Neuroscience 410- Alzheimer’s disease- Basic aspects

Dr. Jack H. Jhamandas
Division of Neurology
Department of Medicine
University of Alberta
Edmonton, Alberta, Canada
Definition: global deterioration of intellectual and cognitive function in the face of unimpaired consciousness.

- Differentiate from delirium, mental retardation and amnesic syndromes.
Alois Alzheimer 1864-1915
CLINICAL FEATURES

**Symptoms**: impairment of memory & attention, language & communication, abstract thinking, judgement, personality changes, depression, and visuo-spatial disorientation.

**Signs**: motor and gait disturbance, extrapyramidal signs, sphincters, seizures
ALZHEIMER'S DISEASE (AD): FACTS

- Most common cause (70-80%) of Dementia.
- 7-9% of Canadian population over 65 have AD*. 35.5% of population over 85 have AD*.
- 4.5 million people in US and Canada have AD. By 2050 14 million.
- 40% of total health care cost associated with neurological diseases (billions of $).

* The Canadian Study of Health and Aging, 1994
EMERGING HORIZONS IN ALZHEIMER'S RESEARCH

- Neurotransmitter Function and Deficits
- Genetics of Alzheimer's Disease
- Molecular Neuropathology
GENETICS OF ALZHEIMER’S DISEASE

Familial Form: 15% of Cases Worldwide

- Chromosome 1
  - Presenilin 2 (only a few families)
- Chromosome 14
  - Presenilin 1 gene (~2-3% of all cases)
- Chromosome 19
  - Apolipoprotein E (>50% of all cases)
- Chromosome 21
  - Amyloid Precursor (only a few families)
GENETICS OF ALZHEIMER’S DISEASE

Susceptibility Genes

- **For Early onset AD:**
  - APP gene
  - Presenilins 1 and 2 gene

- **For Late onset AD:**
  - ApoE4 gene
  - SORL1 gene (*Nature Genetics*-see handout)
Presenilin mutations that cause AD

STM2

S182

cytoplasm

N

C
Presenilin 1 and 2 (PS1 and PS2)

- Integral membrane protein that contains 8 transmembrane domains
- Double KO of the PS1 gene results in perinatal protein
- KO mice reveal decreased Aβ1–40 and Aβ1-42 production
- Implicated as the enzyme responsible for γ-secretase cleavage of APP
From Nussbaum and Ellis, (2003), NEJM 348;14
GENETICS OF ALZHEIMER’S DISEASE

Sporadic Form (so-called common form)
85% of all Cases Worldwide

- Chromosome 19
  Apolipoprotein E gene (50 – 60%)
- Chromosome 14
  Presenilin 1 gene (~ 25%)
- Chromosome 3
  Butyrylcholinesterase K (25%)

(Confirmed in Montreal)
Cholinergic Function and AD

- Cholinergic basal forebrain (CFB) nuclei project to the hippocampus and limbic areas
- Lesions in the CBF have been shown to impair learning and memory
- Degeneration of CBF neurons has been shown to be an important pathophysiological process in Alzheimer’s disease (for review see Yankner, 1996)
Site of action of Cholinergic drugs

Precursors

Ac CoA + choline

Increase release

Ach

M₂

Selective M₁ agonists

M₁(+)

AchE

Cholinesterase inhibitors

Choline + acetate

Image modified from Gauthier (1996)
NEUROPATHOLOGICAL FEATURES OF AD

- Cortical atrophy especially of the temporal and parietal cortices with widened sulci and thinning of gyri
- Neurofibrillary tangles (NFTs)- paired helical filaments composed of hyperphosphorylated microtubule-associated *tau* protein
- Senile (amyloid) plaques
- Granulovacuolar degeneration- hippocampal pyramidal neurons ; Hirano bodies
STRUCTURE AND PROCESSING OF APP

**Extracellular**
- Kunitz protease inhibitor domain

**Cytoplasmic**
- Membrane

**APP (695-770)**
- α-secretase
- β-secretase
- γ-secretase

- Alternative Processing ($\beta + \gamma$-secretases)
- CT fragment

**sAPP**
- Ion channel modulation
- Neuroprotection
- Neuroplasticity

**Aggregated Aβ**
- Ion channel modulation
- Neurotoxicity
- Abnormal outgrowth

**Neurotoxicity?**
AMYLOID PEPTIDES

General Observations

- Amyloid peptide identified in plasma and CSF of normal individuals. Physiological function?
- Longer isoforms more fibrillar and aggregate readily. \( A\beta_{25-35} \) is a neurotoxic fragment.
- Single injection of \( A\beta \) into the basal forebrain causes memory and learning deficits.
- Basal forebrain neurotoxicity is specific to cholinergic neurons. GABA cells are resistant.
113-pS K⁺ channel

166-pS K⁺ channel

YC

AC

AD

β-Amyloid
Soluble Aβ
Age-related factors
APP and S182 Mutations

Aβ fibrils

Membrane Damage
Receptor Binding
Membrane Pore

↑ Free Radicals
Altered Signal Transduction
↑ Ca²⁺
Apoptosis
Tau Phosphorylation

Intracellular
Glutamate is the major excitatory neurotransmitter in the Brain.

Acts via a combination of pre- and postsynaptic receptors (NMDA, AMPA, mGluR).

Excessive glutamate release can cause dysfunction and cell death of CNS neurons (Excitotoxic hypothesis)
Transmitter interactions and neurodegeneration

- GABA
- Ach
- Glutamate

[Ca\(^{2+}\)]\(_i\)

Survival Plasticity

Degeneration Death
APOLIPOPROTEIN E FUNCTIONS IN THE CNS

- Transport of Cholesterol, Phospholipids, Fatty acids and Anti-Oxidant Vitamins in Serum and CSF
- Implicated in Synaptic Remodelling and Regeneration
- Interacts with Amyloid Metabolism
- Interacts with Cytoskeleton Structural Proteins
APOLIPOPROTEIN E4: DIRECT IMPACT ON THE BIOLOGY OF THE DISEASE

Number of Copies of E4 affects:

- Risk of Developing the Disease
- Age of onset
- Accumulation of Brain Markers of AD
  - Amyloid Plaque Load
  - Neurofibrillary Tangles Load
- Neuronal Cell Number (density) in the Hippocampus:
  - Memory and Learning
CORTICAL CHOLINERGIC DYSFUNCTION

CHOLINERGIC LESION

CORTICAL CHOLINERGIC DYSFUNCTION

CHOLINOMIMETIC DRUG RESPONSE

APOE4 POSITIVE
worst response to ChEI

APOE4 NEGATIVE
best response to ChEI

APOLIPOPROTEIN 4
OTHER FACTORS (?)
APOE3 reduces BETA-A4 aggregation.

APOE2 reduces BETA-A4 deposition.

PRS1 promotes clearance-degradation of BETA-A4.

APOE4 promotes BETA-A4 formation.
Are there target receptors for Aβ in the brain?

If so, can they be used as therapeutic targets in AD?
A Major Issue

No “receptors” for Aβ but several candidate receptors for expression of its effects.
Amylin receptor

Nicotinic receptors
$\alpha_7/\alpha_4\beta_2$

$\beta$
Aβ and nicotinic receptors (nAChRs)

- Aβ found to bind to nAChRs ($\alpha_7$ and $\alpha_4\beta_2$) subtypes with affinity in picomolar and nanomolar concentrations.

- Controversy from other (electrophysiological expression) studies – some indicate interactions with the $\alpha_7$ moiety while others support interaction with $\alpha_4$ nAChRs.

- Also unresolved are issues of whether Aβ is an antagonist or an agonist at these nAChRs.
Presenilins

Nicastrin

γ-secretase

APP

β-secretase

Aβ

Notch
Misshapen Tau Secretases snipping Aβ from a larger molecule

Immune-system cells attack

APOE Tangle

Microtubules

Tangle

Plaque

Immune-system cells attack

Misshapen Tau
TREATMENT OF ALZHEIMER DISEASE
WHICH WAY TO GO?

TWO WAYS TO GO:
- ACETYLCHOLINE
  - ChE-inhibitors
  - Muscarinics or Nicotinics
  - Bifunctionals
  - Combinations
- Estrogens
- Anti-oxidants
- Free-radical scavengers
- Anti-inflammatories

THE THIRD WAY
- BETA-AMYLOID
  - APP-releasers
  - Beta-Amyloid processors
  - Anti-aggregation agents
HARRY POTTER
How good is this one?

THE NEW SCIENCE OF ALZHEIMER'S

- The drugs
- The genetics
- The latest theories
- What you can do now

Brain of Alzheimer's Sufferer
Normal Brain