Alcoholism-Associated Brain Disorders: Psychiatric Nosology and Molecular Medicine

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Societal and Healthcare Costs of Substance Abuse

• Estimated US$300 (~NZ$7) billion/year for medical care and lost productivity
• Abuse of alcohol, tobacco, and drugs contribute to each of the ten leading causes of death in U.S.
• Large potential cost-savings in a capitated healthcare environment
EFFECT OF ALCOHOLIC DRINKS AND NARCOTICS ON THE HUMAN SYSTEM.
Major Research Questions

• What are the *molecular mechanisms* that cause brain injury associated with chronic alcoholism?
• Are there *genetic predisposing factor(s)* to development of alcoholism-associated brain damage?
• Are these factors contributory to alcoholism *per se*?
• Can alcohol-induced *brain injury* be prevented and *recovery with abstinence* improved?
Longitudinal Progression of Substance Use Disorders

Antecedents / Sociocultural Context / Consequences of Drug(s) Use / Abuse / Compulsive Use

Psychopharmacologic Effects of Drug(s)

Vulnerable Individual
- Biologic
- Psychologic
- Social

Dependence Neuroadaptation

Complications
- Social
- Neuropsychiatric
- Medical
Carl Wernicke 1848-1905
S.S. Korsakoff 1853-1900
Syndromes of Impairment in Chronic Alcohol Dependent Patients

• 10% of alcoholics have severe brain dysfunction:
  – Alcohol amnestic disorder (Wernicke-Korsakoff syndrome)
  – Alcohol-induced persisting dementia
Syndromes of Impairment in Chronic Alcohol Dependent Patients

- 50-70% of alcoholics have mild to moderate verbal, abstracting/problem solving, learning/memory, perceptual motor deficits

- Continuities of neuropsychological impairments and neuropathological findings among WKS, A-IPD, and less impaired alcoholics
Neuropathological Abnormalities in Alcoholics

- *Cerebellar* degeneration (~40%) - Torvik *et al* (1982)
- Characteristic *brainstem* and *diencephalic* abnormalities of WKS (~13%) - Torvik *et al* (1982); Harper and Kril (1993)
- Reduced *brain weight* and/or *volume* (white matter predominantly) - Harper and Kril (1985)
Alcoholic Cerebellar Degeneration
Wernicke-Korsakoff Syndrome
Demyelination of mammilary bodies in non-WKS alcoholics

Alling and Bostrom (1981)
Top row, slice images from three normal subjects. Bottom row, slice images from three alcoholic subjects showing the large amount of ventricular enlargement and cortical and cerebellar atrophy.
Thiamine Deficiency and Alcohol-Induced Brain Injury

- TD is very common among alcoholics
- Thiamine rapidly reverses signs of TD (Wernicke’s encephalopathy) leaving residual neuropsychiatric/neuropathologic deficits (Korsakoff’s syndrome)
Thiamine Deficiency and Alcohol-Induced Brain Injury

• Brain morphometric abnormalities among alcoholics: WKS > cirrhosis > non-WKS (Harper)
• Findings of functional TD observed in brains of non-WKS alcoholics (Butterworth)
• Experimental TD can mimic and potentiate histological effects of alcohol in animal models (Langlais)
Recovery of Brain Structure/ Functions with Abstinence

- Striking neurological/psychiatric/neuropsychological improvements occur early in abstinence
- Improvements decrescendo for ~3 weeks and may continue for years
- Some abnormalities may never improve (permanent vs. premorbid) and can significantly contribute to clinical course
Recovery of Brain Structure/ Functions with Abstinence

- Ventricular and sulcal enlargement on CT and MRI can reverse with abstinence
- Pathophysiology of brain recovery (especially role of thiamine) poorly understood
- Differential susceptibilities of brain areas (anterior superior cerebellar vermis, frontal white matter)
Volume changes measured between the first and third acquisitions in two different alcoholic subjects
Mid-sagittal MR image of the brain of a representative alcoholic subject (left). The white square in the image represents the scale (8cm\(^3\)) of the cerebellar VOI from which the proton MRS spectra (right) were repeatedly derived.
Mean (±SD) brain concentrations (mM) of N-acetylaspartate (NAA), Creatine (Cr), and Choline (Cho) in normal controls (n=12) and alcoholic subjects (n=31) within 3 to 5 days of last drink.

* P< 0.05  ** P< 0.001
Cerebellar Concentrations (mM) of MRS Metabolites and Clinical Course after 3-5 Days Abstinence

<table>
<thead>
<tr>
<th></th>
<th>Early Relapse</th>
<th>Late Relapse</th>
<th>No Relapse</th>
<th>Normal Control</th>
<th>Bonferroni Adjusted</th>
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<tbody>
<tr>
<td>N=8</td>
<td></td>
<td>N=12</td>
<td>N=11</td>
<td>N=10</td>
<td></td>
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<tr>
<td>NAA</td>
<td>6.6 (0.5)</td>
<td>7.4 (1.1)</td>
<td>7.7 (2.0)</td>
<td>8.0 (1.0) *</td>
<td>ER&lt;NC</td>
</tr>
<tr>
<td>Cr</td>
<td>8.2 (0.7)</td>
<td>9.2 (1.5)</td>
<td>9.0 (1.6)</td>
<td>9.0 (0.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Cho</td>
<td>1.5 (0.1)</td>
<td>1.8 (0.5)</td>
<td>1.7 (0.4)</td>
<td>2.2 (0.3) **</td>
<td>ER, NR&lt;NC</td>
</tr>
</tbody>
</table>
Distinguishing Clinical Features of ER, LR, and NR

• Age: ER<LR,NR
• Gender: NS but ER (all male)
• Family History Positive: NS but ER (100%)
• Age of alcoholism onset: ER, LR<NR
Distinguishing Clinical Features of ER, LR, and NR

- Total years drinking: ER<LR,NR
- Lifetime alcohol intake, daily drinks, dependence severity: NS
- Neurocognitive screening battery (3-5 days): NS
- Neuropsychological battery (3 weeks): LR<NR
Characteristics of early onset alcoholism (Cloninger, 1987)

- High behavioral activation (impulsivity, novelty seeking) - dopamine
- Low behavioral inhibition (harm avoidance, aggression) - serotonin
- Behavioral maintenance (reward dependence) - norepinephrine
Additional characteristics of early onset alcoholism?

- Increased sensitivity to thiamine deficiency and alcohol-induced brain injury
- Premorbid affective symptoms and neurocognitive deficits
- Malignant clinical trajectory
Feb 13, Feb 24, Feb 28
Longitudinal changes in brain NAA, Cr, and Cho concentrations (mM) in frontal lobe white matter and cerebellar vermis during 3 months in eleven NR patients. *P<0.05
Brain tissue (Gray matter + white matter) in frontal and cerebellar VOIs in NR alcoholic patients over three months’ abstinence.
Dominant Hand Finger Tapping Normal Control
Brain Activation During Finger Tapping with Dominant Hand

Normal Volunteer

Alcoholic Patient
T₁-weighted MR image of rat brain showing the location for volume (27 mm³) selected for spectroscopy.
Cho/NAA and Cr/NAA in rats administered thiamine deficient diet and pyrithiamine for 14 days.

(a) Cho/NAA
and
(b) Cr/NAA

2 hours after administration of thiamine hydrochloride (5 or 100 mg/kg, i.p.) in rats made TD by dietary deprivation and daily pyrithiamine (0.5 mg/kg) for 12 days

In vivo localized proton spectra from TD rat brain after physostigmine (0.35 mg/kg i.p.)

- $t = 0$
- $t = 30$ min.
- $t = 60$ min.
Concentrations of metabolites in rat brain (mean±SD, μmol/wet g)

<table>
<thead>
<tr>
<th></th>
<th>*GPC</th>
<th>PC</th>
<th>Cho</th>
<th>PCr/Cr</th>
<th>NAA</th>
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<tbody>
<tr>
<td>Normal</td>
<td>0.46</td>
<td>0.23</td>
<td>0.05</td>
<td>8.00</td>
<td>5.90</td>
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<tr>
<td>Control</td>
<td>+0.06</td>
<td>+0.04</td>
<td>+0.02</td>
<td>+0.91</td>
<td>+0.77</td>
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<tr>
<td>Thiamine</td>
<td>0.12</td>
<td>0.24</td>
<td>0.08</td>
<td>7.72</td>
<td>5.52</td>
</tr>
<tr>
<td>Deficiency</td>
<td>+0.03</td>
<td>+0.03</td>
<td>+0.04</td>
<td>+0.84</td>
<td>+0.89</td>
</tr>
<tr>
<td>Thiamine</td>
<td>0.25</td>
<td>0.24</td>
<td>0.06</td>
<td>7.57</td>
<td>5.33</td>
</tr>
<tr>
<td>Treatment</td>
<td>+0.06</td>
<td>+0.04</td>
<td>+0.02</td>
<td>+1.10</td>
<td>+0.64</td>
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</tbody>
</table>
Molecular Explanations for Decreased Choline-containing Compounds?

• Changes in concentrations of membrane lipid constituents (myelin abnormalities)
• Changes in concentration of acetylcholine precursor choline (partial cholinergic deafferentation)
• Changes in production of glycerophosphocholine from degradation of phosphatidylcholine by phospholipase A₂
**General Hypothesis**

*Genetic susceptibility to thiamine deficiency* may determine why some, but not all individuals develop brain (or other end-organ) damage with equivalent lifetime exposure to alcohol when other risk factors (age, gender, family history, lifetime episodes of documented malnutrition or alcohol withdrawal) are covaried.
Effects of Thiamine Deficiency on Brain Glucose Metabolism
INTER-INDIVIDUAL DIFFERENCES IN THAMINE UTILIZATION

1. Transport
2. Thiamine diphosphokinase
3. Gene expression
4. Enzyme assembly
5. Compartmental distribution
6. Anti-apoptotic function

Diagram:
- Gut, enterocyte, blood, CSF, Cl⁻, Cl⁻ pump, ADP, ATP, PDH, Mg²⁺, ThDP, Th/P, nuclear membrane, mitochondrial membrane, KGDH, activating signals, JNK pathway, anti-apoptosis.
4. Enzyme assembly

\[ 2\text{ThDP\cdotMg} + 2 \xrightarrow{4a} \text{ThDP\cdotMg} + \text{ThDP\cdotMg} \xrightarrow{4b} \text{ThDP\cdotMg} \xrightarrow{4c} \text{ThDP\cdotMg} \]

\[ \text{PDH} \xrightarrow{4} \text{PDH\cdotThDP\cdotMg} \]

\[ \text{ThDP\cdotMg} \xrightarrow{4} \text{\(\alpha\)-KGDH\cdotThDP\cdotMg} \]

\[ \text{\(\alpha\)-KGDH} \]
5. Compartamental distribution

- Th
- ADP
- ATP
- Mg²⁺
- ThTP
- ThDP
- Th/P
- ThDP • Mg
- Mg²⁺
- neuronal membrane
- mitochondrial membrane
- nuclear membrane
- Th/P
- neuronal membrane
- ThDP • Mg
- Tk
Transketolase mRNA during Thiamine Deficiency

high thiamine  high thiamine  low thiamine
+ pyrithiamine
3. Gene expression
6. Anti-apoptotic function

ThDP → mitochondrial membrane
activating signals
MEKK1
MKK4
MKK7
JNK1
cJUN
ATF-2
Elk-1
p53
DPC4
NFATc
→ anti-apoptosis
Conclusions

• Thiamine deficiency is the established cause of Wernicke-Korsakoff Syndrome
• Thiamine deficiency also contributes significantly to other forms of alcohol-induced brain injury
Conclusions

• Thiamine may initiate or facilitate recovery of brain functions with abstinence by modifying Cho-containing compounds (membrane turnover, acetylcholine, signal transduction)

• With repeated episodes of thiamine deficiency neuronal dropout may result (neuronal marker NAA)

• Genetic sensitivity to TD may predispose individuals to alcohol-induced brain injury, the pattern of brain damage, and ultimately a malignant, early-onset alcoholism
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