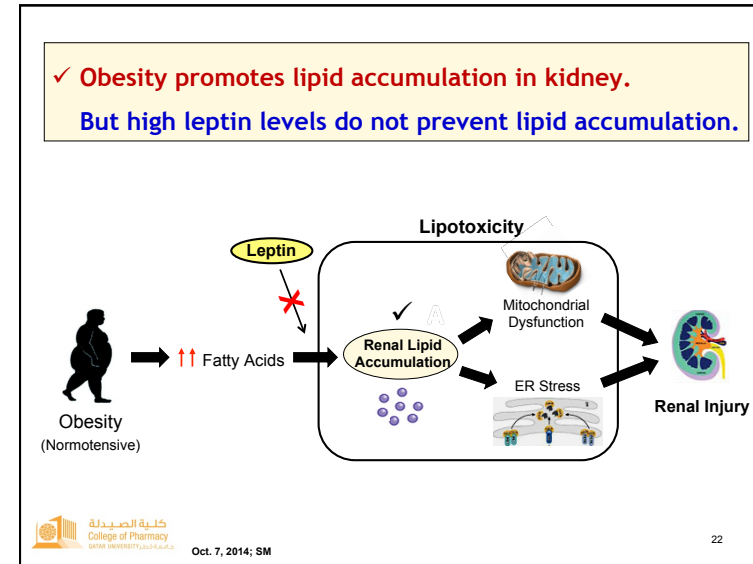
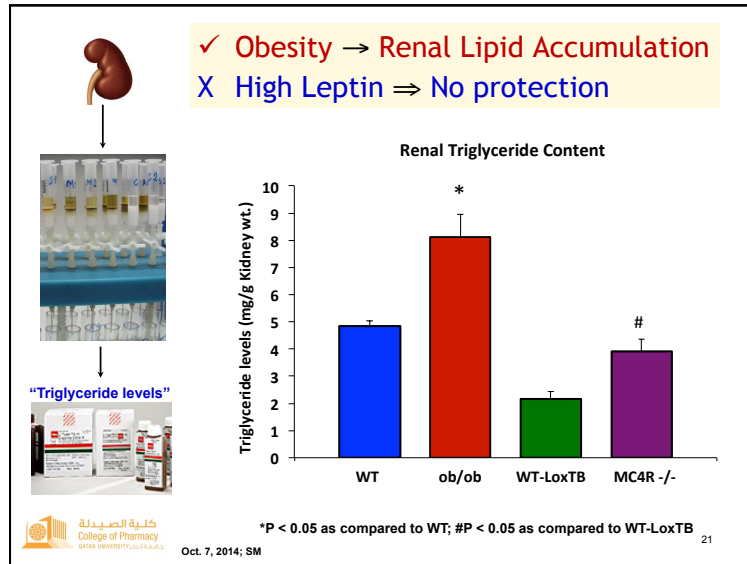
Body Weight: Obese

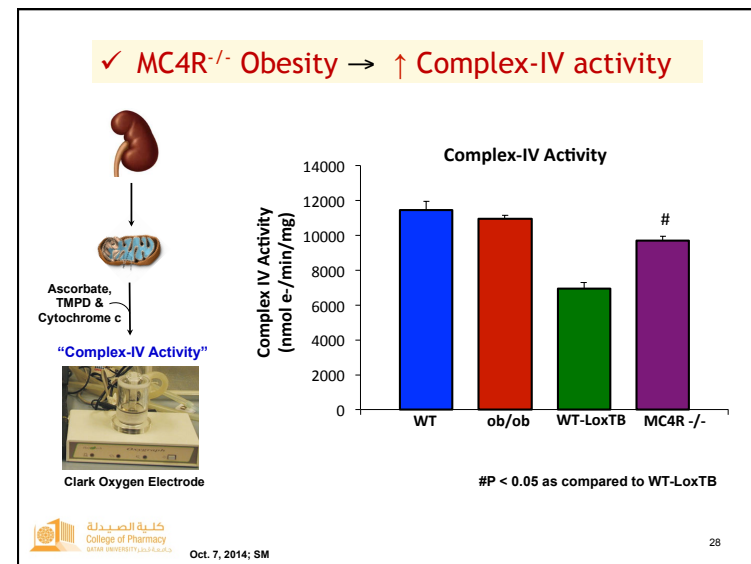
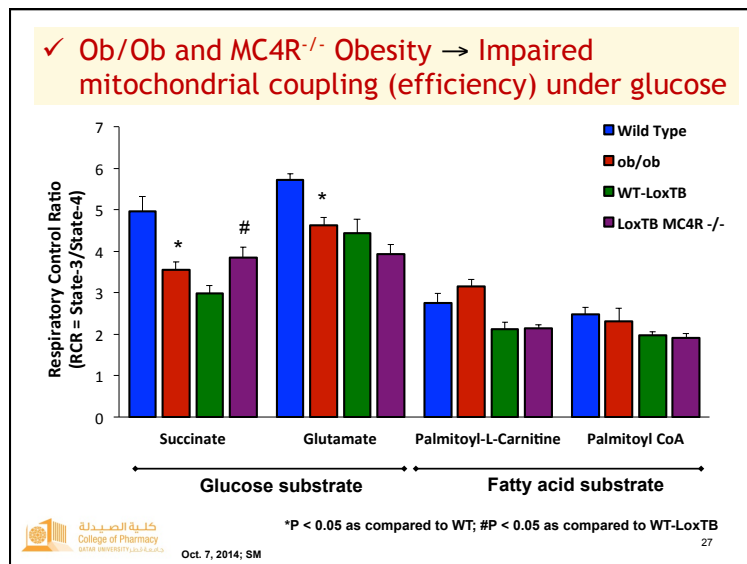
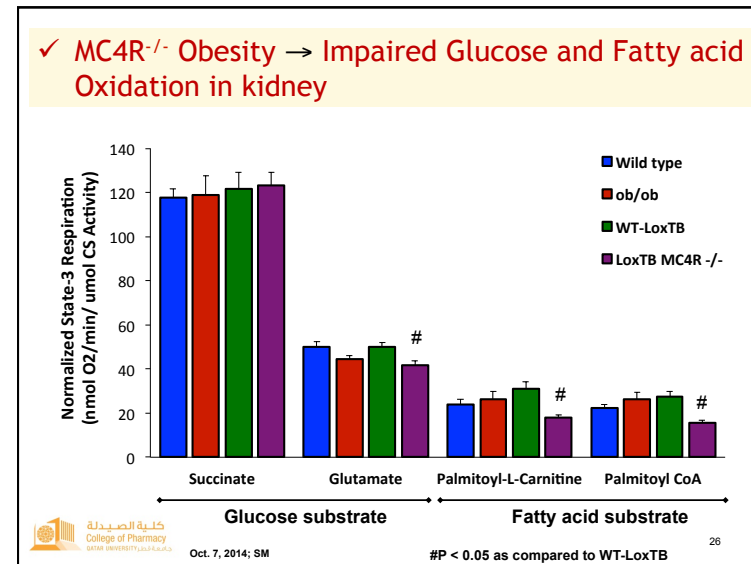
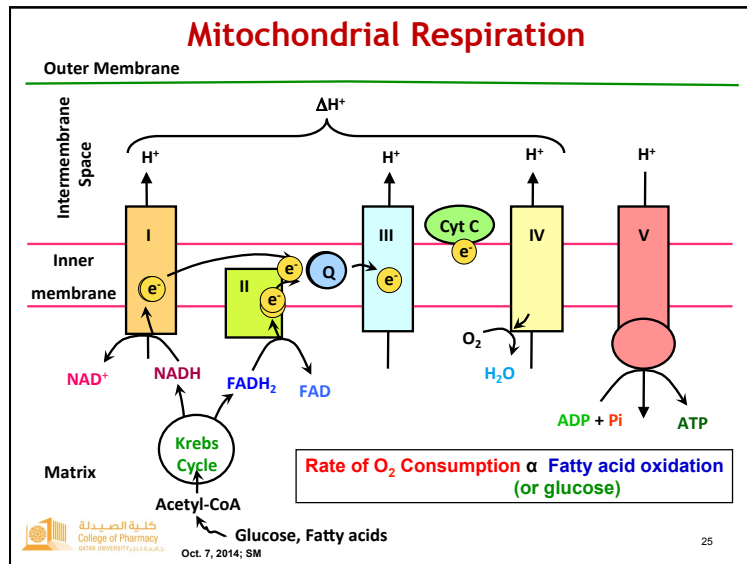
Leptin Levels: Absent

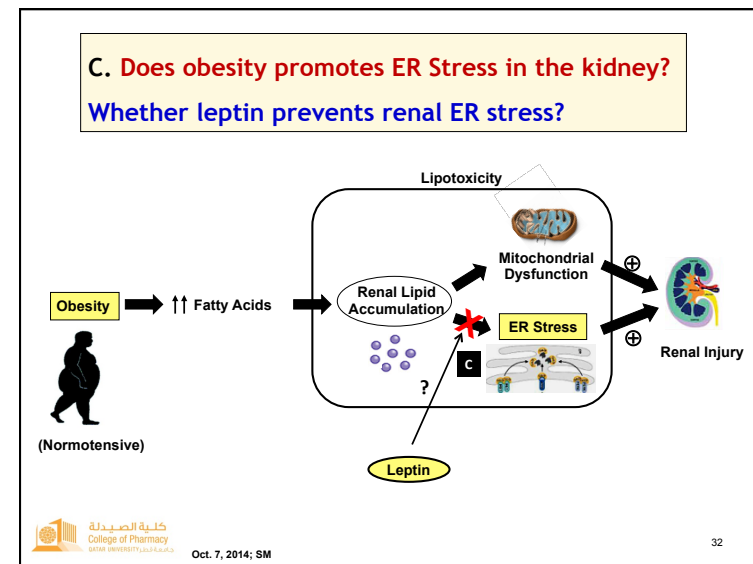
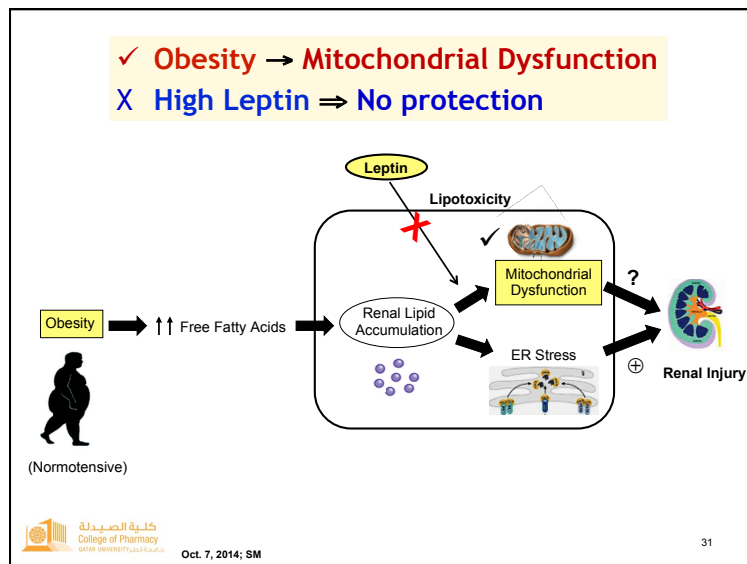
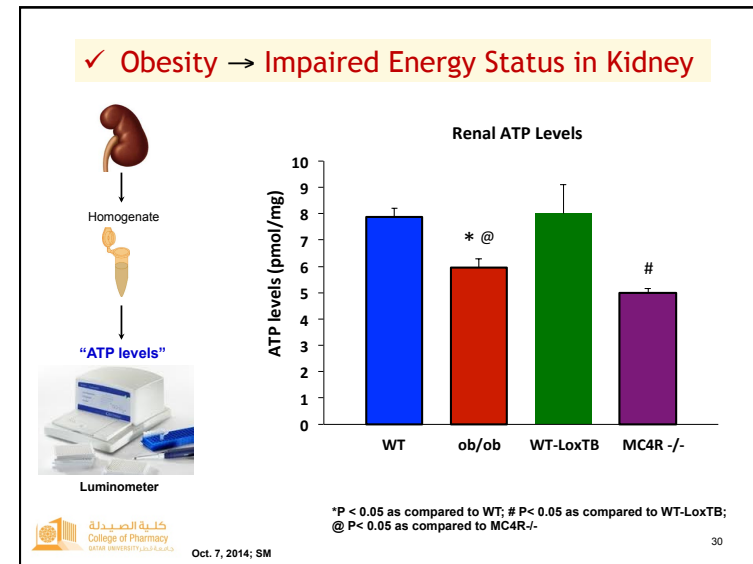
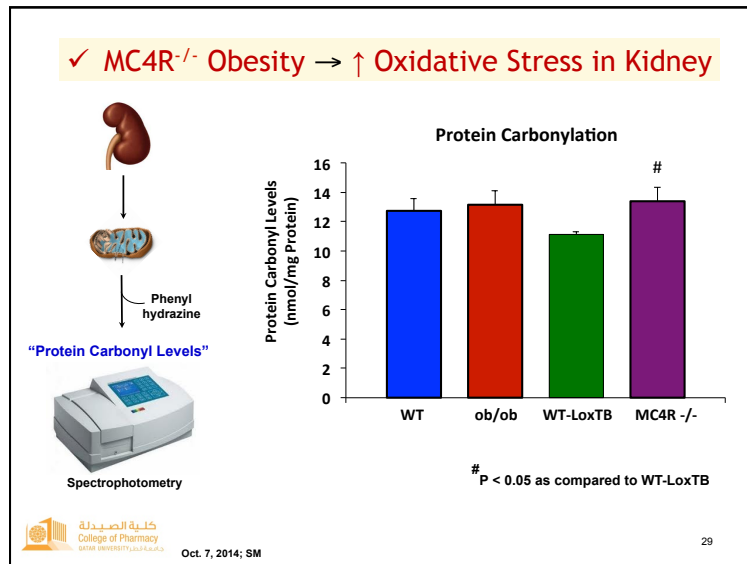
Blood Pressure: Normotensive

A. Does obesity promotes lipid accumulation in kidney?
If so, do high leptin levels prevent lipid accumulation.

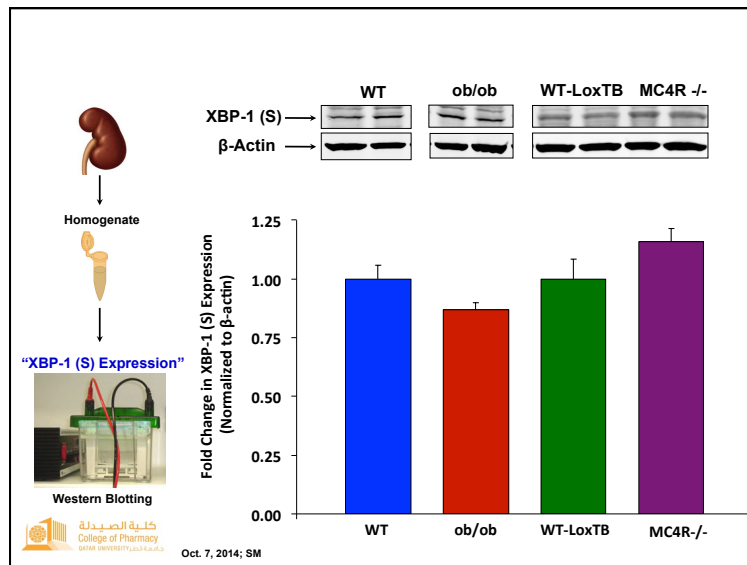
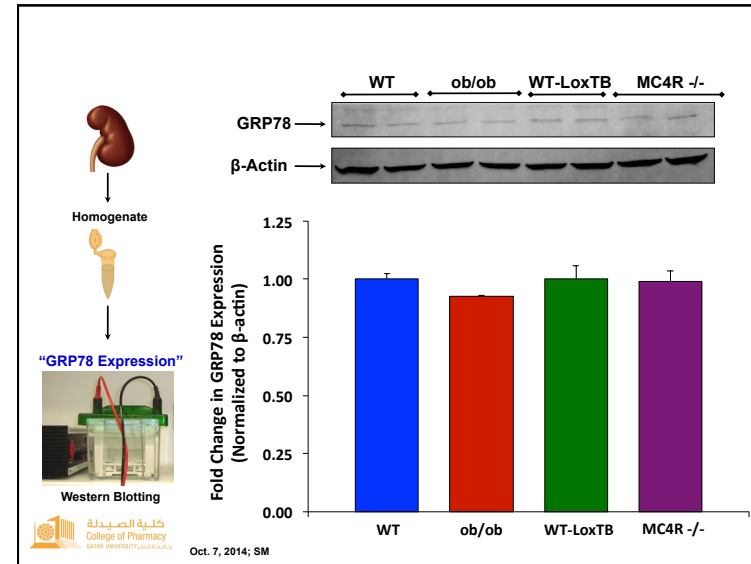
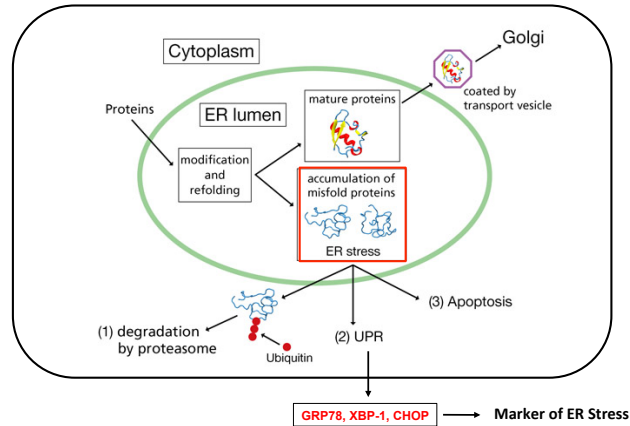




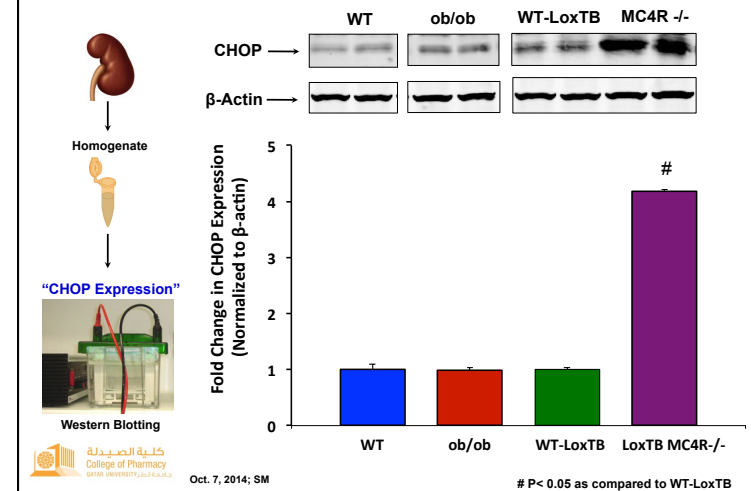




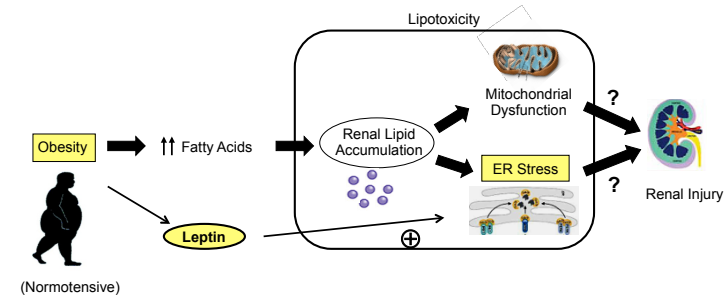
Endoplasmic Reticulum (ER) Stress



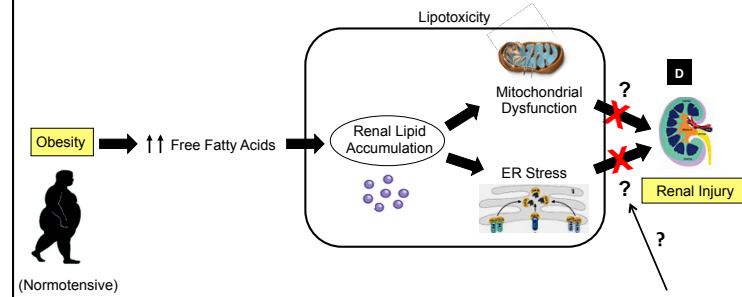
✓ MC4R^{-/-} Obesity → CHOP induction in Kidney



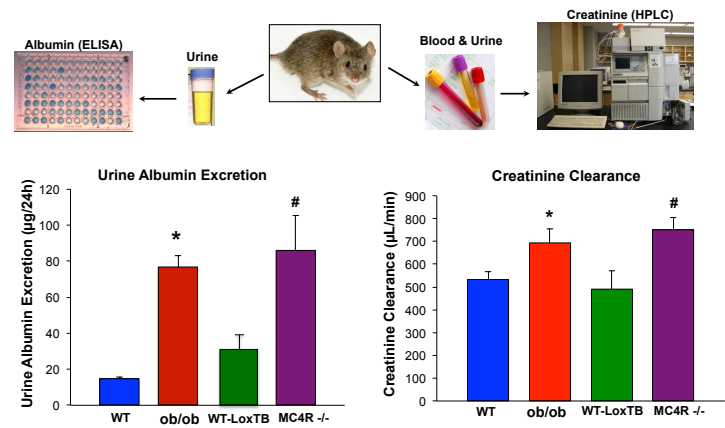
✓ MC4R^{-/-} Obesity → ER Stress activation in Kidney



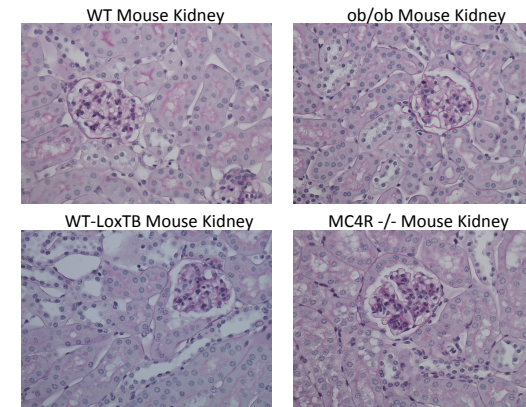
D. Does obesity promotes renal injury?
Whether leptin protects against renal injury?



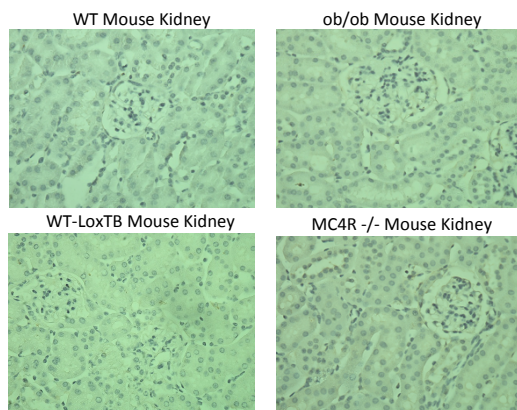
✓ Obesity → Albuminuria & Hyperfiltration



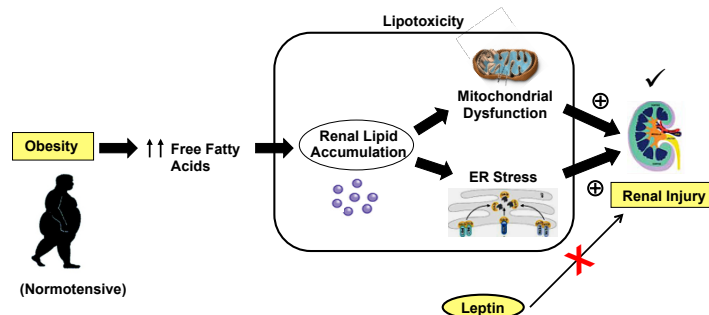
Does obesity cause histopathological changes in kidney? (Periodic acid-Schiff Staining)



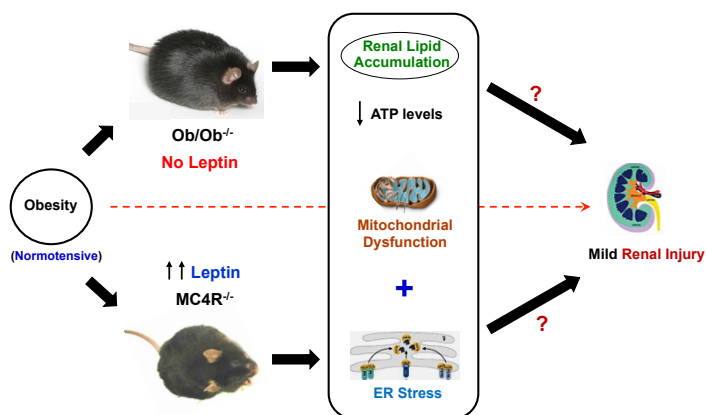
Does obesity promote macrophage infiltration in kidney? (F4/80 Staining)



- ✓ Obesity → Mild Renal Dysfunction
- X High Leptin ⇒ Doesn't alter renal injury

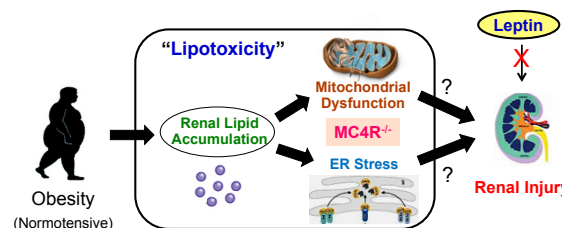


Summary



Conclusions

- ✓ Obesity (in absence of hypertension) causes **lipid accumulation** & **mild renal dysfunction**.
- X High leptin levels (in MC4R deficiency) **do not** protect against the development of renal injury during obesity.
- Obesity due to MC4R deficiency is associated with impairments in **mitochondrial respiration**, **Oxidative stress** & **ER stress** in kidney.



Acknowledgements

Drs. John E. Hall (**Mentor**) & Jonathan P. Hosler



Telemetric Measurements

- Jussara do Carmo, PhD



Lipid Extraction Studies

- Terry Dwyer, PhD



Mitochondrial Studies

- Lakshman Varanasi, PhD



Creatinine Analysis

- Chris Purser



ELISA Measurements

- Ms. Haiyan Zhang



Transgenic Mice Breeding

- Benjamin Pace
- John Rushing



Financial Support:



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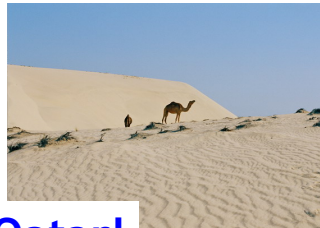
Thank You!



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Our Beautiful Qatar!



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