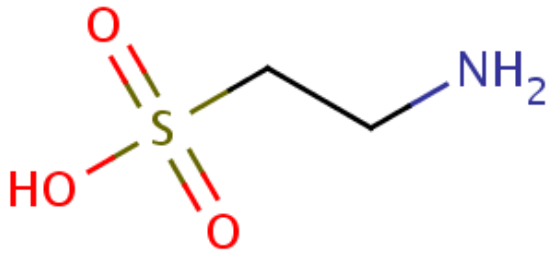

Taurine: A Mysterious Molecule with Intriguing Possibilities

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Wise Traditions Workshop

Weston A. Price Foundation

Monday, Nov. 12, 2012

Download the slides from:

http://people.csail.mit.edu/seneff/

Outline

1. Introduction
2. Some Biochemistry
3. Some Observed Benefits of Taurine
   - The Skin
   - The Heart
   - The Pancreas
   - The Brain
   - The Blood
4. Mitochondrial Diseases
5. Encephalitis
6. Cancer
7. Summary

1. Introduction

Have you thought about taurine?*

* Ann Lauritzen, Wise Traditions Workshop, WAPF 2011, Dallas, TX

What is Taurine?

- Taurine is the most common free amino acid in the body
- Taurine is never incorporated into any protein, and it hardly ever participates in any reaction
- Yet taurine is found in high concen-tration in the heart, brain, and liver
- What is it doing there???

Some Interesting Facts about Taurine*

- Important in many marine species for osmosis (as an osmolyte)
  - Shallow water clams and snails have significantly more than deeper water species

- Cats become blind if raised without taurine
- Brain taurine levels decline with age in mammals; replaced with glutamate
  - Argument used to justify presence in energy drinks

* P.H. Yancey, J Experimental Biology 208, 2819-2830, 2005.

Taurine has Many Known Roles*

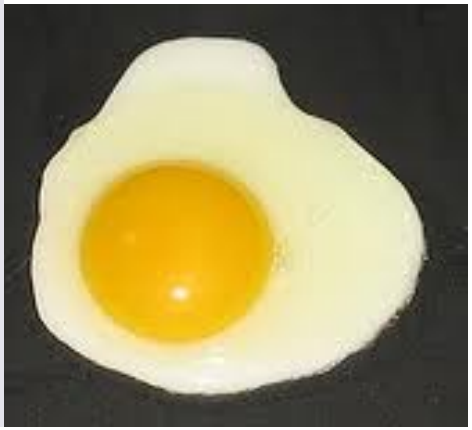
- Maintains osmotic balance in cells
- Bile acid formation (digest fats)
- Roles in mitochondria
  - Helps them maintain their membrane potential
  - Suppresses superoxide synthesis (oxidation damage)
- Clinical observations
  - Maintains healthy skin
  - Protects against diabetes and heart disease
  - Protects against heart arrhythmias
  - Low taurine in blood associated with many cancers

* Wesseling et al., Hypertension. 2009, 53, 909-911

Taurine is found only in animal-based foods

Food Sources of Taurine

Eggs, meat, fish, seafood, dairy



Fish Oil + Taurine*

- Experiment on diabetic/obese mice, three groups
  - Fish oil
  - Fish oil + taurine
  - Soybean oil
- Serum glucose levels significantly lower in mice fed fish oil (with or without taurine)
- Fish oil + taurine group had enhanced GLUT4 distribution in plasma membrane of muscle tissue.
  - GLUT4 is the key catalyst for glucose uptake in muscles

*Mikami et al., J. Food Sci. 2012 Jun, 77(6), H114-20.

A Provocative Hypothesis

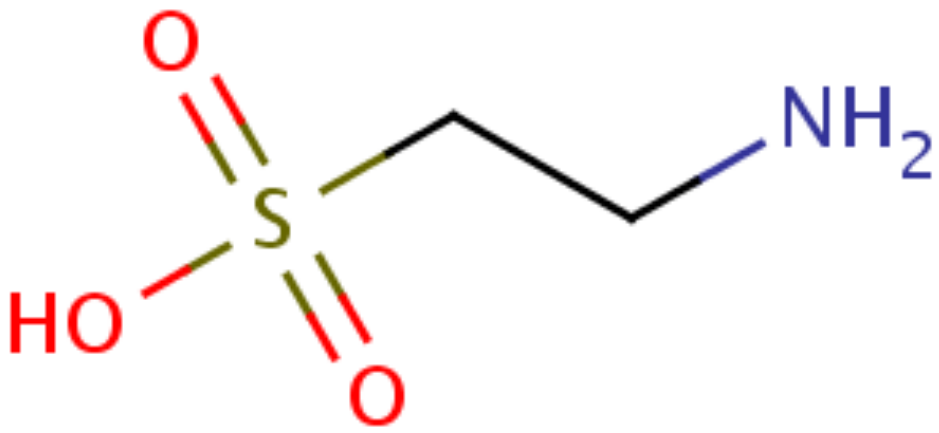
- Taurine is very stable (many claim it is inert)
- Taurine is stored in heart and brain as buffer for sulfate supply during extreme adverse conditions
- Encephalitis leads to sulfate renewal!
  - Hypochlorite (bleach) [released by immune cells to fight infection]
  - Fever [enhances energy of reaction]
  - Seizures [induce electric current and provide free electrons]

The Importance of Sulfate: SO_4^{-2}

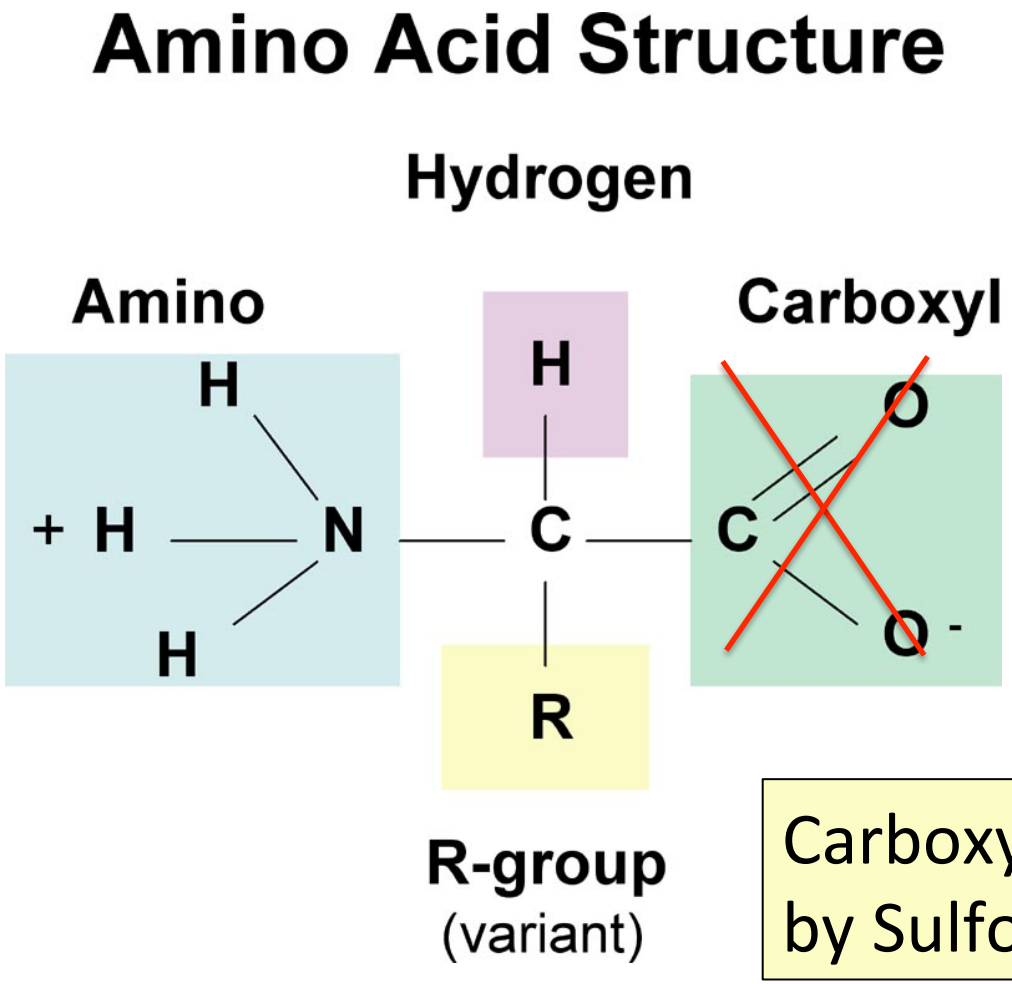
- I have traced most modern diseases to a deficiency in the supply of sulfate (I will talk much more about this tomorrow)
- Two critical points:
  - Sulfation of cholesterol is essential for cholesterol transport – sulfate deficiency implies cholesterol deficiency
  - Sulfation is essential for managing sugar: insufficient sulfate supply leads to diabetes

2. Some Biochemistry

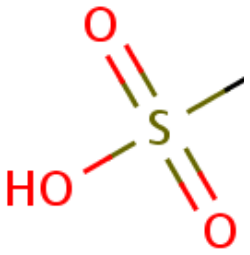
Taurine!



Is Taurine an Amino Acid?

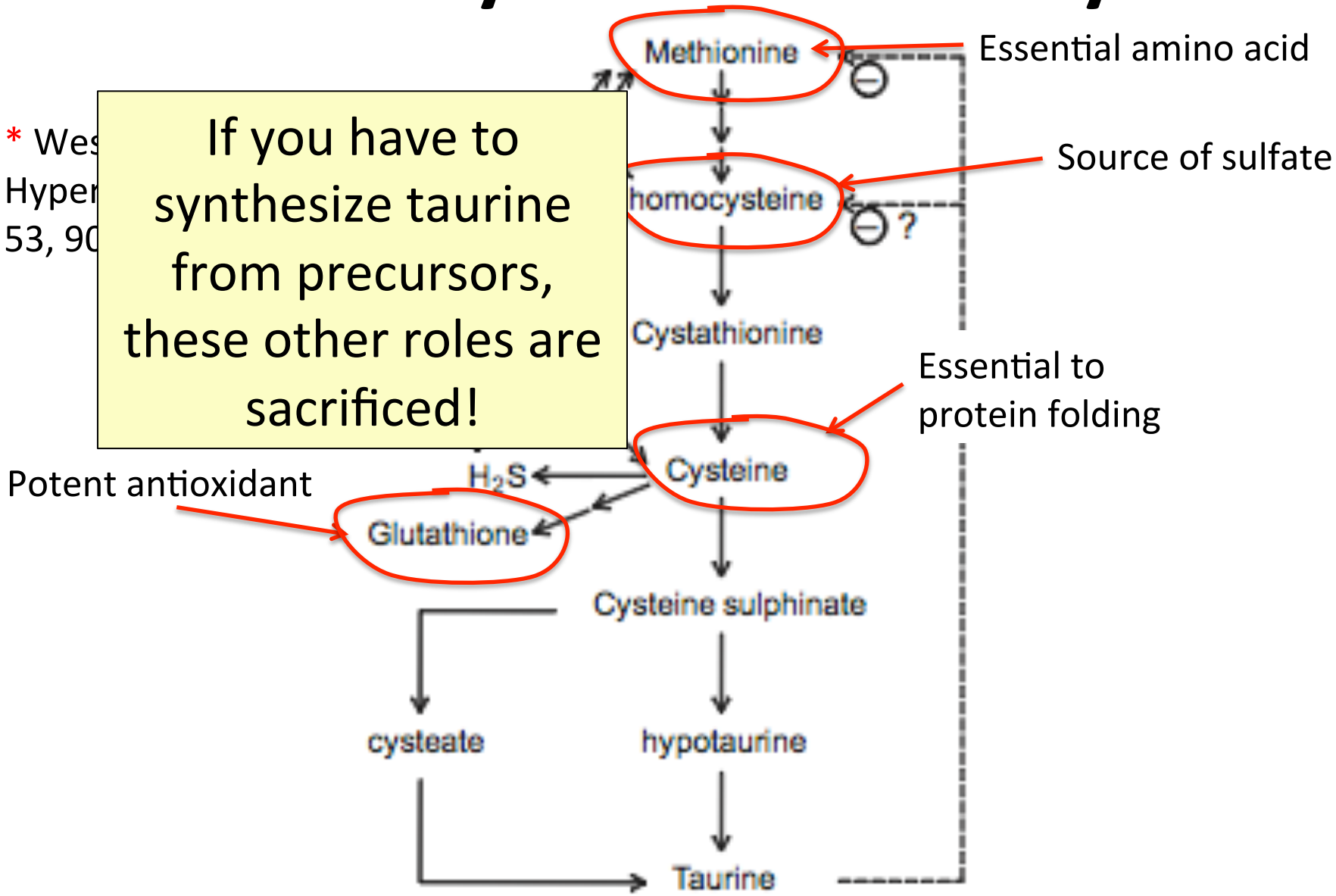


Sulfonyl



Carboxyl is replaced by Sulfonyl

Taurine Synthesis Pathway*



If you have to synthesize taurine from precursors, these other roles are sacrificed!

* Wes
Hyper
53, 90

Big Hints from Early Literature*

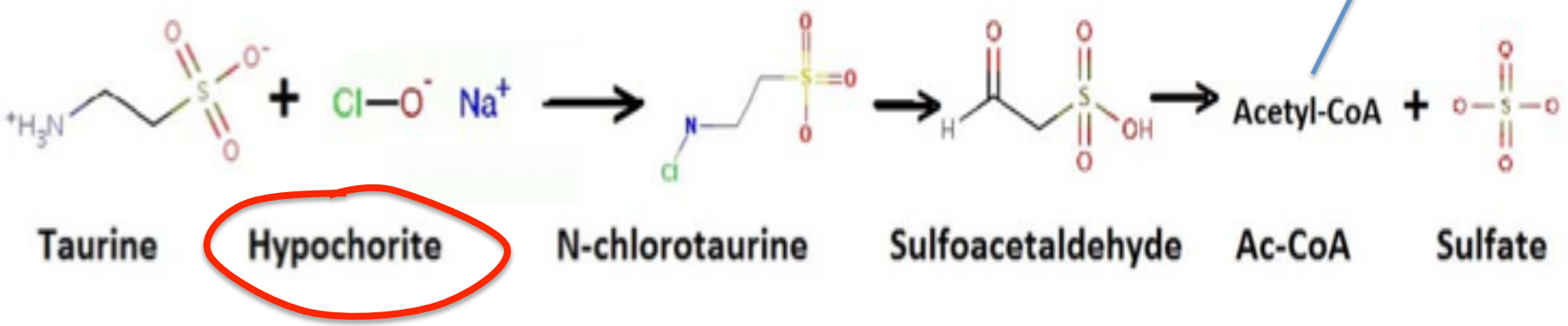
- Article published in 1960
- Fed cholesterol to monkeys
  - Induced atherosclerosis
- If sulfur-containing nutrients are added, atherosclerosis is prevented
- Taurine worked as well as other molecules like cysteine, methionine, and glutathione

* G.V. Mann et al., Am. J. Clin. Nutr. 8, 491-497, 1960.

Breaking down Taurine to get Sulfate

A Hint: hypochlorite is released by neutrophils to fight infection

Citric Acid Cycle



Such a reaction might be possible in the human, but it's not easy

Another Useful Reaction

$$C_2H_7NO_3S + H_2O \rightarrow NH_4 + CH_3COO^- + H_2S + O_2$$

taurine + water → ammonia + acetate + hydrogen sulfide + oxygen

Vasorelaxation
Oxidize to thiosulfate & cholesterol sulfate
Generate ATP

cysteine

N-acetyl cysteine

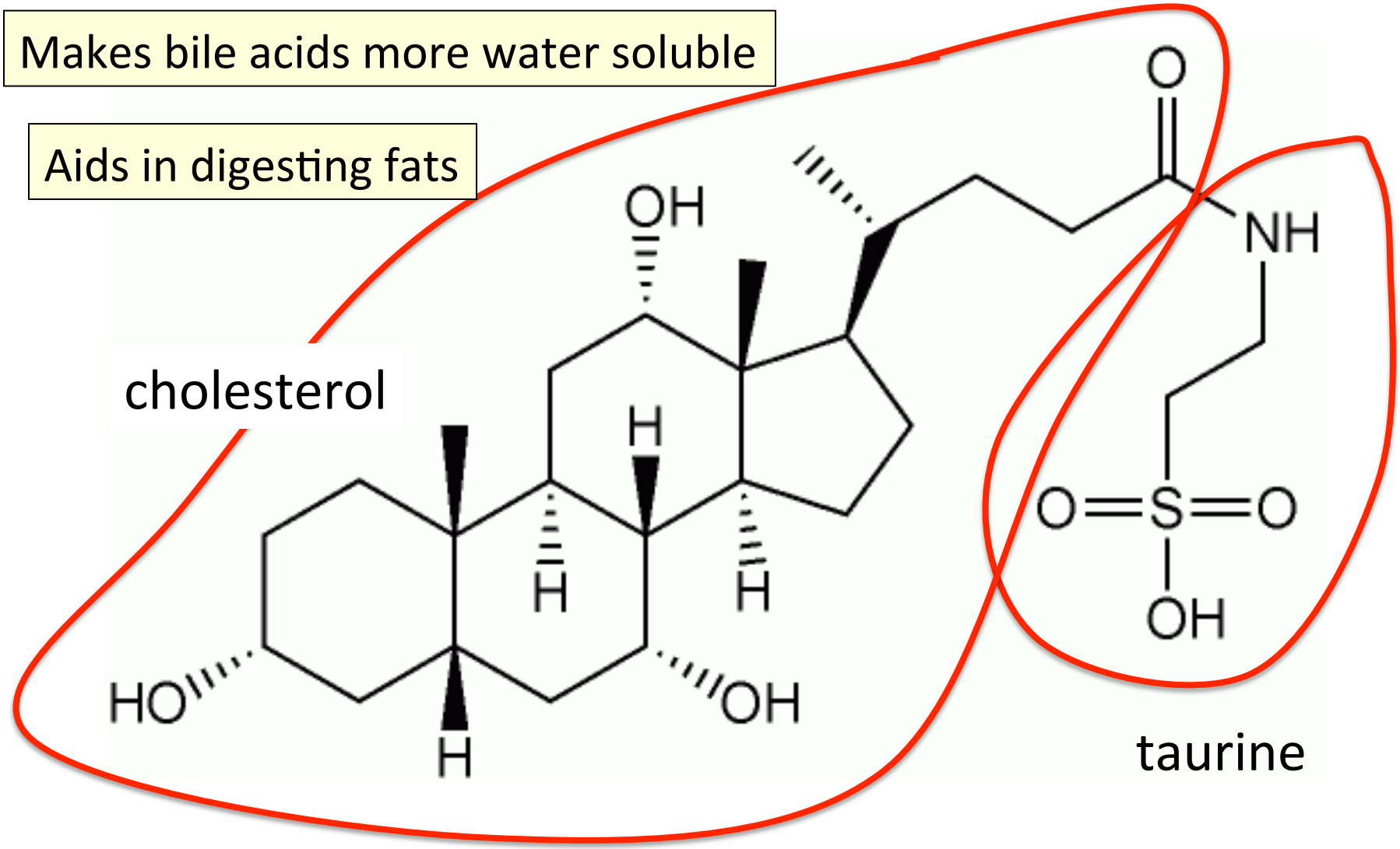
Nutritional supplement for Tylenol overdose and to treat sulfate deficiency in autism

3. Some Observed Benefits of Taurine

Taurocholic Acid: in Bile Acids

Makes bile acids more water soluble

Aids in digesting fats



The Skin

SLS: a Skin Irritant*

- Sodium lauryl sulfate (SLS) is added to shampoos mainly to make them foamy
- Surfactant (= “surface active agent”)
- Used in many commercial formulations because it is inexpensive, offers great foaming, and can be thickened easily with salt
- SLS is a skin irritant -- induces dry, scaly skin due to its surfactant effects

* Lee and Maibach, Contact Dermatitis, 1995, 13, 1-7

Taurine, SLS, and the Skin*

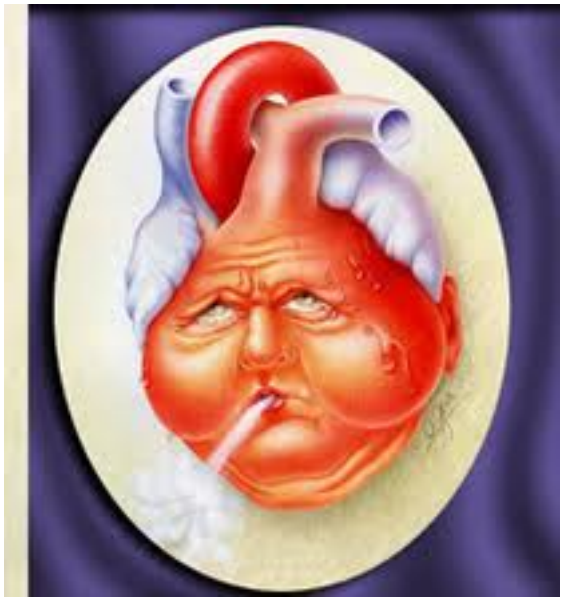
- Taurine accumulates in outermost keratinocyte layer of the skin following UV exposure
  - Stimulates synthesis of ceramides, cholesterol, and fatty acids
- SLS induces an increase in water loss through the skin, inflammation, and proliferation
- Incubation w/ SLS + taurine
  - Decrease in IL-1α and prostaglandin E2 (inflammatory agents)
  - Stabilization of membrane integrity
  - Improvement in keratinocyte viability

* B. Anderheggen et al., J Cosmet Sci. 2006 Jan-Feb;57(1), 1-10

The Heart

Sudden Cardiac Death*

- Sudden cardiac death is the leading cause of death in industrially developed countries
  - Accounts for 300,000 - 500,000 deaths per year in U.S.
  - Due to ventricular fibrillation: life-threatening heart arrhythmia
  - Manifested by low heart rate variability
- Triggered by adrenalin in response to stress
- Intracellular potassium and calcium dysregulation
  → insufficient membrane cholesterol?



* G.E. Billman, Am J Physiol Heart Circ Physiol 297:H1171-H1193, 2009

Cardioprotective Effects of Taurine*

- Taurine is normally found in highest concentration in the heart
- Antiarrhythmic effects observed experimentally in cats, dogs and guinea pigs.
- Addition of taurine
  - Prevents loss of potassium by myocardium
  - Reverses adverse effects of adrenalin and digoxin
  - Eliminates the pathological ECG changes caused by strophanthin in isolated guinea pig hearts.
- My hypothesis: Is taurine a source of sulfate for cholesterol sulfate synthesis?

* Georgy Eby, Taurine Role in Cardiology and Cardiac Arrhythmias http://george-eby-research.com/html/taurine.html

High Dietary Taurine Reduces Apoptosis (Cell Death) and Atherosclerosis*

- High dietary fish associated with decreased cardiovascular death rate
  - Taurine is highly concentrated in fish
- High dietary taurine reduces risk of coronary heart disease and insulin resistance
- Taurine deficiency can also lead to obesity, a risk factor for heart disease

* A. Zulli et al., Hypertension, 53, 1017-1022, 2009

High Dietary Taurine Reduces Apoptosis and Atherosclerosis: Experiment*

- Rabbits fed high cholesterol diet
- Examined effect of taurine supplements on left main coronary artery
- Results
  - Reduced serum homocysteine levels
  - Endoplasmic Reticulum stress reduced in endothelial cells which protected them from apoptosis
  - Reduced atherosclerosis in artery wall
  - Reduced serum HDL

* A. Zulli et al., Hypertension, 53, 1017-1022, 2009

High Dietary Taurine Reduces Apoptosis and Atherosclerosis*: My Interpretation

- Taurine reacted with hypochlorite which allowed it to be metabolized to sulfate
  - Protected LDL from hypochlorite toxicity
  - Reduced uptake of LDL into plaque
- Platelets utilized newly available sulfate to produce cholesterol sulfate from cholesterol obtained from HDL
  - Depleted HDL
- Homocysteine could be diverted to cysteine and glutathione instead of being held in reserve as an alternative source of sulfate.
  - Serum homocysteine levels dropped

* A. Zulli et al., Hypertension, 53, 1017-1022, 2009

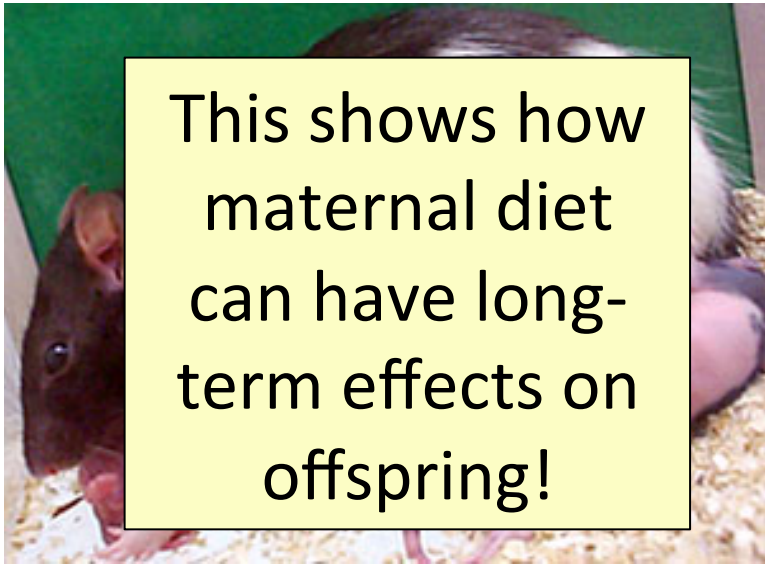
Recapitulation

- Sudden cardiac death is leading cause of death in Western nations
- Taurine is highly concentrated in the heart
  - Protects from sudden cardiac death
- Low dietary taurine associated with increase in insulin resistance, obesity, and heart disease
- Taurine protects rabbits from cholesterol-diet-induced cardiovascular disease
- I hypothesize that these effects are due to taurine's ability to promote cholesterol sulfate synthesis

The Pancreas

Taurine and Pancreatic Islet Cells*

- Mother rats fed low-protein diet during gestation and lactation
- Offspring had vulnerable islets in their pancreas (leading to diabetes)
  - Excess production of toxic nitric oxide
  - Increased apoptosis (cell death)
- Supplement with taurine in protein-deficient mothers alleviates these effects



* K Goosse et al., Journal of Endocrinology (2009) 200, 177–187

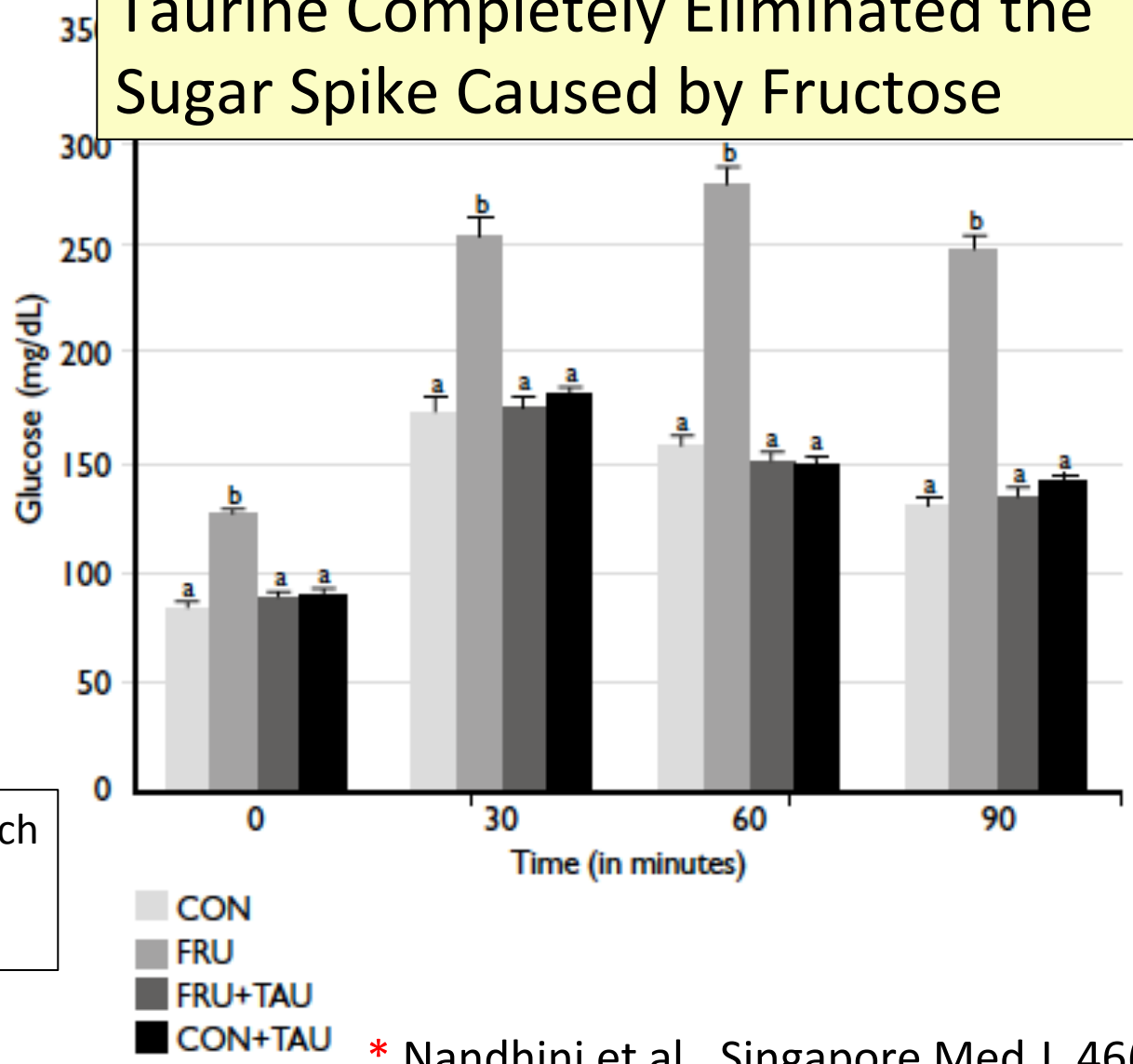
Taurine, Fructose, and Diabetes*

- Fructose induces diabetes
  - Rats fed cornstarch compared with rats fed fructose (60% of dietary calories)
  - Fructose induced insulin resistance (well-known response)
- Supplement with 2% taurine solution *ad libitum* protected rats from insulin resistance

* Nandhini et al., Singapore Med J, 46(2), 82-87, 2005

Taurine, Fructose, and Diabetes*

Taurine Completely Eliminated the Sugar Spike Caused by Fructose



CON= cornstarch
FRU = fructose
TAU = taurine

* Nandhini et al., Singapore Med J, 46(2), 82-87, 2005

The Brain

Taurine in Development*

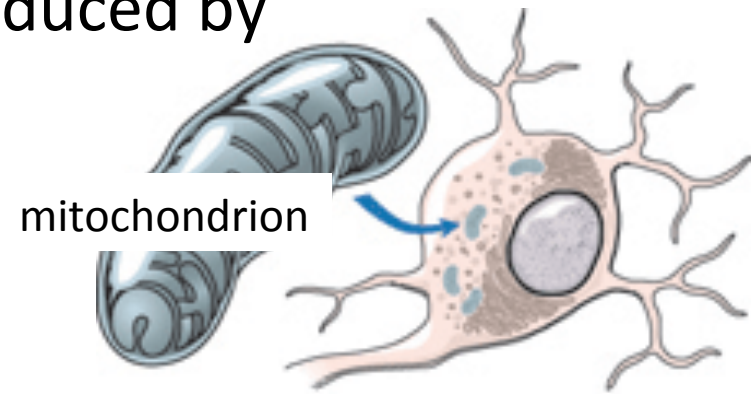
- Highest concentration occurs in developing brain
- Taurine concentrations fall during development
  - Converted to sulfate?

- Neonates have 3x levels of adults
- True for humans, monkeys, mice, rabbits, rats, and insects

* R.J. Huxtable, Physiological Reviews 72(1), 101-163, Jan 1992

Taurine is Neuroprotective*

- Taurine prevents excitotoxicity induced by glutamate in neurons
- Mitochondrial electron gradient is calcium regulated
- Activation by glutamate →
  - Extracellular calcium influx
  - Mobilization from internal stores (mitochondria)
  - Associated with decrease in mitochondrial energy metabolism
- Pretreatment with taurine normalized calcium homeostasis and prevented mitochondrial impairment



* A. El Idrissi and E. Trenkner, J. Neuroscience, 19(21), 9459-9468, 1999.

The Blood

Taurine Protects Platelets from Blood Clots*

- Taurine is especially concentrated in nervous system and platelets
- Cats are often afflicted with a taurine-deficiency cardiomyopathy along with arterial thromboembolism
  - Blood clot blocks flow to heart

- Taurine suppresses release of thromboxane by platelets which triggers blood clot formation
  - Study confirmed this is true for humans as well

* K.C. Hayes et al., Am. J. Clin. Nutr. 1989; 49:1211-6.

Sub-optimal taurine status may promote platelet hyperaggregability in vegetarians*

"Plasma taurine levels are lower, and urinary taurine excretion is substantially lower, in vegetarians than in omnivores. Platelets are rich in taurine, which functions physiologically to dampen the calcium influx evoked by aggregating agonists – thereby down-regulating platelet aggregation."

* M.F. McCarty, Medical Hypotheses, 63(3), 426-433, 2004.

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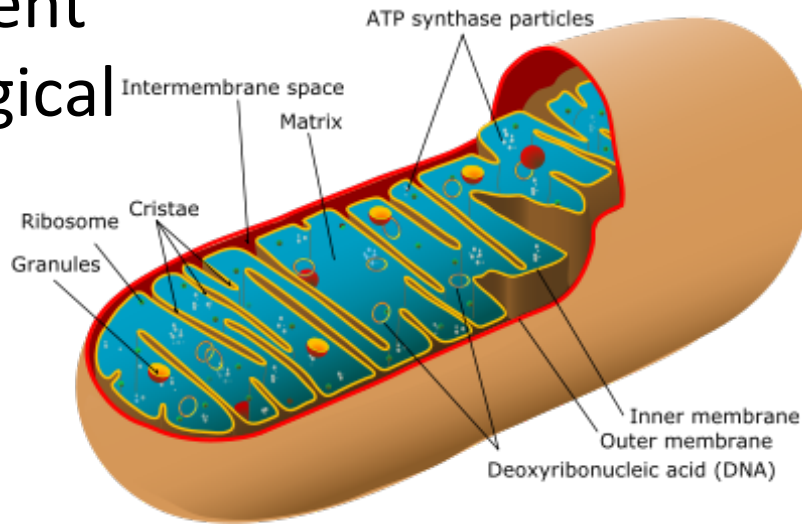
4. Mitochondrial Diseases

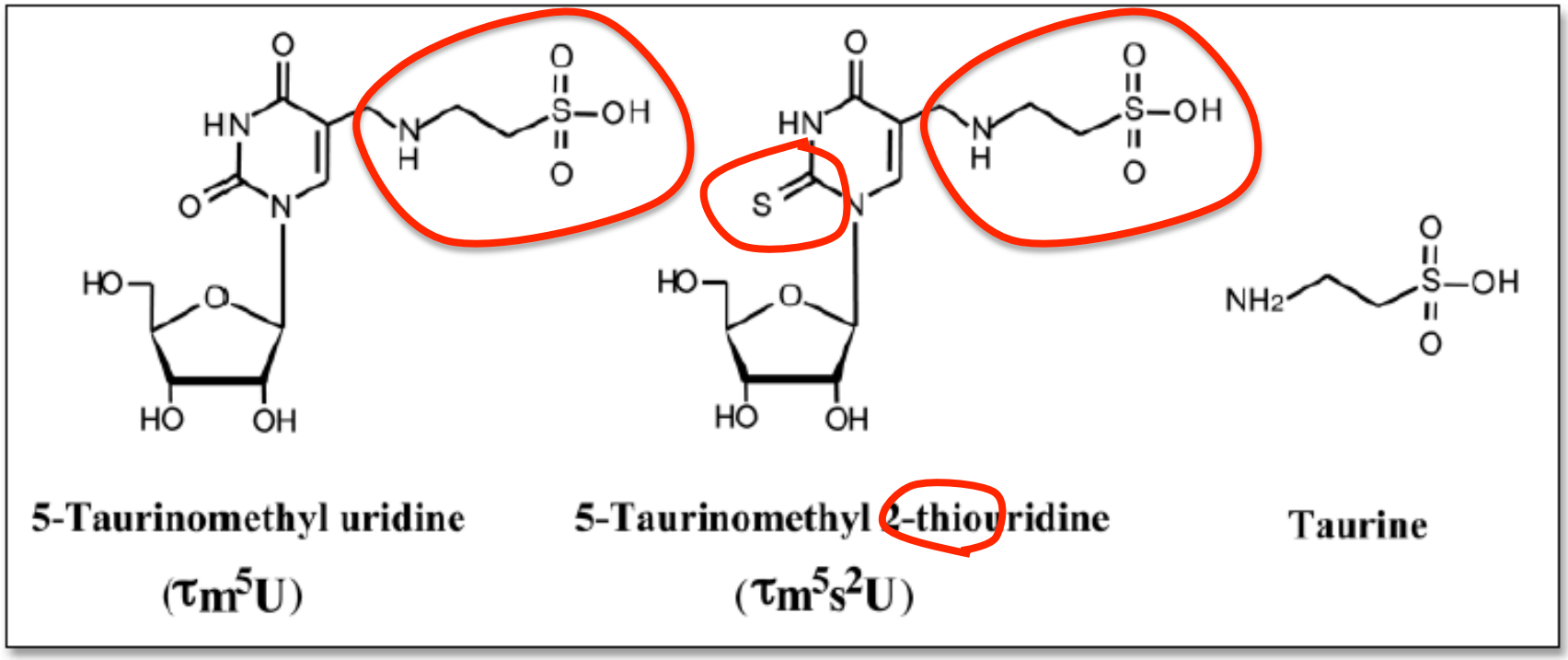
Mitochondrial Diseases*

- Mitochondria convert food into ATP for energy
- Mitochondrial stage I impairment associated with many neurological and muscular disorders
- Mitochondrial Diseases
  - Often caused by mutations in mitochondrial genes
  - Symptoms include poor growth, loss of muscle coordination, muscle weakness, visual problems, hearing problems, learning disabilities, heart disease, liver disease, kidney disease, gastrointestinal disorders, respiratory disorders, neurological problems, autonomic dysfunction, and dementia.



* From Wikipedia

"Human mitochondrial diseases caused by lack of taurine modification in mitochondrial tRNAs"*



* Kirino and Suzuki, RNA Biology 2(2), 41-44, June 2005.

Defects from Genetic Mitochondrial Disorders*

- Mutations prevent taurine attachments to tRNAs

  (1) Impair UUG gene translation (taurine)

  - NADH-Coenzyme Q reductase impaired
  - Mitochondrial Complex I disrupted

  (2) Impair AAA and AAG (taurine + S)

  - Defect in whole mitochondrial translation
  - Question: Does the additional S play a highly significant role in enabling gene translation??

Generic taurine deficiency might lead to similar mitochondrial impairments

* Kirino and Suzuki, RNA Biology 2(2), 41-44, June 2005.

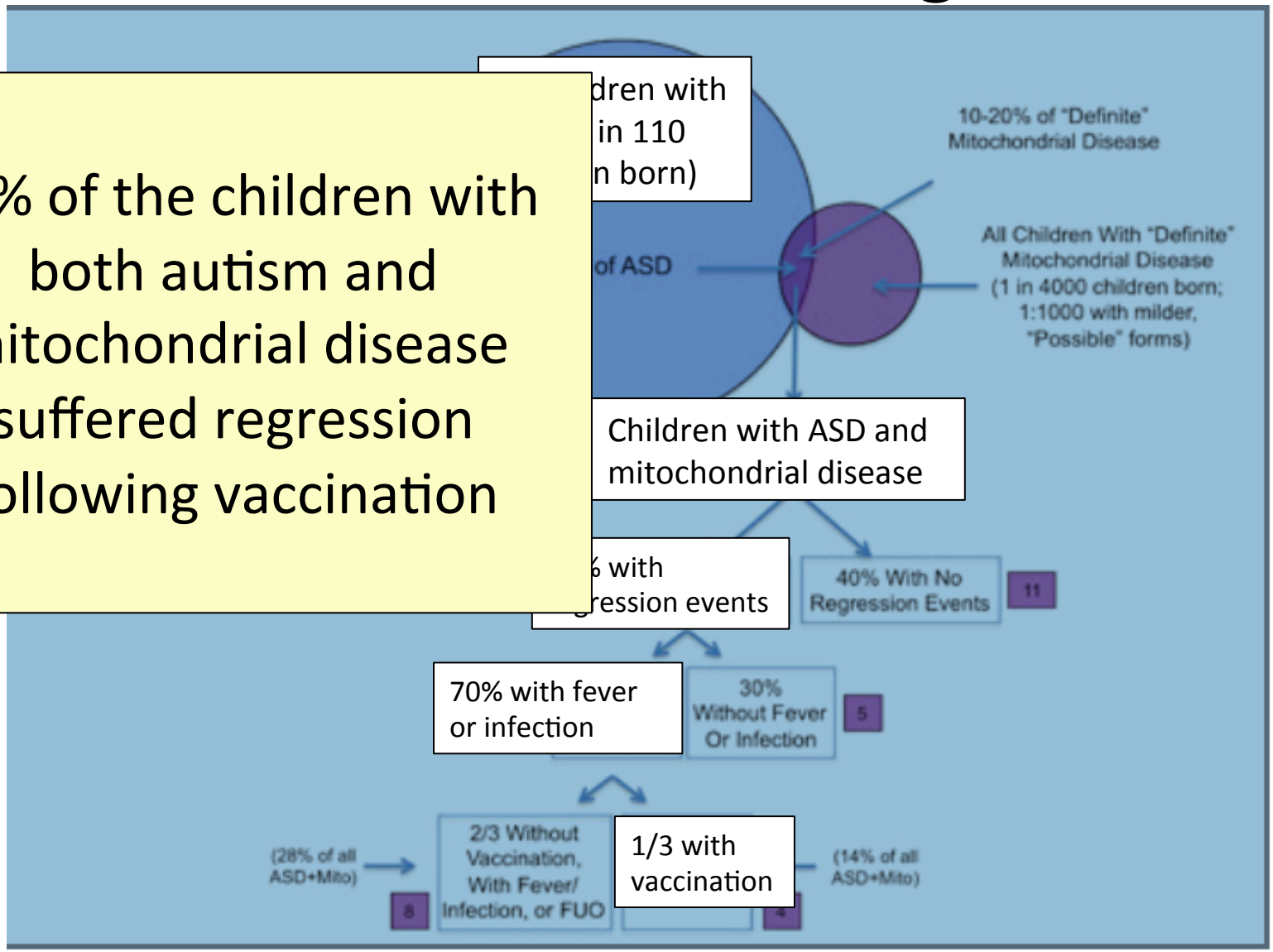
Fever, Autism, and Mitochondria*

- Found a plausible link between mitochondria, fever, and taurine
- Fever impacts autism
  - Some regress after fever, some improve
  - Subset with mitochondrial dysfunction regress
- Aggressive treatment may worsen outcome
  - Acetaminophen (Tylenol) depletes sulfate
  - *Fever suppression prevents sulfate regeneration from taurine?*

* Shoffner et al., J Child Neurol. 2009 Sep 22

"Fever Plus Mitochondrial Disease Could Be Risk Factors for Autistic Regression"*

14% of the children with both autism and mitochondrial disease suffered regression following vaccination



* http://blog.autismspeaks.org/2010/03/11/fever-regression/

5. Encephalitis

A Provocative Proposal: Encephalitis is Protective!

Taurine is kept in reserve as a buffer for sulfate supply

Encephalitis enables conversion of taurine to sulfate

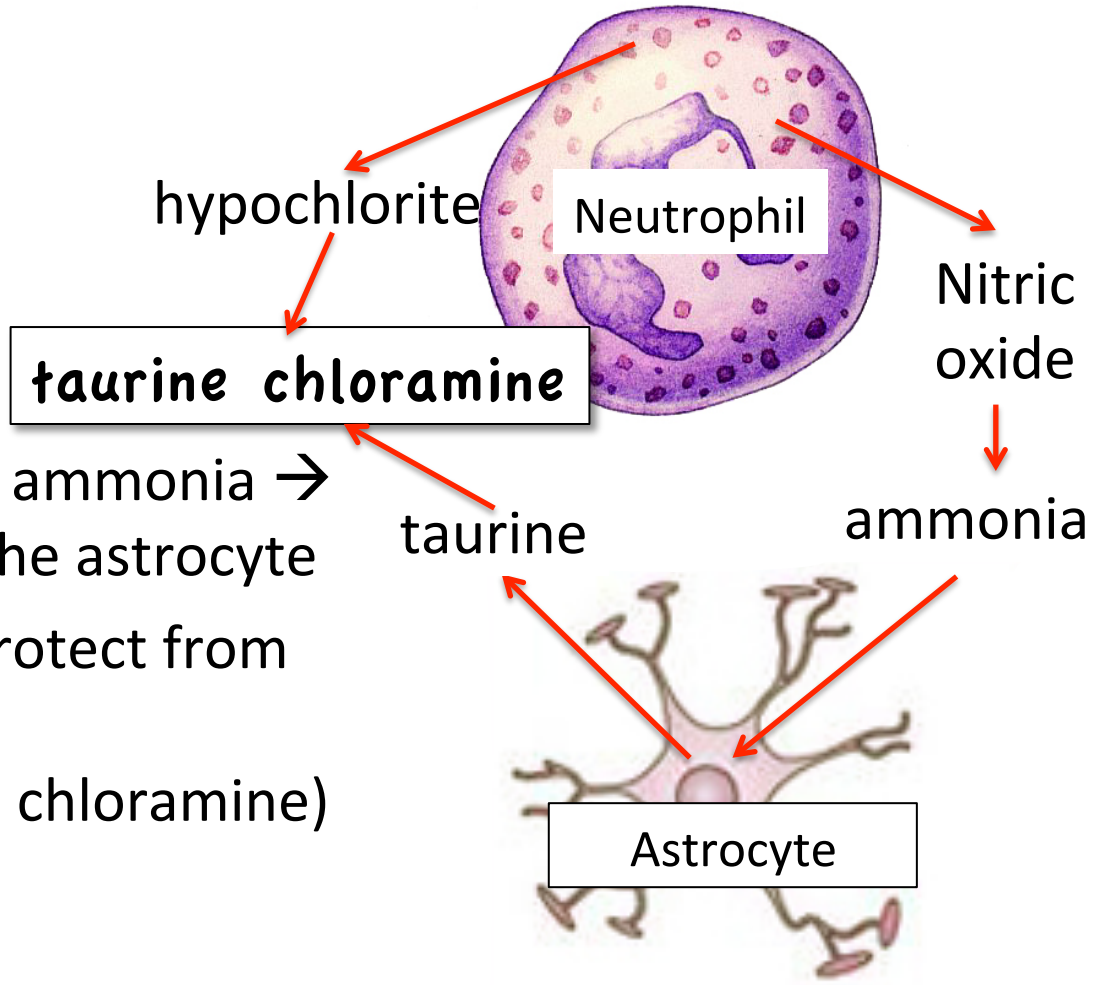
This is an important positive outcome of encephalitis

What is Encephalitis?

- Encephalitis is an acute inflammation of the brain
  - Usually caused by infection, most often by a virus, but sometimes by bacteria, a fungus, or a parasite.
- Symptoms
  - Headache
  - Fever
  - Confusion
  - Sleepiness
  - Fatigue
  - Seizures and convulsions
  - Tremors
  - Memory problems

Fighting the Infection: Nitric Oxide and Hypochlorite

- Neutrophils follow microbes into brain
- Attack microbes with antimicrobial agents:
  - Nitric oxide
  - Hypochlorite
- Excess nitric oxide → ammonia → complex reaction in the astrocyte
- Frees up taurine to protect from hypochlorite damage (by becoming taurine chloramine)



Taurine Chloramine is Energized!

- Although it is believed that taurine is inert, taurine chloramine can be metabolized to sulfate!! (at least by some species)

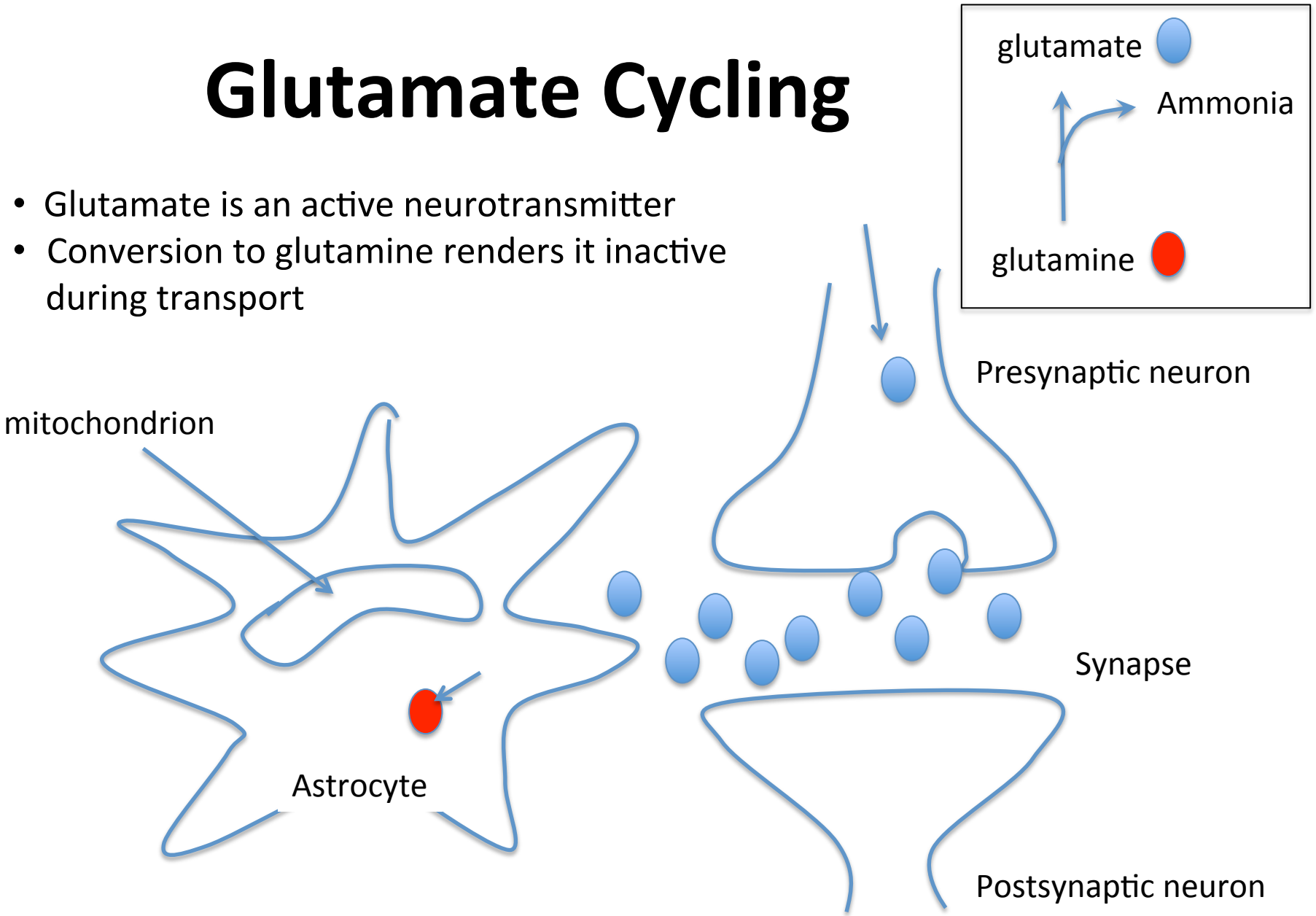
- Can humans do this?? – maybe!

Some More Help from Astrocytes

- Astrocytes release both taurine and glutamate after swelling in response to ammonia exposure
- Glutamate is an active neurotransmitter capable of inducing a 2Hz resonance phenomenon
  - This could be a key source of seizures
  - Seizures provide electric current

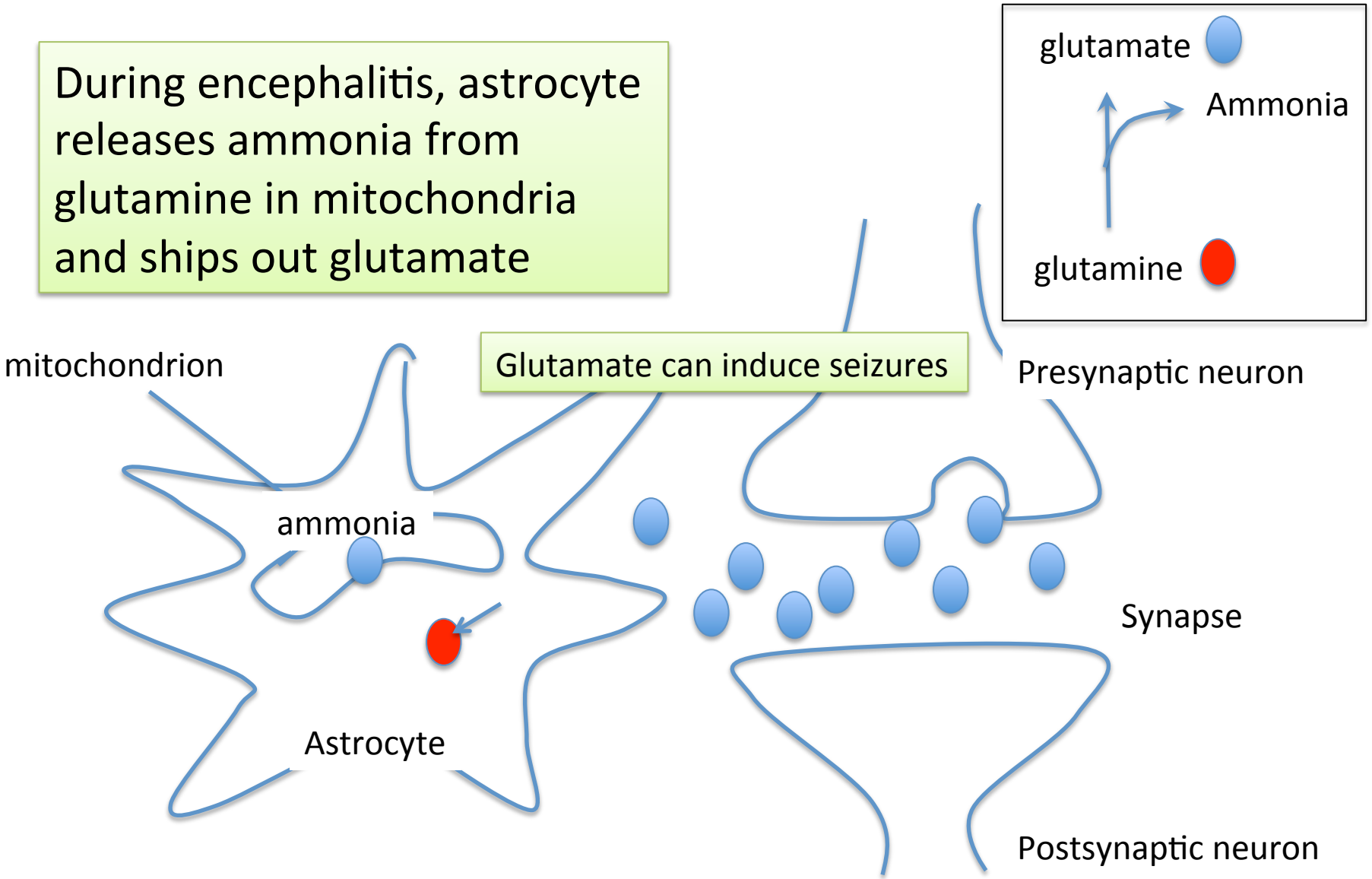
Glutamate Cycling

- Glutamate is an active neurotransmitter
- Conversion to glutamine renders it inactive during transport



Glutamate during Encephalitis

During encephalitis, astrocyte releases ammonia from glutamine in mitochondria and ships out glutamate



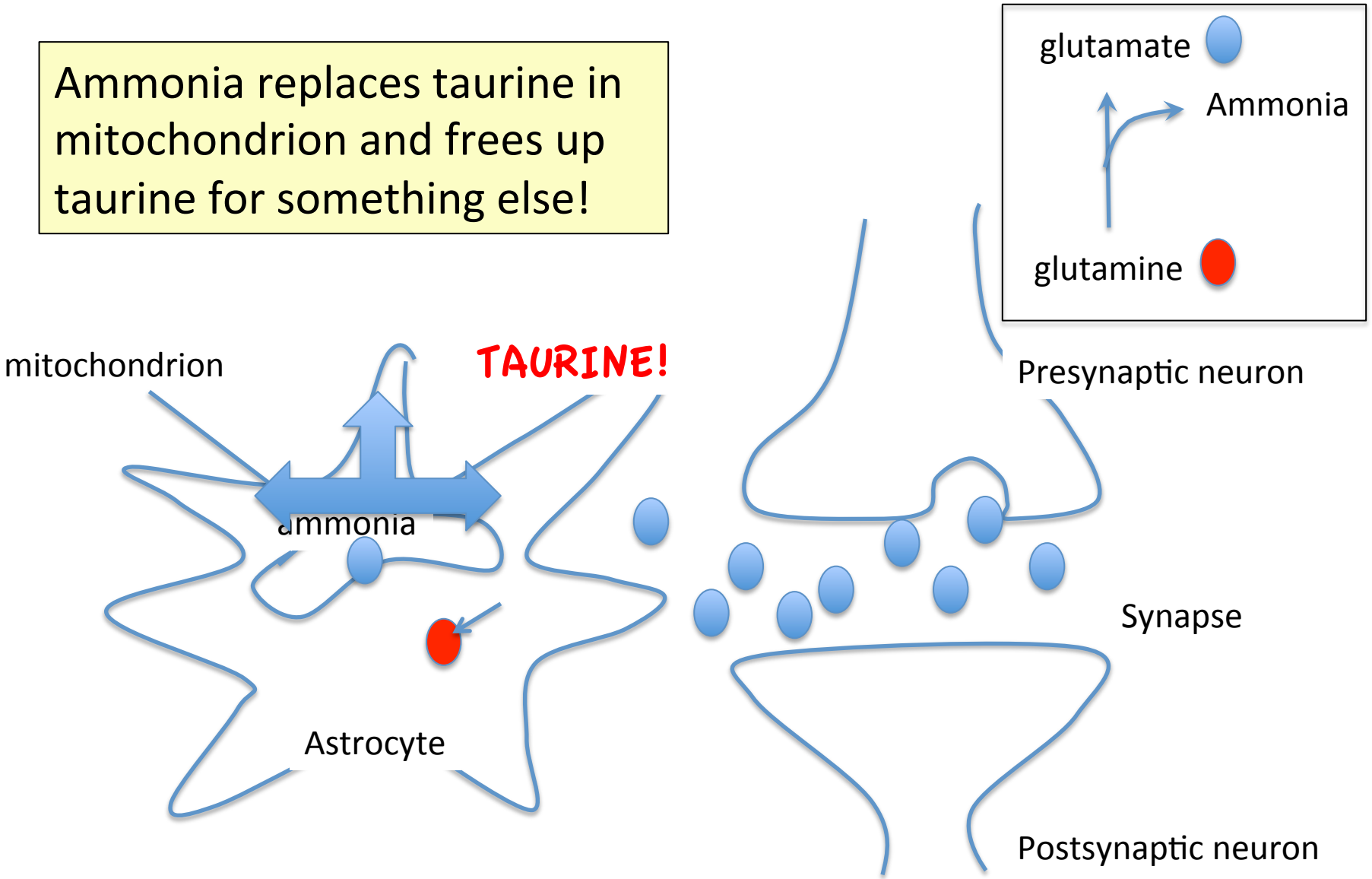
Why is Ammonia Needed in the Mitochondrion?

- To replace taurine!
- Astrocyte releases both taurine and glutamate into the medium
- Ammonia replaces taurine as buffering agent in mitochondria
  - Helps them maintain basic pH

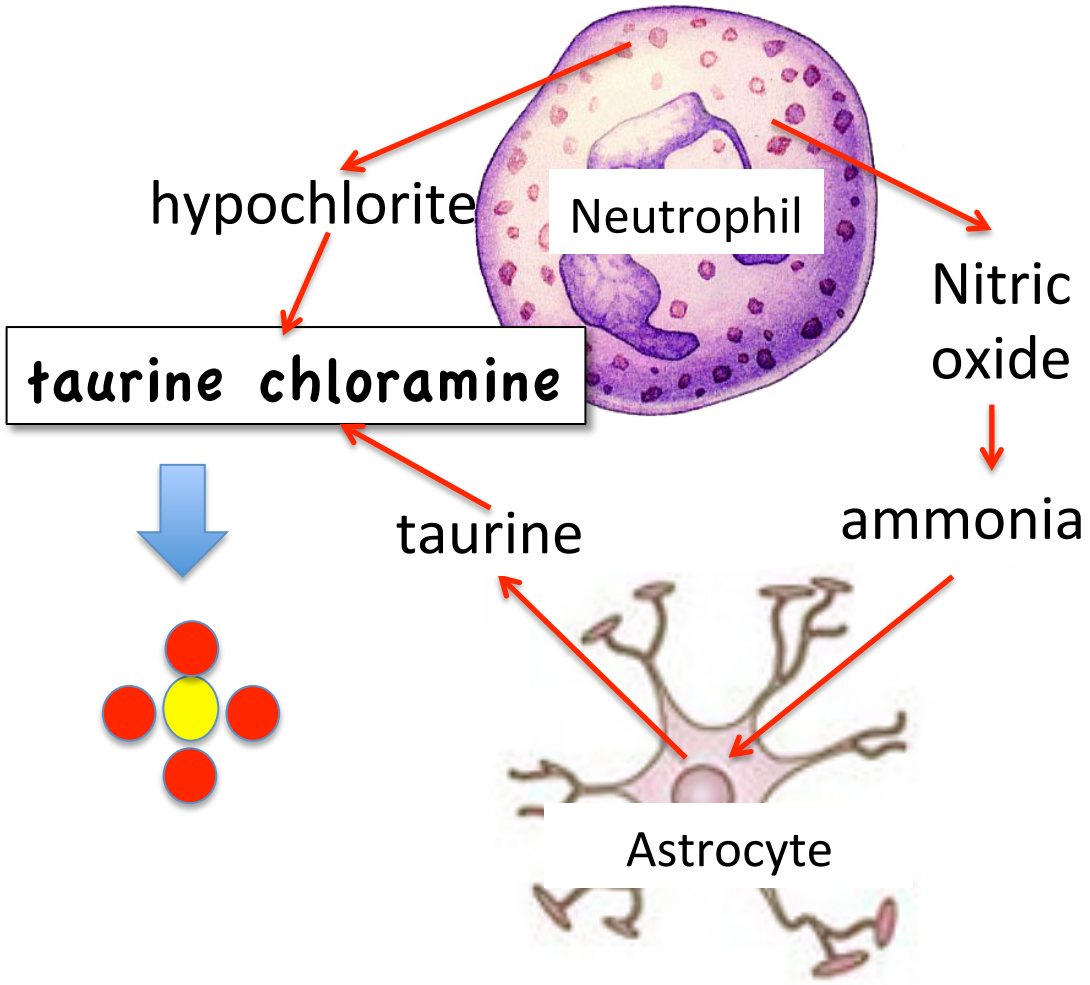
THIS FREES UP TAURINE TO PRODUCE SULFATE!!!

Glutamate during Encephalitis

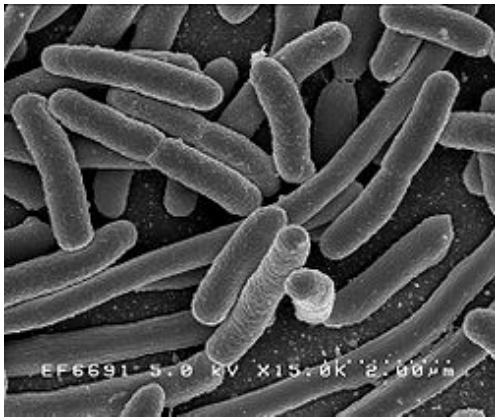
Ammonia replaces taurine in mitochondrion and frees up taurine for something else!



Hypochlorite + Taurine → Salvation!



A Role for Microbes!*



- Hypothesis: brain infection allows bacteria to supply sulfate to the brain
- Under stress conditions, glutamate is released by astrocytes in the brain and metabolized to α-ketoglutarate in the neurons (substitutes for glucose metabolism to generate energy)
- E coli and many other bacteria can utilize the enzyme α-ketoglutarate dioxygenase to metabolize taurine
  - Inputs oxygen, α-ketoglutarate, taurine
  - Outputs carbon dioxide succinate, sulfite and aminoacetaldehyde
  - This enzyme is induced during sulfate starvation
  - Sulfite is easily oxidized to sulfate
- Microbes allowed to flourish in the brain to supply sulfate!

*K.P. McCusker and J.P. Klinman *Tetrahedron Letters 50 (2009) 611–613

Recapitulation

- Encephalitis may be a mechanism to renew sulfate supply to the brain, by breaking down taurine
- Complex mechanism involves glutamate, hypochlorite, nitric oxide, ammonia, etc.
- Fever and seizures also provide catalysis
- Bacteria may be permitted into the brain to help carry out the reaction

6. Cancer

Taurine and Breast Cancer*

- Progressive inhibition of apoptosis (cell death) and induction of angiogenesis (blood vessel growth) contribute to tumor initiation, growth and metastasis in the pathogenesis of breast cancer
- Taurine displays antineoplastic effects through
  - Downregulation of angiogenesis
  - Enhancement of tumor cell apoptosis

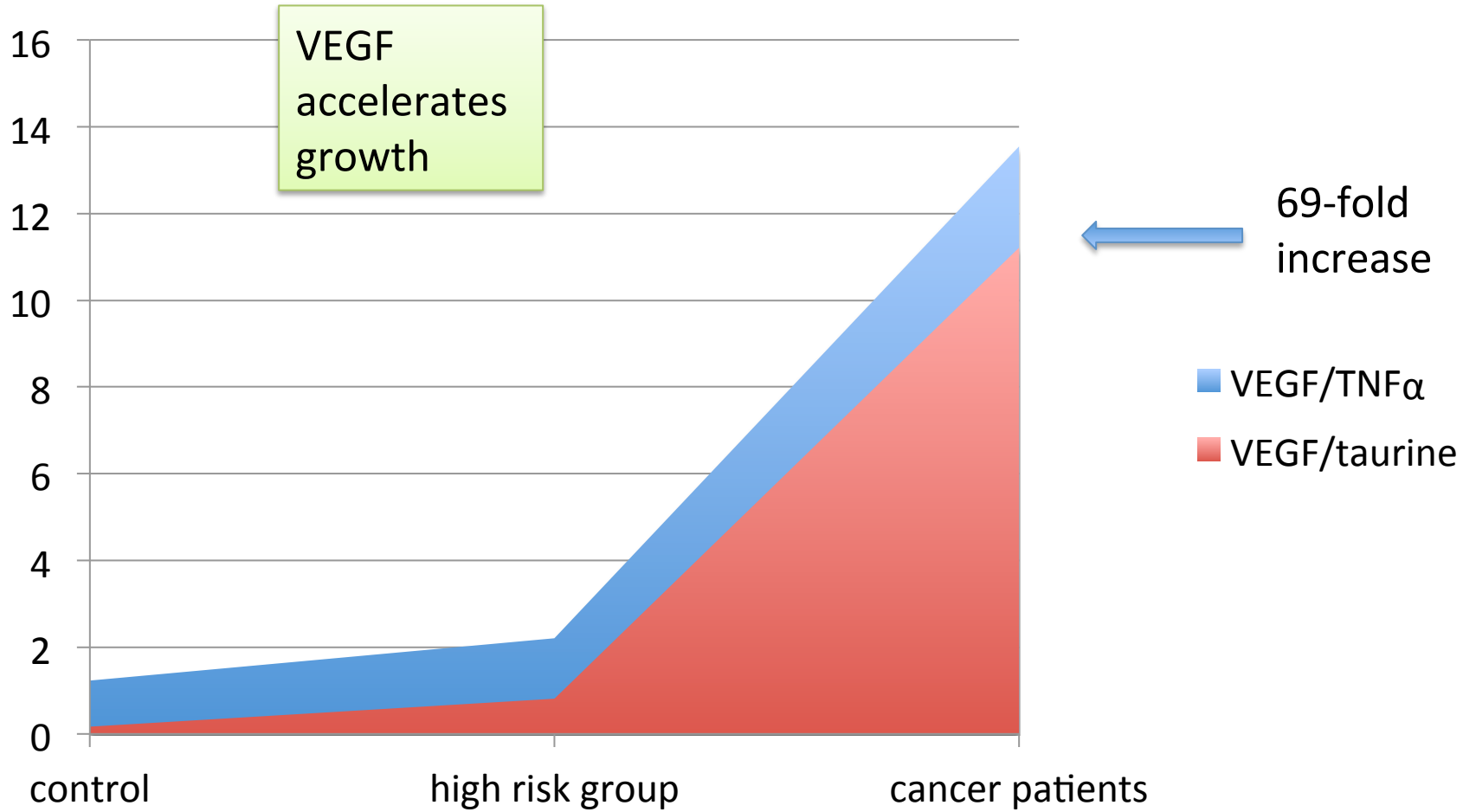
* I. M. El Agouza et al. Angiogenesis 14, 321–330, 2011

Taurine and Breast Cancer*

- 85 women
  - 50 with diagnosed breast cancer
  - 10 with benign tumors
  - 5 with family history
  - 20 controls
- Serum taurine sharply reduced in women with breast cancer ($p<0.001$)
  - 100% detection, 0% false alarms

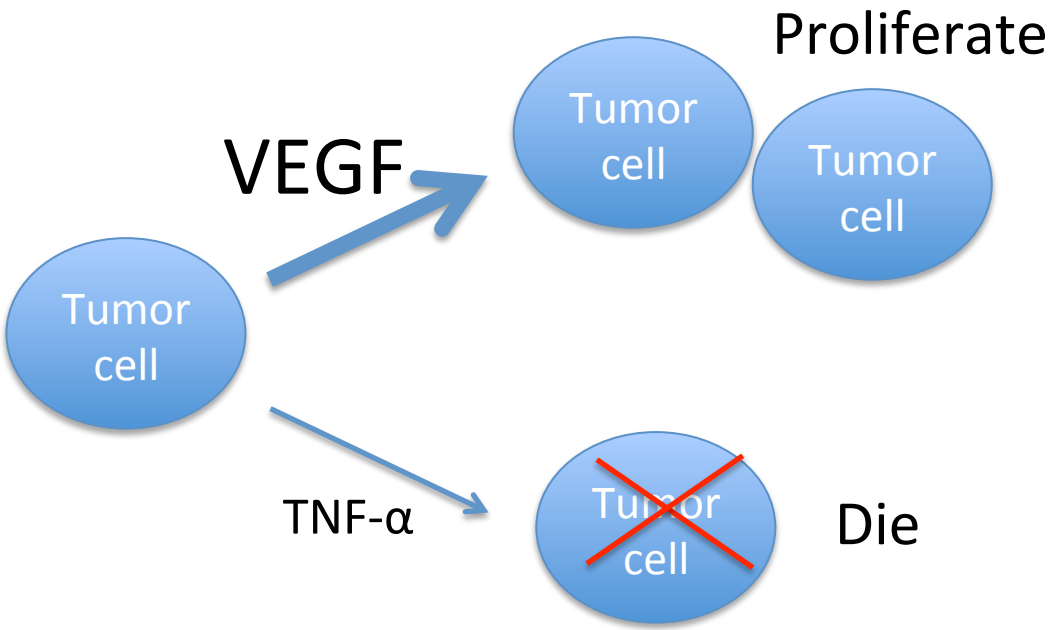
* I. M. El Agouza et al. Angiogenesis 14, 321–330, 2011

Taurine and Breast Cancer*



* I. M. El Agouza et al. Angiogenesis 14, 321–330, 2011

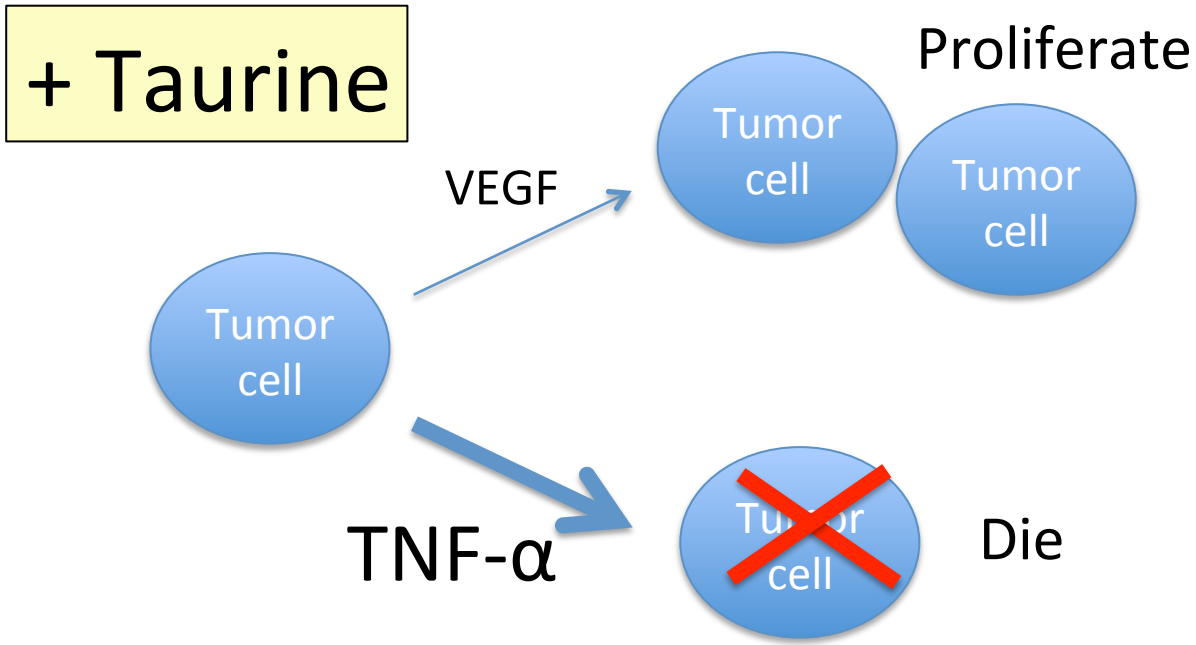
Taurine Induces Apoptosis*



Tumor cells are robust against exposure to toxic agents; they proliferate while other normal cells die

* A. Jacobi et al, Anticancer Drugs 16(9), 917-921, 2005.

Taurine Induces Apoptosis*



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Low Serum Taurine and Cancer

- Many different cancers have been found to be associated with unusually low serum taurine levels
  - Breast cancer
  - Ovarian cancer
  - Bladder cancer
  - Lung cancer
  - Uterine cancer
  - Liver cancer
  - Colon cancer
  - Gastro-intestinal cance
  - Endometrial cancer

Hypothesis: cancer depletes taurine by converting it to sulfate

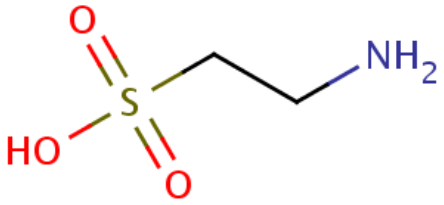
Tumor cells typically overproduce sulfated polysaccharides

7. Summary

Food Sources of Taurine

Eggs, meat, fish, seafood, dairy

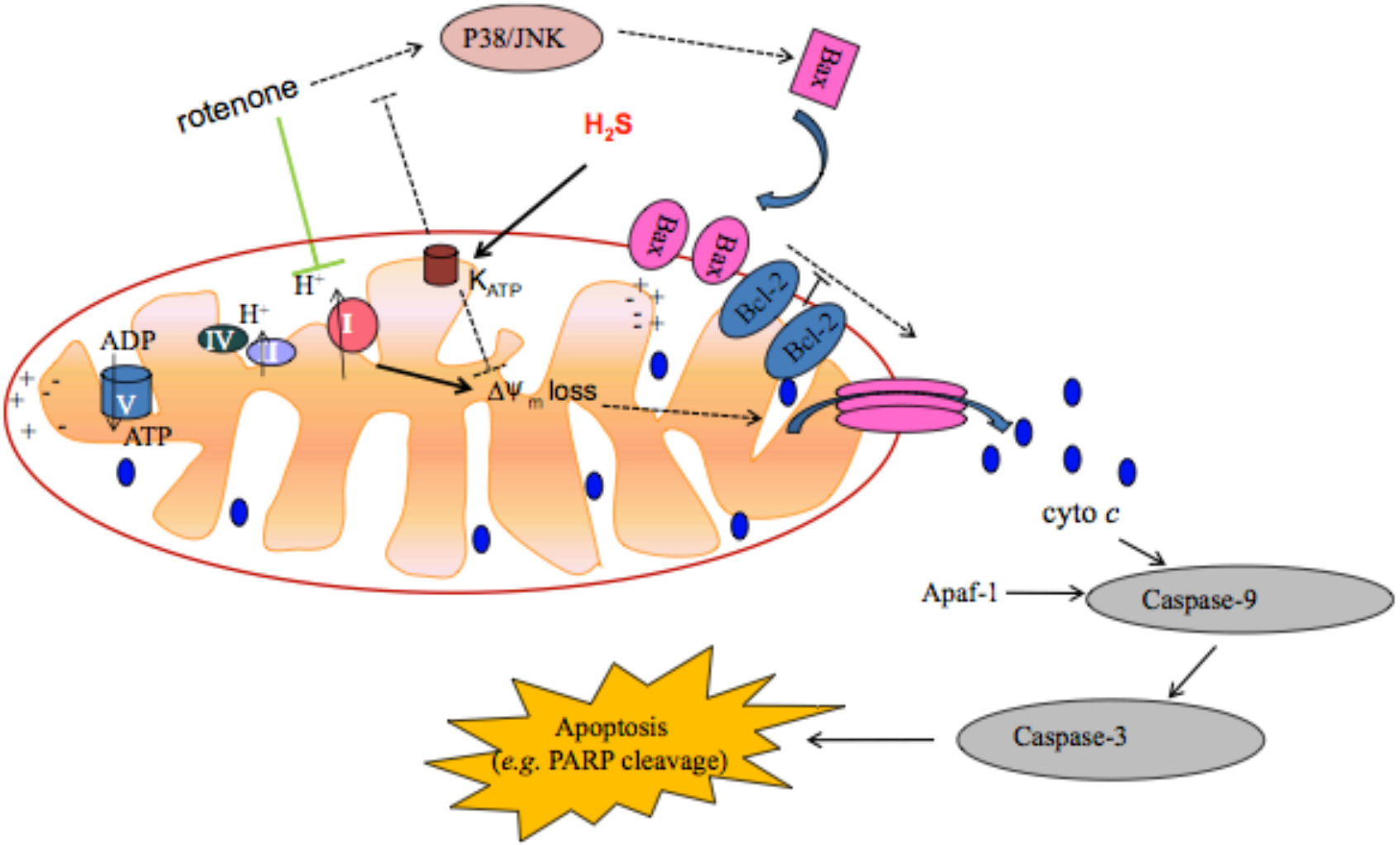
Summary



- Taurine is a fascinating and poorly understood molecule!
- We need to worry about dietary deficiencies, especially vegetarians
- Taurine is protective in cancer, heart disease, and diabetes – i.e., the major diseases of modern times
- Taurine plays an essential role in development
- Taurine's many benefits may stem from its role in supplying a buffer for sulfate to the body

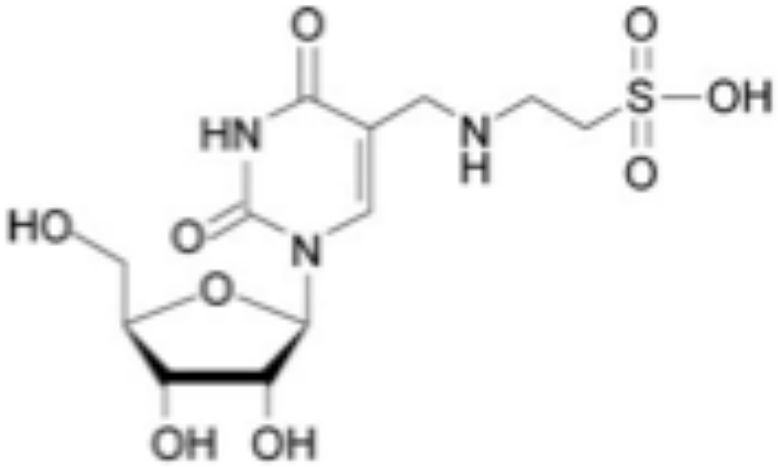
Thank you!

Hydrogen Sulfide Protects Mitochondria *



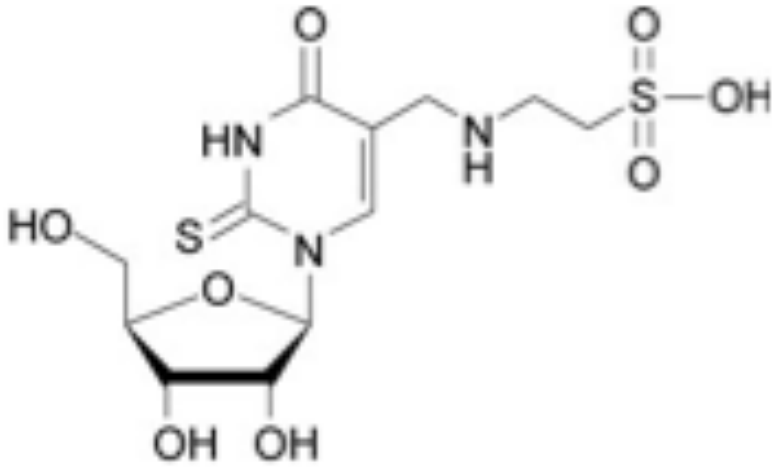
* Figure 10 in L.-F. Hu et al, Mol Pharmacol 75:27–34, 2009

Taurine-modified tRNAs in Mitochondria*



τm^5U

5-taurinomethyluridine



τm^5s^2U

5-taurinomethyl-2-thiouridine

* From Suzuki et al., WIREs RNA 2011, 2, 376-386