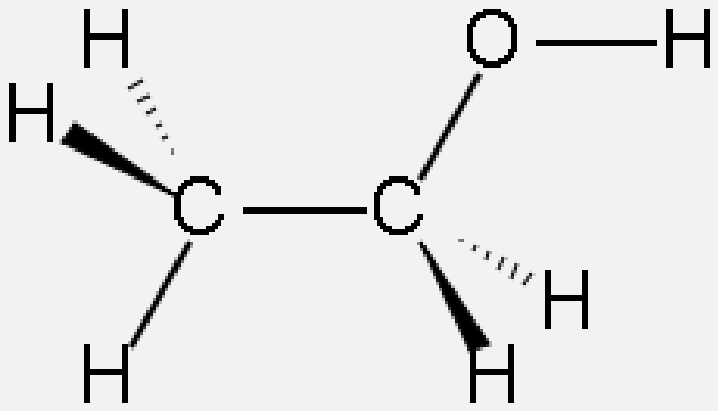
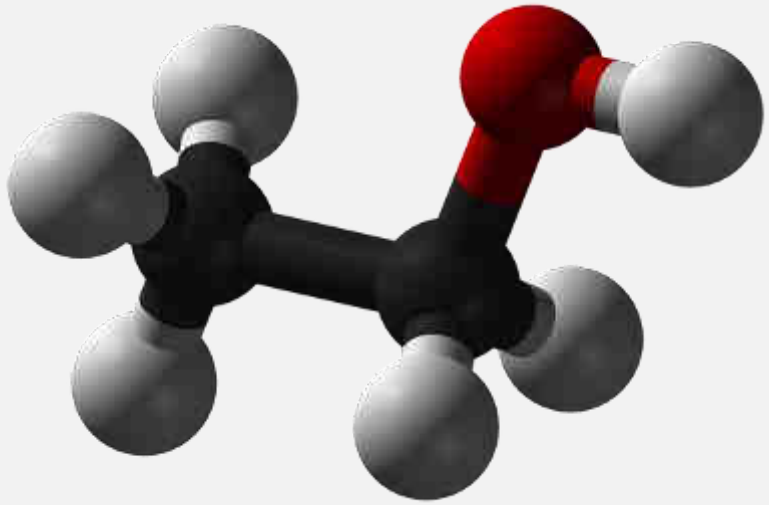
Does drinking alcohol give you brain damage?

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H
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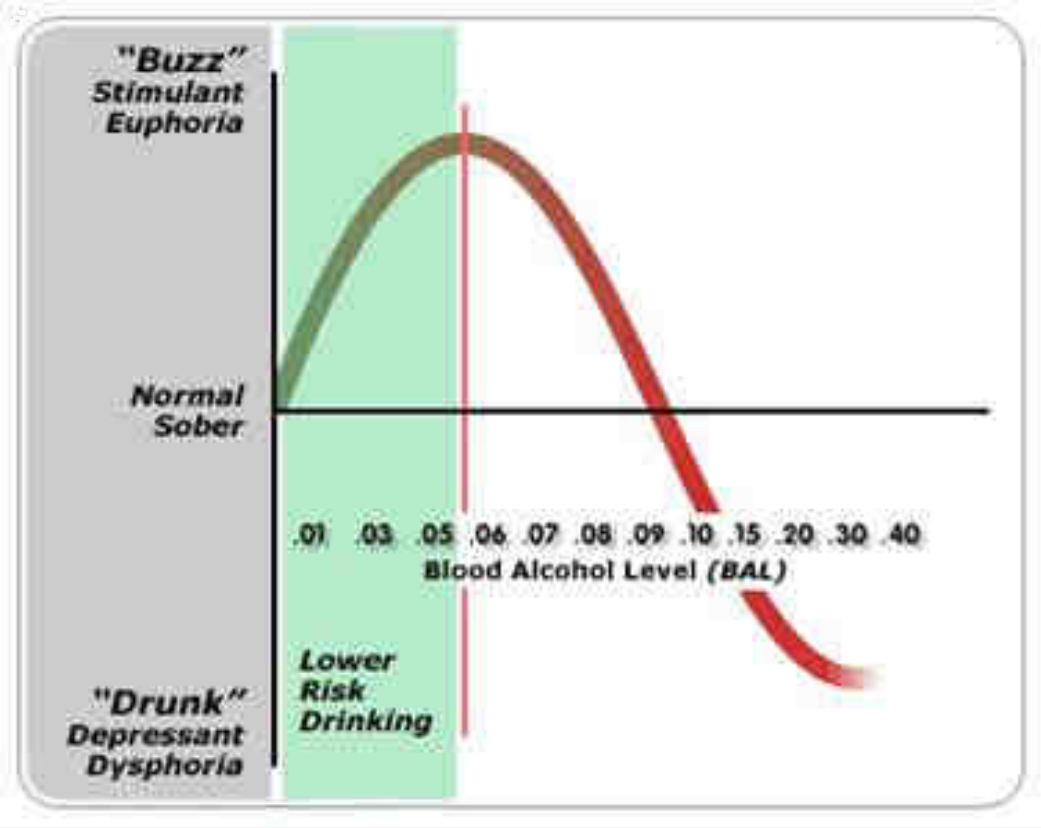


- ADH4 ~10 million years
- Alcohol fermentation ~10000 years ago
- Wine making ~5000 years ago

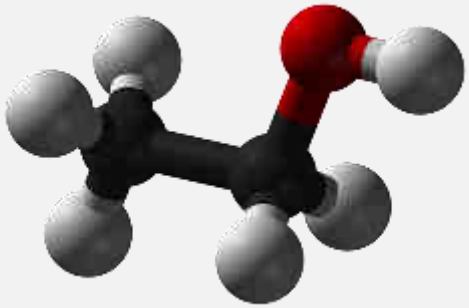




Deaths attributed to alcohol: 3.3 million/year, ~6 % of all deaths


"Buzz"
Stimulant
Euphoria
Normal
Sober
"Drunk"
Depressant
Dysphoria
.01 .03 .05 .06 .07 .08 .09 .10 .15 .20 .30 .40
Blood Alcohol Level (BAL)
Lower
Risk
Drinking

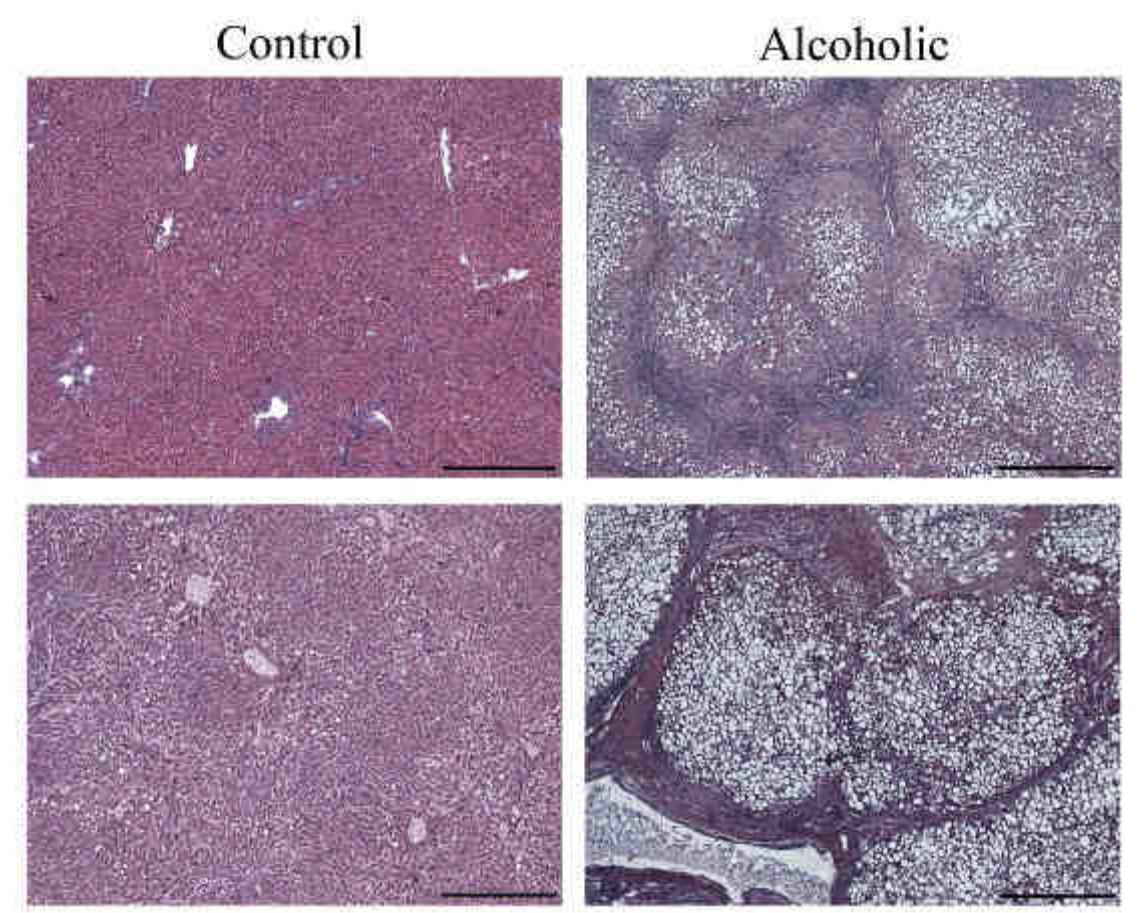
Molecular consequences:

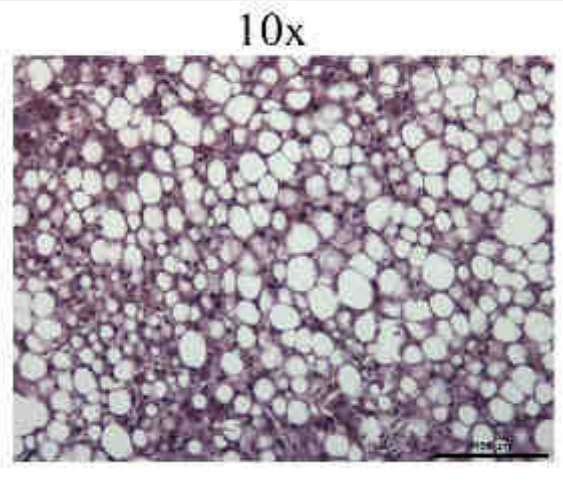


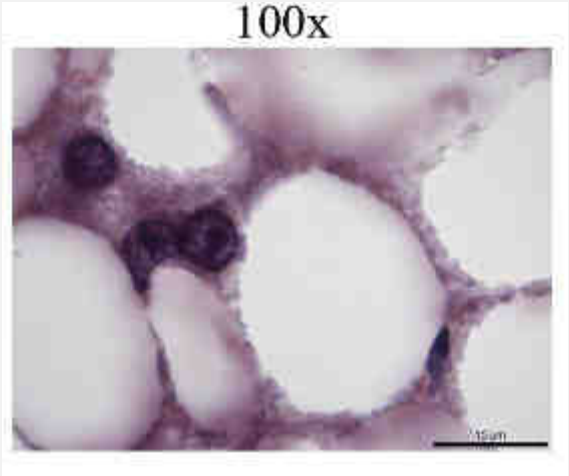
- Altered cellular signalling
- Hypoxia, altered redox state, increased NADH:NAD+ ratio
- Increased fatty acid synthesis, decreased fatty acid oxidation
- ROS: lipid peroxidation, protein adducts, membrane damage
- Disruption of the methionine metabolic pathway:
  reduced *SAM* and increased *SAH*.
- Cell toxicity, apoptotic and necrotic cell death.



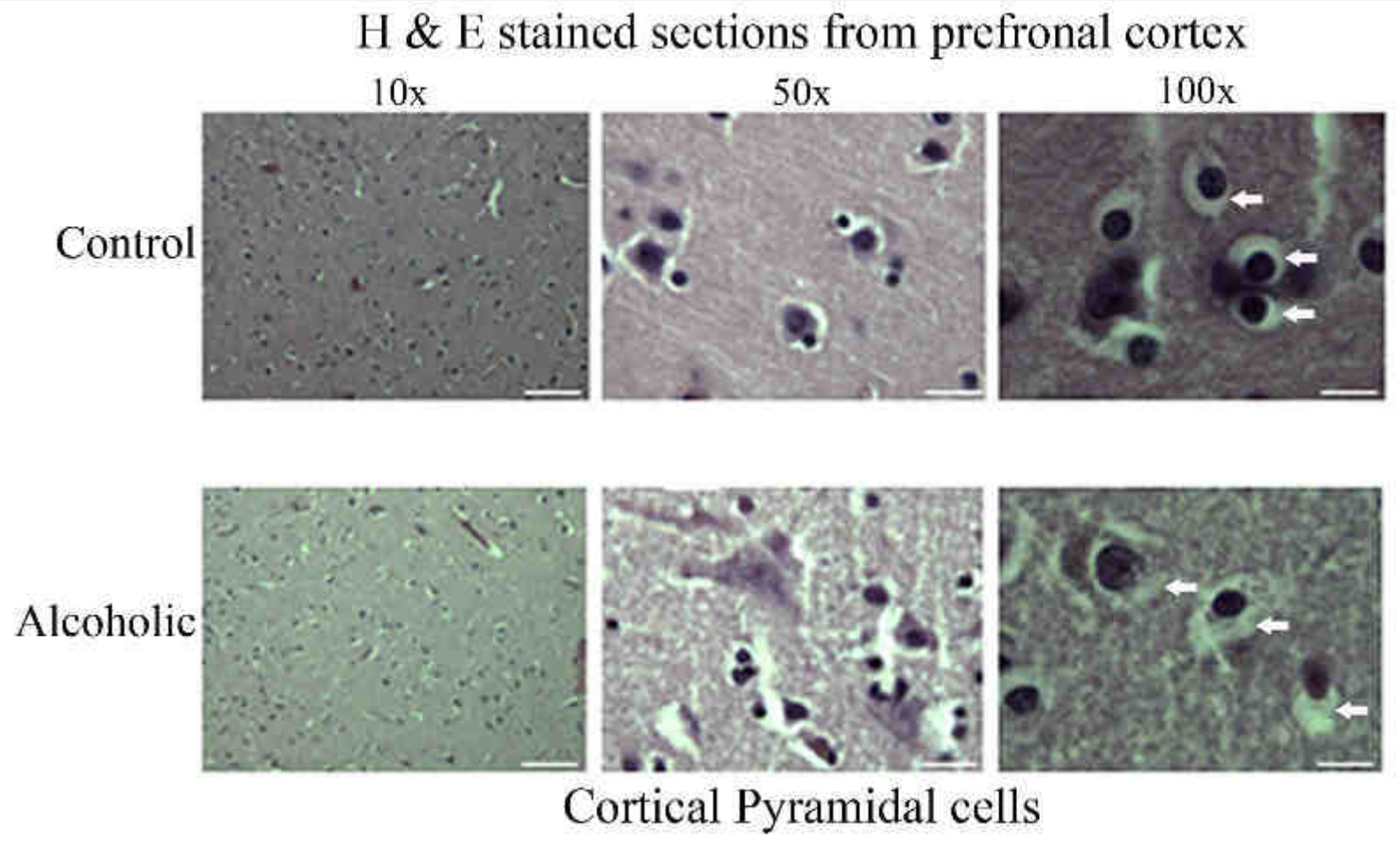


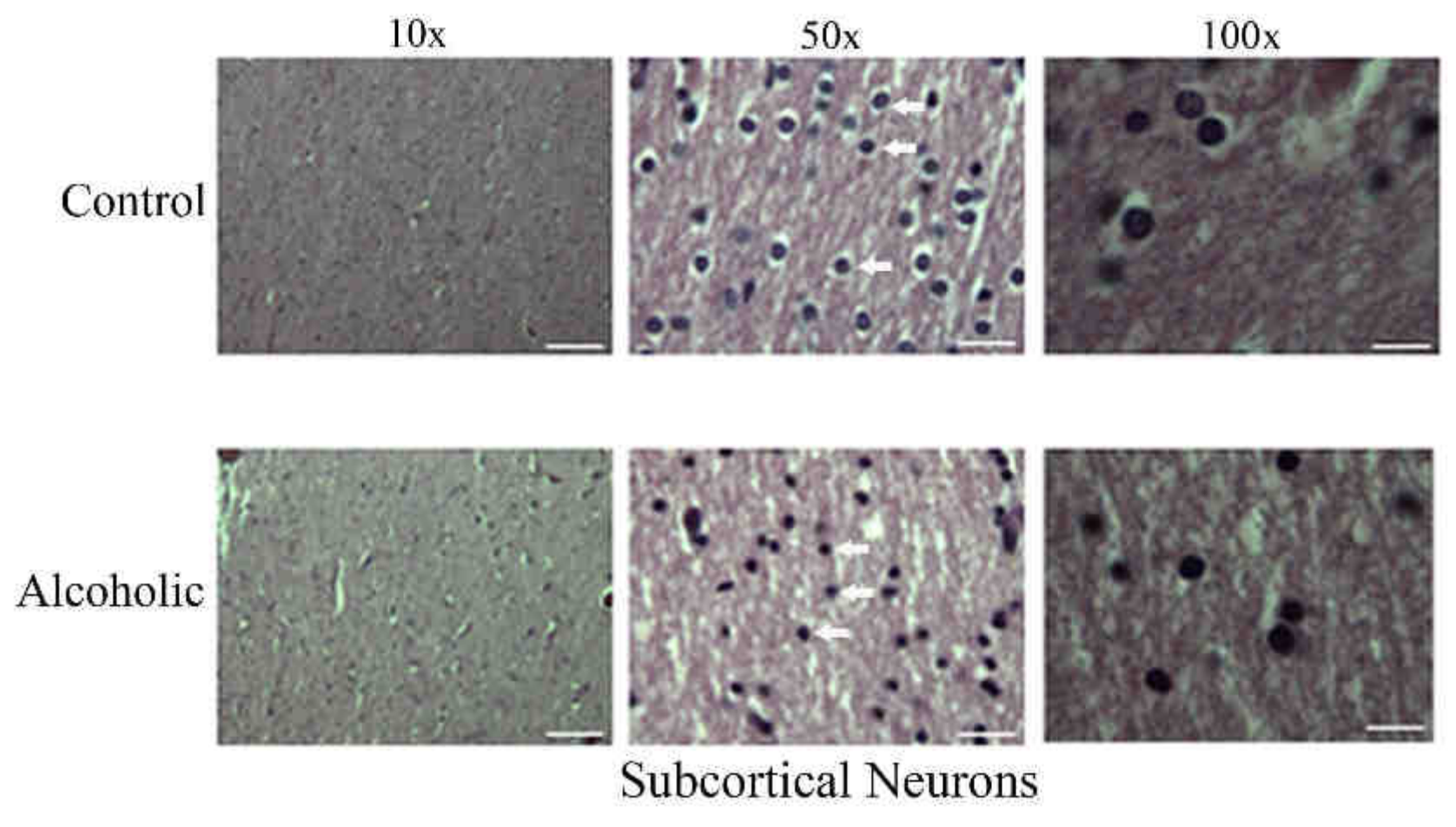


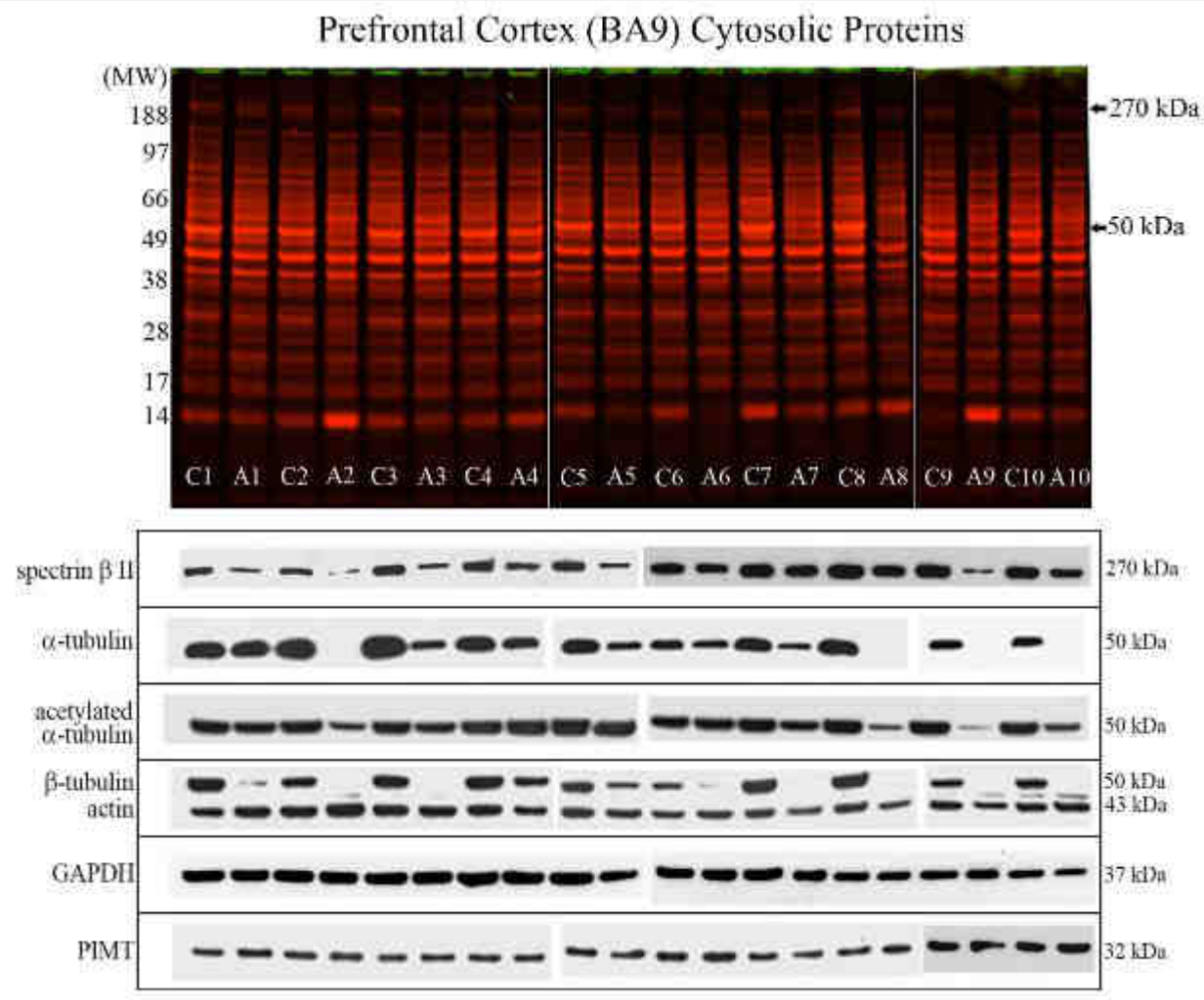


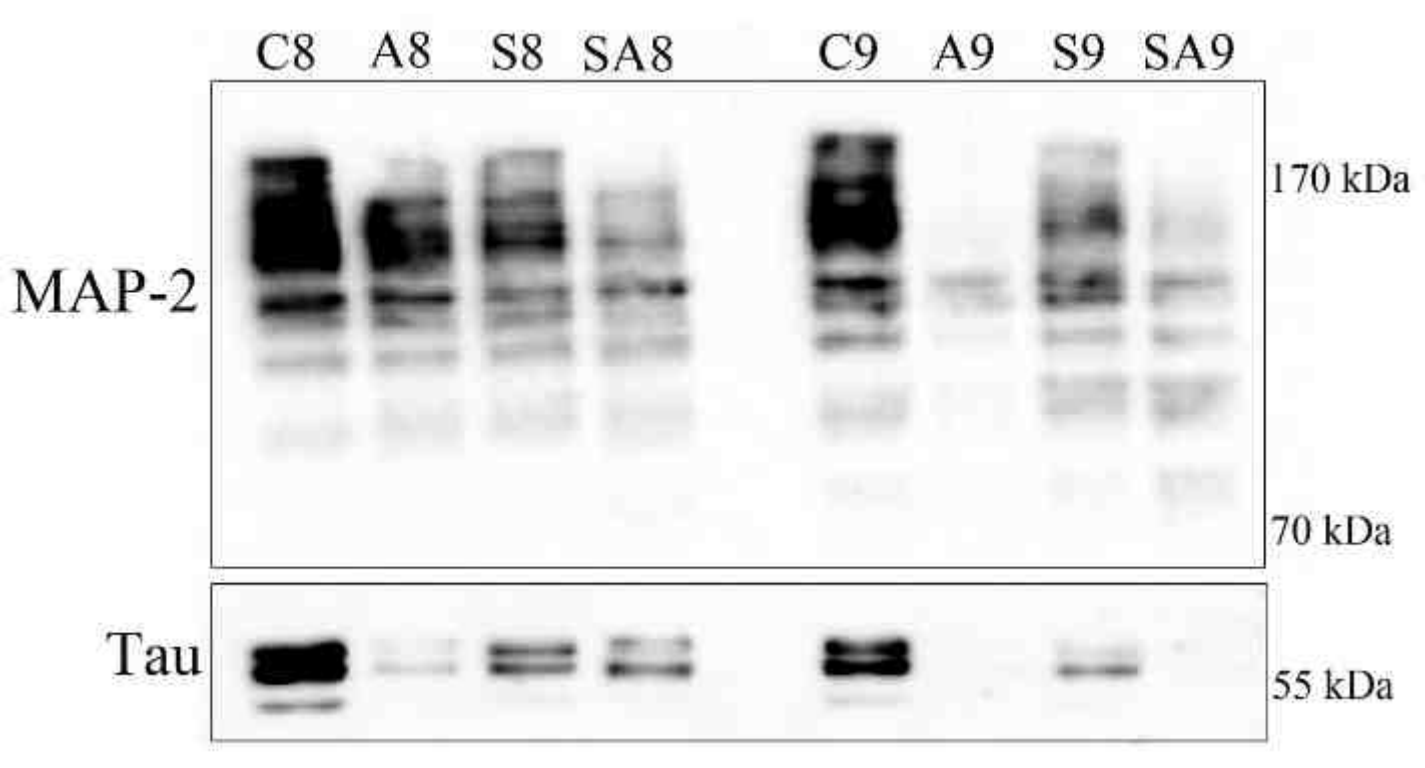


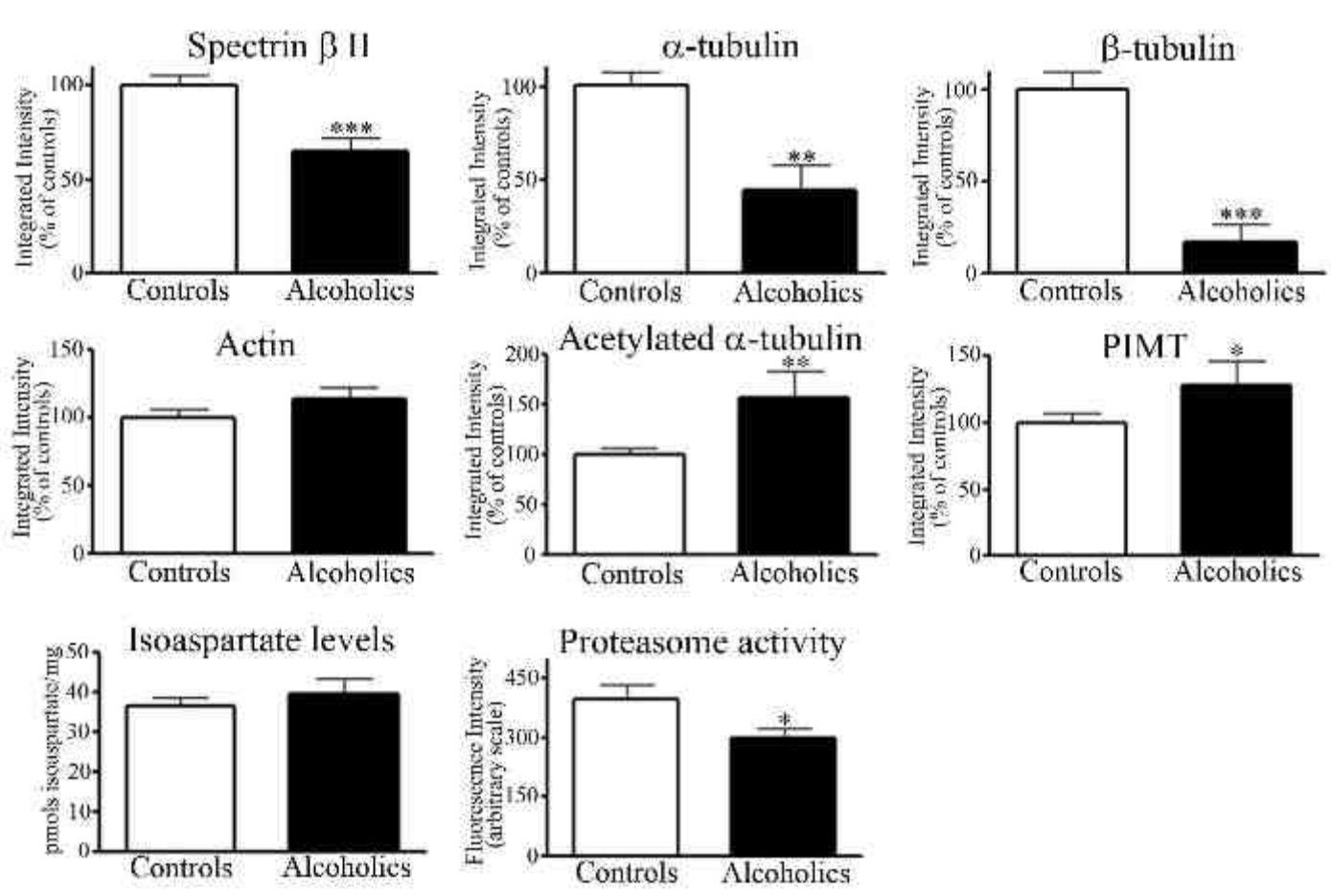
Liver Damage

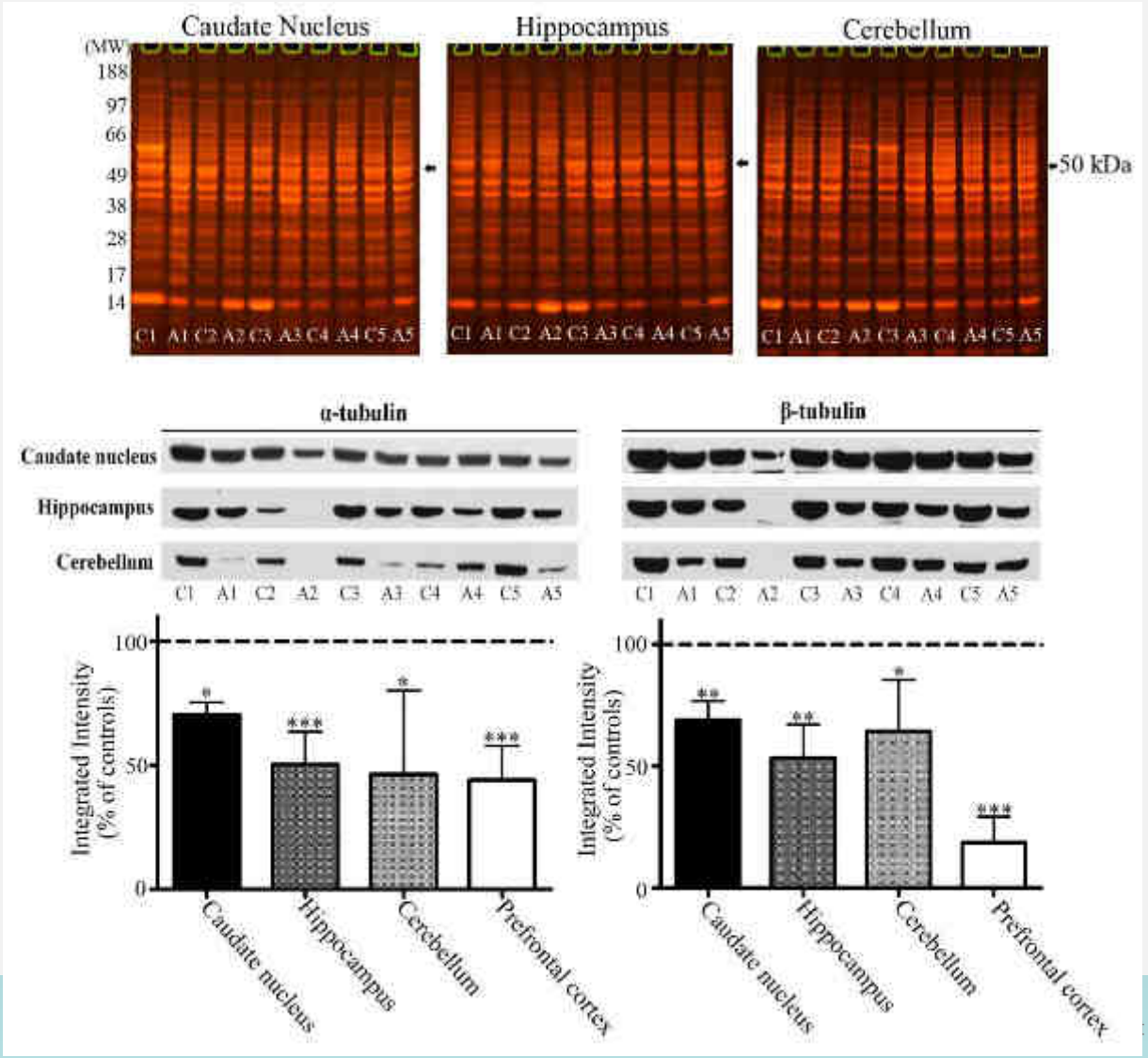

H & E stained sections from prefronal cortex
10x
50x
100x
Control
Alcoholic
Cortical Pyramidal cells


10x
50x
100x
Control
Alcoholic
Subcortical Neurons


Prefrontal Cortex (BA9) Cytosolic Proteins
(MW)
188
97
66
49
38
28
17
14
C1 A1 C2 A2 C3 A3 C4 A4 C5 A5 C6 A6 C7 A7 C8 A8 C9 A9 C10 A10
270 kDa
50 kDa
spectrin β II
270 kDa
α-tubulin
50 kDa
acetylated α-tubulin
50 kDa
β-tubulin
50 kDa
actin
43 kDa
GAPDH
37 kDa
PIMT
32 kDa


C8
A8
S8
SA8
C9
A9
S9
SA9
MAP-2
170 kDa
70 kDa
Tau
55 kDa


Spectrin β II
Integrated Intensity (% of controls)
100
50
0
***
Controls
Alcoholics
α-tubulin
Integrated Intensity (% of controls)
100
50
0
**
Controls
Alcoholics
β-tubulin
Integrated Intensity (% of controls)
100
50
0
***
Controls
Alcoholics
Actin
Integrated Intensity (% of controls)
150
100
50
0
Controls
Alcoholics
Acetylated α-tubulin
Integrated Intensity (% of controls)
200
150
100
50
0
**
Controls
Alcoholics
PIMT
Integrated Intensity (% of controls)
150
100
50
0
*
Controls
Alcoholics
Isoaspartate levels
pmols isoaspartate/mg
50
40
30
20
10
0
Controls
Alcoholics
Proteasome activity
Fluorescence Intensity (arbitrary scale)
450
300
150
0
*
Controls
Alcoholics


Caudate Nucleus
Hippocampus
Cerebellum
(MW)
188
97
66
49
38
28
17
14
C1 A1 C2 A2 C3 A3 C4 A4 C5 A5
50 kDa
α-tubulin
β-tubulin
Caudate nucleus
Hippocampus
Cerebellum
Integrated Intensity (% of controls)
100
50
0
Caudate nucleus
Hippocampus
Cerebellum
Prefrontal cortex

Male Wistar Rats



Control (C) or Ethanol-fed (E), liquid diet

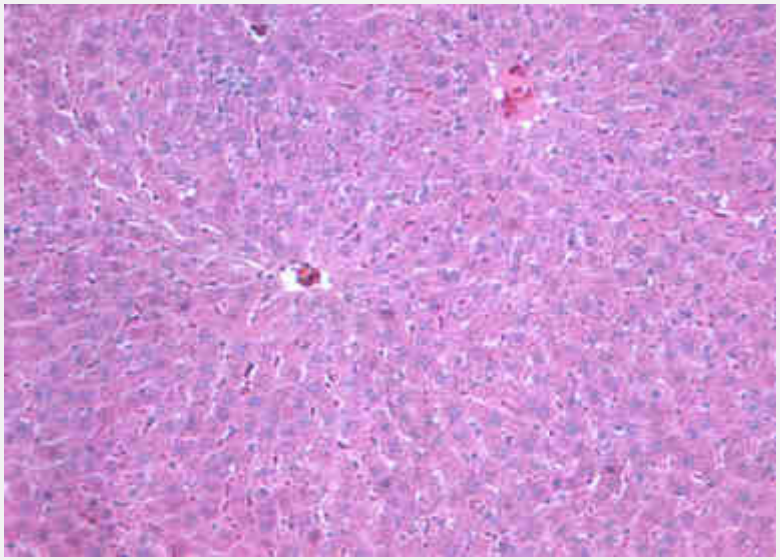
4-weeks, 36 % of calories as ethanol



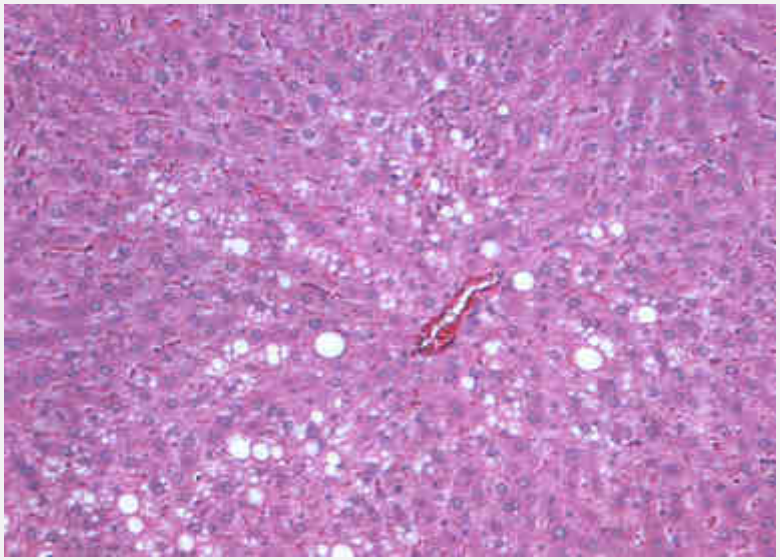
25-50 mM blood ethanol concentration

2-3x the legal driving limit of 17.4 mM (0.08 % blood alcohol) in UK or USA.

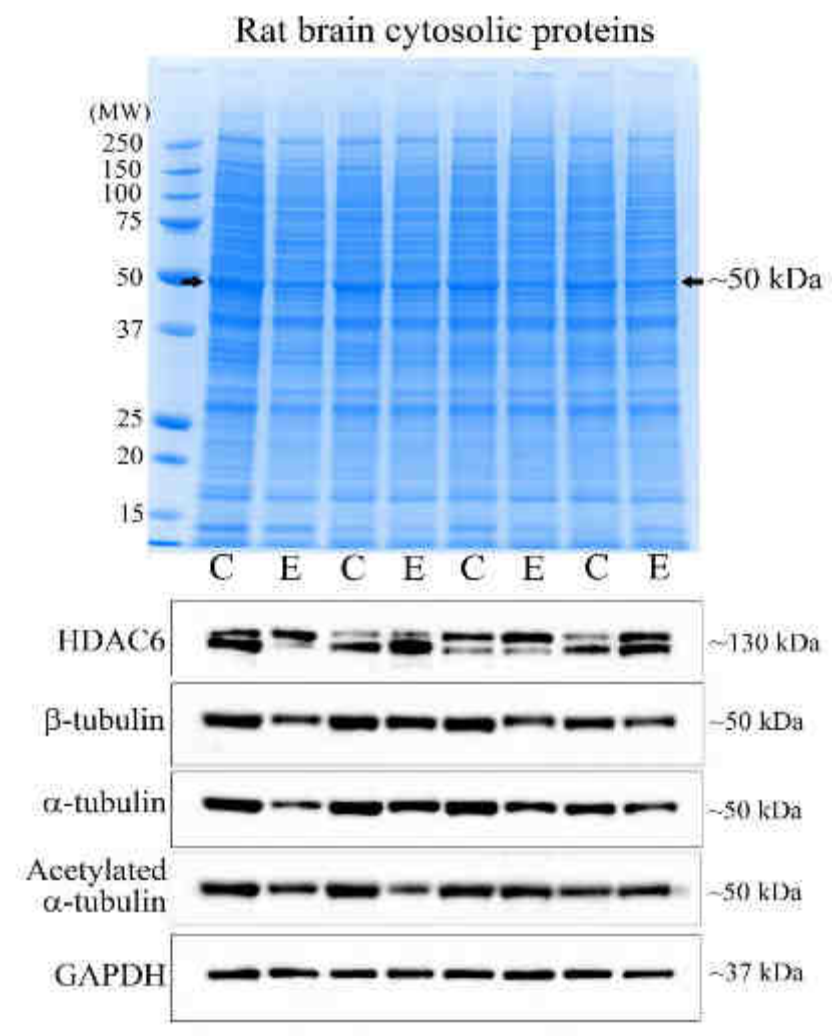
Control

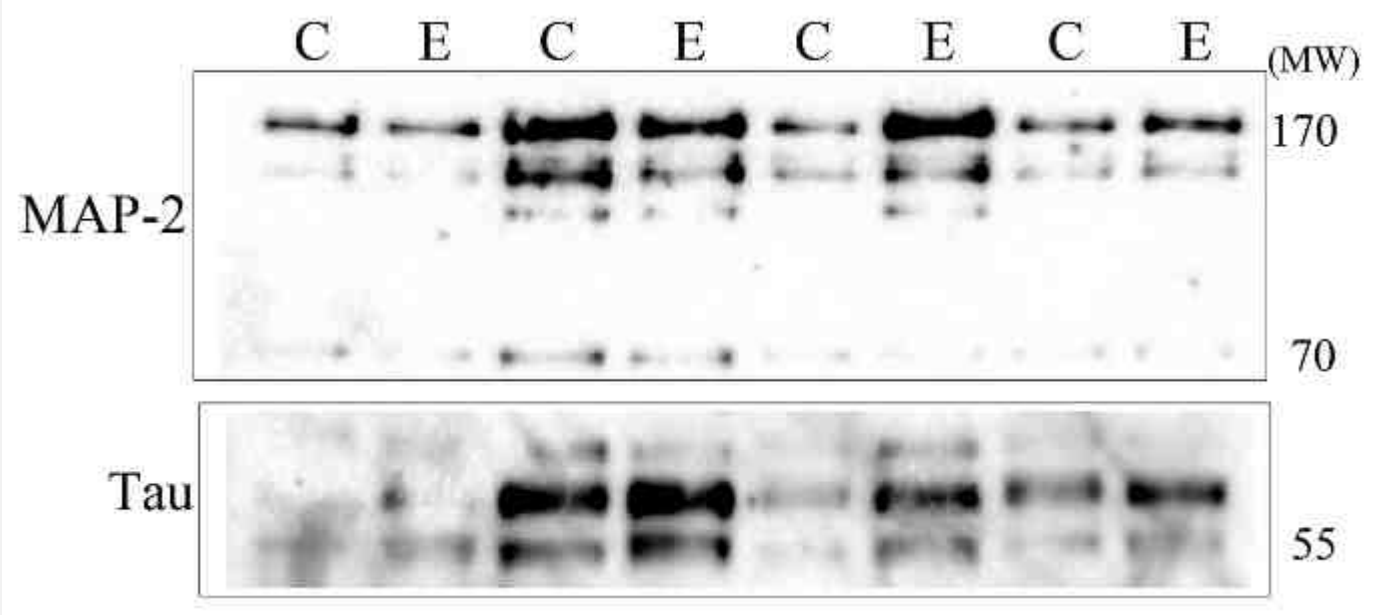


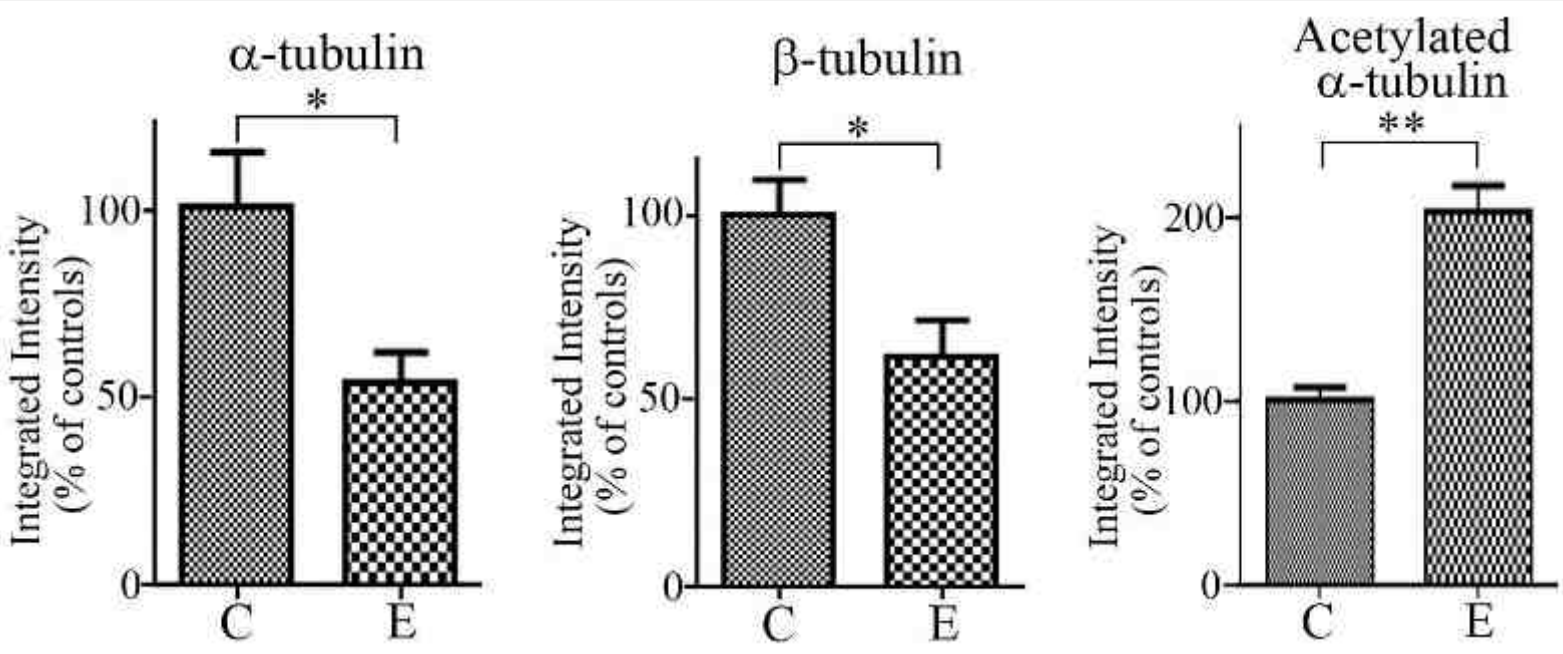
Ethanol



Liver damage

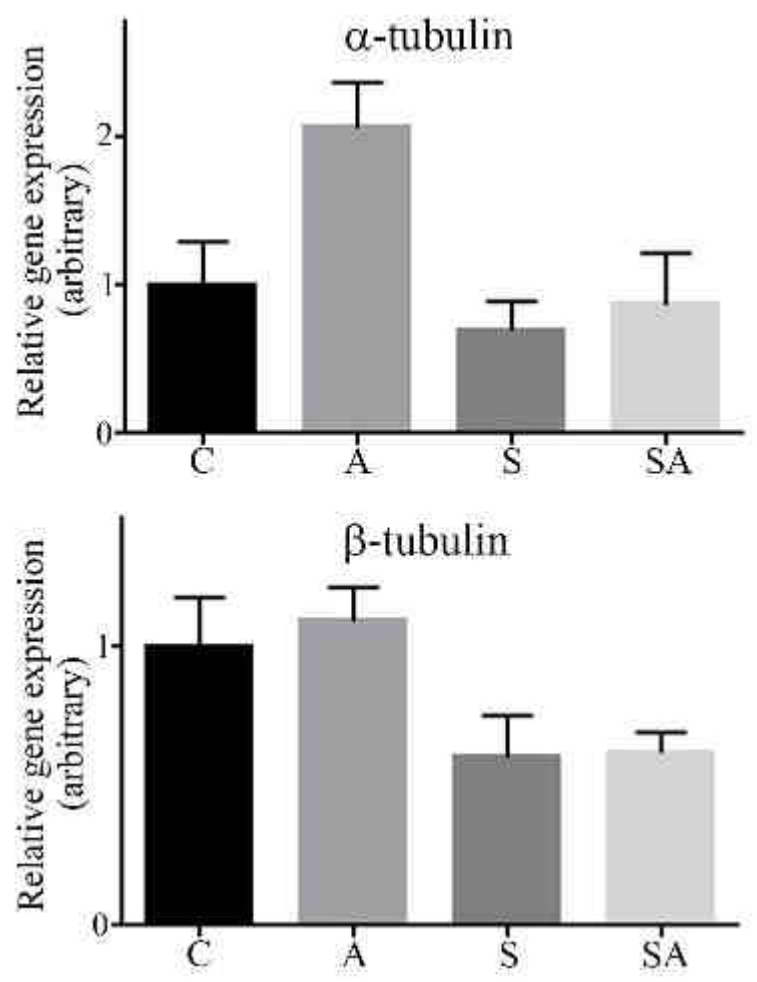

Rat brain cytosolic proteins
(MW)
250
150
100
75
50
37
25
20
15
~50 kDa
C E C E C E C E
HDAC6
~130 kDa
β-tubulin
~50 kDa
α-tubulin
~50 kDa
Acetylated α-tubulin
~50 kDa
GAPDH
~37 kDa


C
E
C
E
C
E
C
E
(MW)
MAP-2
170
70
Tau
55


α-tubulin
*
Integrated Intensity (% of controls)
100
50
0
C
E
β-tubulin
*
Integrated Intensity (% of controls)
100
50
0
C
E
Acetylated α-tubulin
**
Integrated Intensity (% of controls)
200
100
0
C
E

What is the mechanism that drives reduced tubulin levels?




α-tubulin
Relative gene expression (arbitrary)
2
1
0
C
A
S
SA
β-tubulin
Relative gene expression (arbitrary)
1
0
C
A
S
SA

‘Tubulin code’

Modification
Acetylation
Detyrosination
Deglutamylation
Glutamylation
Polyamination
Glycosylation
Palmitoylation
Phosphorylation
Sumoylation
Ubiquitination
Isoaspartate formation
Succination


Consequences
Just Ahead

Acknowledgements

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Dean Tuma

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