Preventing Dementia: The Depression-Diabetes Nexus

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Toronto Dementia Research Alliance
University of Toronto Psychiatry

- 14 Academic divisions/programs across 7 fully affiliated hospitals
- 17 endowed chairs and 2 endowed professorships
- 682 Active Faculty members, 183 full-time and 499 part-time
- 79 members hold appointments in the Institute of Medical Science.
- 155 Residents
- 60 Fellows
Mood Disorder Psychopharmacology Unit (MDPU)/ UHN

- **Lead Centre**: International Mood Disorders Collaborative Project. UHN- Cleveland Clinic (University of Texas, SA)
  - n=1250 patients

- **Lead Centre**: International Centre of Excellence in Mood Disorder Research UHN-Gulf Region (Kuwait and Saudi Arabia)
MDPU Capabilities

- Biomarkers (neuroimaging, biofluids, genetics)
- Endophenotypes
- Predictors (i.e. illness, treatment)
- Transdisciplinary intervention
MDPU-Research Mission Statement and Synergism with TDRA

- To identify avenues that cause, prevent and modify disease course in mood disorders

- To identify ultra-high risk individuals for dementing disorders and initiate primary and secondary prevention

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Major Depression Associated with Decreased Brain Volume

- 3-year prospective study comparing 38 patients with 30 healthy controls
- Significant decline in gray matter density was noted in hippocampus, amygdala, anterior cingulate cortex, and dorsomedial prefrontal cortex
- Threshold was set at $P<.001$

Frodl TS, et al. *Arch Gen Psychiatry*. 2008;65:1156–1165. Copyright © 2008 American Medical Association. All rights reserved.
Multiple Episodes/Longer Illness Duration Associated with Greater Hippocampal Volume Loss

MacQueen et al. PNAS Feb. 2003; Vol. 100 no.3:1387-1392.
Greater Decline in Gray Matter Volume in Unremitted Compared with Remitted MDD Patients

- 3-year prospective study comparing 38 patients with 30 healthy controls
- Significantly greater decline in gray matter density was noted in non-remitted versus remitted major depressive disorder patients in:
  - Hippocampus
  - Anterior cingulate cortex
  - Dorsomedial prefrontal cortex
  - Dorsolateral prefrontal cortex
- Threshold was set at $P<0.01$
Mood Disorder Episode Frequency Increases Risk for Dementia

Hazard Ratio

Number of Episodes

MDD
Bipolar Disorder

Kessing LV Anderson PKJ Neurol Neurosug Psychiatry 2004; 75:1662-1666
Major Depression Increases AD Neuropathology in the Hippocampus

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Insulin: Critical for Normal CNS Function

- Neurotrophic
- Synaptic plasticity (i.e. memory formation)
- Neurodevelopment
- Neuroprotection
- Neuromodulation (e.g. acetylcholine)
- Feeding and behavior

Insulin: A Mediator of AD Neuropathology?

Blood-brain barrier

Insulin

Pancreas

Glucose

Periphery

NMDA-R=N-methyl-D-aspartate receptor.

Insulin-Degrading Enzyme and Alzheimer’s Disease

(A) IDE has higher affinity for insulin, illustrated by binding "fit".

(B) IDE gene variations result in altered proteins or altered expression levels.

Result: variations that decrease enzyme activity.

Thus:

- Aβ and insulin
- AD and type-2 diabetes.

Aβ=amyloid β. IDE=insulin-degrading enzyme.

Greater Suppression of Neurogenesis with Concurrent Diabetes Mellitus and Depression

C: control rats injected with vehicle alone; DM: streptozotocin-induced diabetic rats without depressive-like behaviour; DM+D: streptozotocin-induced diabetic rats with depressive-like behaviour; DM+D+AG: aminoguanidine (AG, 10 mg/kg) administrated in DM+D rats for 4 weeks

*p<0.001 DM+N, DM+D vs CON value; *p<0.001 DM+N vs DM+D; *p<0.001 DM+D+AG vs DM+D value. Values are means ± SD.

Diabetes Mellitus and Dementia

- DM increases risk of both AD and VaD, regardless of age of onset
- Type 2 DM/Abnormal FBG present in up to 80% of AD
- Altered brain metabolism noted prior to cognitive deterioration
- “Type 3 Diabetes Mellitus”
Hippocampal Volume Changes in Diabetes Mellitus

MRI=magnetic resonance imaging. Hippocampal volumes (+SE) on brain MRI in participants with diabetes (n=41) and without diabetes (n=465). Volumes are adjusted for age and sex and normalized to average head size.

Diabetes Medication is Associated with less AD Neuropathology

Beeri MS et al., Neurology 71, September 2008, 750-757
The Depression-Diabetes Nexus

Mood Disorders

Diabetes Mellitus

Insulin
Insulin-Growth Factor
Pro-inflammatory Cytokines
Reactive Oxygen Species
Glucocorticoids

Preventing Dementia: The Opportunity of the TDRA

- Identifying ultra-high risk individuals (latent, prodrome)
- Biomarkers
- Multi modal probabilistic modeling
- Sample size
- Specificity
- Primary/secondary prevention

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NARSAD The Brain and Behavior Research Fund

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