Neurochemistry of Dementia

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Organisation of the Brain – Cellular Building Blocks

- Brain cells comprise neurones and glial cells
  - Neurones: basic signalling units distinguished by form, function and structure
  - Glia: three categories *astrocytes*, *oligodendrocytes*, *microglia*
Neurone Structure
Neuronal Communication

- Neurones activated at synapse by chemical or physical activation
- Results in change in membrane potential and electrical signal
  - Current flow mediated by electrically charged ions (e.g. Na$^{2+}$, Cl$, K^+$
  - Signals sent if action potential threshold reached
  - Results in signal reaching axon terminal and neurotransmitter release
Neuronal Communication

- Action potential must be reached
  - Results in depolarisation at axon terminal
  - Influx of Ca$^{2+}$
  - Vesicles fuse with membrane
- Neurotransmitter released into synaptic cleft
- Reaches postsynaptic membrane and binds with receptor
  - Results in depolarisation or hyperpolarisation of postsynaptic cell
- Neurotransmitters activate *one or more* types of receptors.
  - Effect on the postsynaptic cell depends on the properties of those receptors
# Neurotransmitter Types

<table>
<thead>
<tr>
<th>Class</th>
<th>Neurotransmitter</th>
<th>Function</th>
<th>Malfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acids</td>
<td>Glutamate</td>
<td>Excitatory neurotransmitters (or facilitate action at excitatory synapses)</td>
<td>Over stimulation of brain (e.g. excitotoxicity, seizures)</td>
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<tr>
<td></td>
<td>Aspartate</td>
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<tr>
<td></td>
<td>Glycine</td>
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<td></td>
<td>D-serine</td>
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<td></td>
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<tr>
<td></td>
<td>GABA</td>
<td>Main inhibitory neurotransmitter</td>
<td>Undersupply in e.g. seizures, tremor, insomnia</td>
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<tr>
<td>Biogenic amines</td>
<td>Dopamine</td>
<td>Movement, attention, emotion</td>
<td>Excess – schizophrenia</td>
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<td></td>
<td>Serotonin</td>
<td>Mood, hunger, arousal</td>
<td>Depression, anxiety</td>
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<td></td>
<td>Noradrenaline</td>
<td>Alertness, arousal</td>
<td>Depression, apathy</td>
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<tr>
<td></td>
<td>Adrenaline</td>
<td></td>
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<tr>
<td></td>
<td>Histamine</td>
<td>Sleep modulation, sexual function</td>
<td>Impotence, lack of vigilance</td>
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<td>Peptides (over 50)</td>
<td>Somatostatin</td>
<td>Cognitive function</td>
<td>Memory loss?</td>
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<td>Substance P</td>
<td>Regulation of glutamate function</td>
<td>Mood disorders, anxiety</td>
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<tr>
<td></td>
<td>β endorphin</td>
<td>Pain, pleasure</td>
<td>Addiction (inappropriate pleasure)</td>
</tr>
<tr>
<td>Others (e.g.)</td>
<td>Acetylcholine</td>
<td>Muscle action, cognition, learning and memory</td>
<td>Alzheimer’s disease</td>
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<tr>
<td></td>
<td>Adenosine</td>
<td>Inhibition of excitatory action</td>
<td>Seizure?</td>
</tr>
<tr>
<td></td>
<td>Nitric oxide</td>
<td>Vasorelaxant agent</td>
<td>Oxidative stress</td>
</tr>
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</table>
Receptor Types – Ionotropic

• Contains both a ligand binding site and an ion channel
  – normally closed but opens in response to binding of the ligand (i.e. neurotransmitter)
  – e.g. ACh receptor also responds to nicotine, thus called the ‘nicotinic’ acetylcholine receptor - nAChR

[Diagram showing ion flow and neurotransmitter]
Receptor Types – Metabotropic

- Acts through secondary messenger
- Indirectly linked with ion channels on the plasma membrane of the cell through signal transduction mechanisms
  - Often G-protein-linked
- Much longer-lasting (seconds-minutes) effect than ionotropic receptors
Agonist and Antagonists

- If it facilitates a response, it's an agonist
- If it causes a response that is relatively smaller than the response to another agonist, it's a partial agonist
- If it inhibits the response caused by an agonist, it's an antagonist
- If it binds to the same receptor as an agonist but results in an opposite pharmacological effect it’s an inverse agonist

Effects of GABA receptor agents

- Agonist
  - ↓Anxiety
  - ↑Sleep
  - ↑Muscle relaxation
  - Anticonvulsant

- Antagonist
  - No effect (e.g. use in benzo overdose)

- Inverse agonist
  - ↑Anxiety
  - Convulsant

- Diazepam
  - Clonazepam
  - Alprazolam

- Flumazenil
  - Experimental drugs only
Neurotransmitter Systems in the Brain
Cholinergic System – Terminals

Synthesising enzyme choline acetyltransferase (ChAT)

Acetylcholine released from synaptic vesicles in response to depolarisation

Acetylcholine interacts with receptors (muscarinic and nicotinic) on the pre and postsynaptic membrane

Acetylcholine in the synaptic cleft is removed by degrading enzyme acetylcholinesterase (AChE)
Cholinergic System – Nuclei

- The nucleus basalis of Meynert projects to neocortex
- Brainstem pedunculopontine and laterodorsal tegmental nuclei neurones project to thalamus
- Cholinergic cells in the medial septum/diagonal band project to hippocampus and entorhinal cortex
- Cholinergic interneurones unique to the striatum
Nicotinic Receptors (nAChR)

- Ligand-gated ion channel receptors (ionotropic)
  - 11 different subunits (α2–9 and β2–4)
  - Ca$^{2+}$, Na$^+$
  - Rapid signalling
  - Local changes
- Presynaptic activation of nAChRs – transmitter release of several different neuronal types (heteroreceptors)
Muscarinic Receptors

- Five subtypes $M_1$–$M_5$
  - $M_1$, $M_3$, $M_5$ stimulate
  - $M_2$, $M_4$ inhibit
- All *metabotropic* (G-protein coupled receptors)
Dopaminergic System – Terminals

- Tyrosine converted to L-dopa by tyrosine hydroxylase
- L-dopa decarboxylated to dopamine by dopa decarboxylase
- Dopamine oxidised to noradrenaline by dopamine beta hydroxylase
- Catabolism of dopamine:
  - Monoamine oxidase (MAO)
  - Catechol O-methyltransferase (COMT)
Dopaminergic System – Nuclei

- Nigrostriatal
- Mesolimbic
- Mesocortical
- Dopamine pathways

Diagram showing the brain with labels for the cortex, striatum, thalamus, and other relevant structures.
Dopamine Receptors

- Five subtypes ($D_1 – D_5$)
  - ALL metabotropic ($G$-protein-linked)
  - $D_1$ and $D_5$ stimulatory
  - $D_2$, $D_3$ and $D_4$ inhibitory
- Variable distribution
  - $D_1$ and $D_2$ receptors – striatum, thalamus, cortex
  - $D_3$ – nucleus accumbens, ventral pallidum, limbic thalamus (not cortex)
  - $D_4$ – low density in human
    - high affinity for clozapine, & links to ADHD, receptor protein
  - $D_5$ – low density in human
    - cholinergic neurons, sub-thalamic nucleus

Hall et al, 2002
Noradrenergic System

- Converted from dopamine by dopamine β-hydroxylase
- Multiple α- and β-adrenergic receptors
  - all metabotropic G-protein-linked
- Degraded by COMT methylation or MAO deamination
Noradrenergic System – Nuclei

- Thalamus
- Locus coeruleus
- Hippocampus/Amygdala
- Temporal cortex
- Parietal cortex
- Occipital cortex
- Cerebellum
- Frontal cortex
Serotonergic (5-HT) System

- L-tryptophan converted to 5-hydroxytryptophan by the enzyme L-tryptophan hydroxylase (TPH)
- 5-hydroxytryptophan converted to 5-hydroxytryptamine by enzyme aromatic-L-amino-acid decarboxylase
- Metabolism by monoamine oxidase A>B
  - Early antidepressant target (e.g. moclobemide, selegiline)
Sero tonergic System – Nuclei
Glutamate and GABA

- Glutamate and GABA (γ-amino butyric acid) form basis of neurotransmission
  - Primary drivers behind neuronal function influenced by neuromodulator receptor activation in the cortex
  - Cortical excitability reflects a balance between excitation and inhibition

- GABA formed from the alpha-decarboxylation of glutamate
  - Glutamic acid decarboxylase (GAD)
  - Recycled by citric acid cycle
Glutamate and GABA Neurones

• Glutamate neurones
  – ALL projection neurones
  – cortico-cortical
  – thalamo-cortical
  – cortical-subcortical (corticofugal)

• GABA neurones
  – interneurones in cortex
  – can be interneurones or projection neurones in subcortical areas (e.g. striatal projection neurones)
Glutamate Receptors

- Multiple glutamate receptor subtypes, subunits and splice variants
  - NMDA glutamate receptor
    - Ionotropic
    - Ca$^{2+}$/Na$^+$ in, K$^+$ out
    - Voltage-dependent Mg$^{2+}$ block
    - Long term potentiation (LTP), learning and memory
  - AMPA/kainate receptor
    - Ionotropic
    - Na$^+$ channel
  - MGluRs
    - Metabotropic (G-protein-linked)
    - Group I – increase NMDA receptor activity
    - Group II – decrease NMDA receptor activity
Glutamate: Pathology

- Glutamate has role in cognition (LTP) at normal concentrations
  - Disordered glutamate signalling affects learning and memory
- Excess glutamate leads to excitotoxic cell death (Ca$^{2+}$)
- Alzheimer’s disease and depression – disorder in glutamate/GABA interplay implicated
- Glutamatergic pyramidal neurones in entorhinal cortex and hippocampus are particularly vulnerable to tangle formation and cell loss
GABA Receptors

- **GABA\textsubscript{A}** - chloride ion channel, post-synaptic
  - Different combinations of subunits have different pharmacology and cellular and regional distributions
  - Diverse pharmacological properties of GABA\textsubscript{A} drugs

- **GABA\textsubscript{B}** - metabotropic G-protein coupled receptor (GPCR)
Dementia

• Definition:
  – acquired losses of cognitive and emotional abilities severe enough to interfere with daily functioning and quality of life

• Prevalence
  – 815,827 people with dementia in the UK
  – 1,142,677 by 2025 and 2,092,945 by 2051 (Alzheimer’s Society, 2014)
Common causes of Dementia

- Alzheimer’s disease
- Lewy body disease
- Vascular dementia
- Frontotemporal dementia
- Others
  - Huntingdon’s disease
  - AIDS
  - Alcohol-related
Alzheimer’s Disease - Pathology

- First described by Alois Alzheimer in 1906
  - ‘Auguste D.’ patient with profound memory loss, unfounded suspicions about her family, and other worsening psychological changes. In her brain at autopsy, he saw dramatic shrinkage and abnormal deposits in and around nerve cells.
- Pathologically defined by extracellular *plaques* of insoluble deposits of beta-amyloid peptide and intracellular *tangles* of aggregates of the microtubule-associated protein tau
- Neurofibrillary tangles and neuritic plaques: transentorhinal region of the temporal lobe > lateral to the hippocampus > entorhinal cortex > hippocampus > association neocortex (Braak and Braak, and Thal staging systems)
Alzheimer’s Disease – Clinical Features

• Global *cognitive* and *memory* impairment plus
  – Impaired language (aphasia)
  – Impaired movement (apraxia)
  – Impaired recognition (agnosia)
  – Disturbed executive functioning
  – Additional non-cognitive features (e.g. anxiety, depression, psychosis)
Alzheimer’s Disease – Neurochemistry

- Drug treatment largely based around ‘cholinergic hypothesis’
- Substantial neocortical deficits in choline acetyltransferase (ChAT)
- Reduced choline uptake, ACh release
- Loss of cholinergic perikarya from the nucleus basalis of Meynert
Cholinergic Changes in AD

<table>
<thead>
<tr>
<th>Marker</th>
<th>% loss</th>
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<tbody>
<tr>
<td>ChAT activity</td>
<td>35‒50</td>
</tr>
<tr>
<td>Choline uptake</td>
<td>60</td>
</tr>
<tr>
<td>AChE activity</td>
<td>40‒60</td>
</tr>
<tr>
<td>Nicotinic binding</td>
<td>30‒70</td>
</tr>
</tbody>
</table>
Lewy Body Diseases – Pathology

- Lewy bodies neuronal inclusions composed of abnormally phosphorylated α-synuclein aggregates
- Extensive depletion of acetylcholine in neocortical areas as a result of degeneration in the brain-stem and basal forebrain cholinergic projection neurones
- In Lewy body dementias, significant Lewy body formation also in paralimbic and neocortical structures
Lewy Body Diseases – Clinical Features

Dementia with Lewy Bodies

• Progressive cognitive decline, plus two out of three core features
  – Cognitive fluctuation of with variation in attention and alertness
  – Recurrent visual hallucinations
  – Spontaneous features of parkinsonism
• Other cognitive and non-cognitive symptoms
  – REM sleep behaviour disorder
  – Neuroleptic sensitivity
  – Low DaTSCAN dopamine receptor binding
  – Falls and syncope
  – Transient loss of consciousness
  – Severe autonomic dysfunction

Parkinson’s Disease with Dementia

• Very similar clinically and pathologically to DLB
• Movement disorder before dementia by > one year  ➔ PDD
• Movement disorder within one year of dementia, or later, or not at all  ➔ DLB
• Begins with levodopa-responsive parkinsonism
• Some dopaminergic and cholinergic receptor differences
  – Compensatory changes in PD (especially D2 up-regulation in PD)
Cholinergic Changes in Lewy Body Diseases

- More extensive cholinergic loss than AD
  - Cortex and brainstem rather than hippocampus
  - *In vivo* PET – loss of cortical acetylcholinesterase in DLB exceeds AD
  - Cortical ChAT loss greater than in AD
  - Striatal ChAT loss
- Reduced striatal M1 receptors
- Cortical $\alpha_4\beta_2$ nicotinic receptors reduced as in AD, but much more reduced in striatum
Clinical Consequences of Cholinergic Losses – Anatomical Correlates

- **Hippocampus** – memory
- **Hippocampus, cortex** – memory, learning
- **Cortex, thalamus** – Attention
- **Brainstem, thalamus, cortex** – Consciousness, sleep, and dreaming, hallucinations
- **Striatum, brainstem, thalamus** – movement, balance and motor regulation
- **Cortex, thalamus** – visual function
Dopamine in Dementia
Decreased dopamine concentration and transporters in DLB/PDD

- Dopamine concentration and dopamine transporters are reduced in DLB, almost to the same extent as in Parkinson’s disease
- Significant loss in striatal dopamine transporter binding

Piggott and Perry
Serotonin in Dementia

• Neurone loss & tangles in raphe - reduced 5HT in AD
• 5-HT$_{2A}$ receptors more reduced in severe dementia
• 5-HT receptor polymorphisms linked to aggression, psychosis, depression, anxiety
Noradrenaline in Dementia

- Extensive neuron loss in locus coeruleus
- Reductions in noradrenaline levels
- Increased turnover in surviving neurons linked to upregulation of the noradrenaline transporter
- In PD, noradrenaline loss linked to progression to PDD
- Noradrenaline changes may be related to aggression, psychosis, depression
Glutamate in Dementia

- Reduced NMDA binding and NMDAR$_1$ mRNA expression in AD
- Cortical pyramidal neurone loss leads to reduced glutamate activity and cognitive impairment in AD
Glutamate in Dementia

- In AD, reduced membrane potential (due to pathology, reduced energy metabolism) → release of voltage dependent Mg\(^{2+}\) block of NMDA → and excessive, neurotoxic entry of Ca\(^{2+}\)

- Memantine efficacy in moderate-severe AD (with heavier pathology)
  - uncompetitive, low-affinity, open-channel blocker
  - limits excessive glutamate
  - also a D\(_2\) agonist, 5HT\(_3\) antagonist
Conclusions

- Can cholinergic (and dopaminergic) mechanisms explain all cognitive and neuropsychiatric symptoms in dementia?
- Not quite! Glutamate, serotonin and noradrenaline also important
  - other influences need elucidation
PLEASE CONTACT US IF YOU WOULD LIKE TO FIND OUT MORE

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Campus for Ageing and Vitality
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Further Reading

THE OXFORD TEXTBOOK OF OLD AGE PSYCHIATRY
(Psychiatry in the Elderly 4th edition)
Chapter 6
Neurochemical pathology of neurodegenerative disorders of old age
Piggott MA and Court JA (2008)

Parkinson’s Disease Dementia, edited by Professor Murat Emre
Chapter 13 - Neurochemistry of Parkinson’s disease dementia
Piggott MA and Perry EK (2010)

Early-Onset Dementia, edited by Professor John R Hodges
Chapter 9 – Neurochemical pathology in degenerative dementias
Elaine Perry, Rose Goodchild and Margaret Piggott (2001)