Systems pharmacology

CNS pharmacology

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Introduction

• Challenging problem

• Most administered without prescription

• CNS is the most complicated system in the body - structure & function provides a means to modify CNS function (inhibition/excitation)

• Many drugs act within the CNS

• Special significance, therapeutic importance
We will Cover:

- Anti-depressants
- Anxiolytics and hypnotics
- Anti-psychotics (neuroleptics)

Special focus on:

- Cannabinoid pharmacology
Review: Central neurotransmitters

**Biogenic amines:** dopamine, nor-adrenaline, adrenaline, serotonin, histamine

**Acetylcholine:** mainly excitatory (e) in CNS vs., inhibitory (i) effects in the PNS

**Amino acids:** GABA (i), glycine (i), glutamate (e), aspartate (e)

**Neuropeptides:** vasopressin, oxytocin, endorphins, enkephalines

**Purine nucleotides:** adenosine, ATP

**Neurolipids:** anandamide, 2-arachidonoyl glycerol, ceramide
Anti-depressants - heterogenous disorder  
- 10% life time risk

Symptoms

- Impaired concentration
- Inability to experience pleasure
- Increased fatigue
- Missed deadlines or drop in standards
- Significant change in personality/behaviour
- Increased alcohol/drug use
- Thoughts of suicide
3 Major Types of Depression
- Diagnostic & Statistical manual of Mental Disorders (DSM-IV)
- Based on the cause/origin (simplified)

**Reactive or Secondary (~60%)**
Related to some “loss”, physical illness (MI, Cancer), Drugs, Other psychiatric disorders (senility)

**Major or Endogenous (~25%)**
No clear/adequate precipitating event, re-current, inability to exp. ordinary pleasure/cope with everyday life

**Bipolar affective/ manic-depression (10-15%)**
Episodes of mania associated with depression
Depression alone - occasional; Mania alone - rare
Depression - Causes

Most focus on neurochemical processes

- abnormal amounts of NTs
- decreased post-synaptic sensitivity

NB serotonin, nor-adrenaline and dopamine
- all effected by anti-depressants

Anti-depressants therapeutic effect:
increasing NT levels
or
decreasing re-uptake
The Amine Hypothesis - provides pharmacological evidence for a bio-genic disorder

- 1950’s - Reserpine
  - Alkaloid from root of Indian snake root plant (*Rauwolfia serpentina*). Primitive Hindu medicine for hypertension, insomnia & insanity.
  - Investigated for hypertension (still available)
  - Found to interact with storage vesicles & deplete NA & 5-HT in CNS & PNS
  - Induced severe depression
  - Suicide was common with early use of high dose
Single biologic abnormality is not supported

Underlying role for several brain circuits with the potential for dysfunction

Amine hypothesis has provided experimental models used for the discovery of new antidepressant drugs.
Anti-depressant drugs

1. **Tricyclic antidepressants**
   - desipramine (Nor-pramin), imipramine (Tofranil), nor-triptyline (Pamelor), pro-triptyline (Vivactil)

2. **Selective serotonin reuptake inhibitors**
   - citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline, (Zoloft)

3. **Monoamine oxidase inhibitors**
   - phenelzine (Nardil), isocarboxazid (Marplan)
TCAs

- Imipramine investigated for schizophrenia
  - Found to be ineffective antipsychotic
  - But elevated mood in depressed patients
  - Sedative effects in non-depressed patients

- **Conclusion**: Imipramine *selectively* reverses depression (*vs*, producing a general activating effect)
Mechanism of action

inhibits the reuptake of NA & 5-HT by blocking their membrane transporters
Side Effects

- anti-muscarinic: dry mouth, constipation, urinary retention, aggravation of glaucoma
- anti-histamine: sedation (tolerance can develop)
- Na channel block: arrhythmias
- alpha-1 blockade: orthostatic hypotension, tachycardia, erectile dysfunction

Now used for severe depression refractory to other treatments (e.g. SSRIs)
Selective serotonin reuptake inhibitors (SSRIs)

- 2nd generation anti-depressants
- First line therapy
- Also used to manage other disorders (panic, OCD)
- Inhibit the re-uptake of serotonin (indefinitely)
Side Effects: SSRIs

- Fewer side effects vs. TCAs (better tolerated), lack anti-cholinergic effects, no cardiac effects, no postural hypotension
- Safer than TCAs (less potential for overdose)
- Equally effective as TCAs in depression, effect reached in 3-4 weeks
MONOAMINE OXIDASE (MAO)

Enzyme present on:

1. **Mitochondria**
   Inactivation of endogenous and ingested amines (oxidative de-amination)
   Food and endogenous sources

2. **Synaptic cleft**
   Regulates free intraneuronal [ ] of NA, A, D and 5-HT

2 subtypes MAO-A (NTs) & MAO-B (dietry amines)
MONOAMINE OXIDASE INHIBITORS (MAOI)

Form an irreversible complex with MAO

• Increase 5-HT, NA, dopamine content of brain

• “cheese reaction” – due to exogenous tyramine (hypertensive crisis due to release of endogenous amines)
  
  tyramine free diet

* MAO-B not targetted
Anxiolytic and hypnotic drugs

ANXIETY:
- Verbal complaint
- Somatic and autonomic symptoms ( anticipatory)
  restless, tachycardia, sweating
- pathological state of anxiety not clear

DRUG GROUPS:
1. Benzodiazepines (valium, anxiolytic and hypnotic)
2. Barbiturates
Pharmacological effects

- Reduction in anxiety and aggression
- Sedation and induction of sleep
- Reduced muscle tone and coordination
- Anticonvulsant
**GABA_A receptor**
- Bezodiazepines (Bz/BDZ) act specifically
- enhance response to GABA
- allosteric binding site $\uparrow$ receptor affinity for GABA

Enhanced excitatory transmission
Adverse effects Benzodiazepine

• Overdose risk low
• Drowsiness, confusion, impaired co-ordination
• Dependence
• Treatment withdrawal
  – increased anxiety
  – Tremor
  – nervousness
Barbiturate

- Overdose risk high

- Tolerance
  - pharmacokinetic (upregulation of liver enzymes)
  - tissue tolerance (downregulation of receptors)
Anti-psychotic (neuroleptic) drugs

Drugs used to manage psychosis

Psychosis definition:
  impaired capacity to - recognise reality
    - communicate
    - relate to others
    - deal with ordinary life

Psychosis is associated with schizophrenia

  - disturbances in multiple psychological processes
Schizophrenia

• It is a disease that affects 1% of the world’s population (1/100)

• It is a disease that affects men and women equally

• It is a disease of the brain (disturbed thinking)

• Has a genetic component

• Exact pathogenesis is unknown

• It is now recognised as a biological illness
Symptoms

Excesses, exaggerations or distortions

- Unchanging facial expression (flattening)
- Disorganized thinking/speech
- Inappropriate affect (emotion)
- Hallucinations
  sensory experiences without external stimulation
  commonly auditory
- Delusions
  beliefs that are contrary to reality
  commonly persecutory in nature
  sometimes delusions of grandeur
Subtypes

- **Paranoid** — delusions, hallucinations, anxiety (present)
  - disorganised thought/behavior & flattening (absent)

- **Disorganised** — thought disorder & flattening (both present)

- **Catatonic** — disturbed movement (immobile/agitated)

- **Undifferentiated** - symptoms of > 1 type of schizophrenia

- **Residual** – some of the symptoms above, not many/all
Causes of Schizophrenia

1. Familial incidence

2. Anatomical changes
   - ventricular enlargement
   - underdevelopment of neurons in parahippocampal region
   - abnormalities cause circuitry abnormalities

3. **Dopamine hypothesis** - dopamine hyperactivity
   - receptor hypersensitivity

4. Drugs/Environmental- cannabis induced psychosis
Dopamine Hypothesis

• Increased dopamine receptors & metabolites in brains of schizophrenics

• Drugs that increase dopaminergic activity aggravate schizophrenia

• Effective anti-psychotic drugs block dopamine receptors in CNS

• BUT! Only partially effective in many patients
Side effects of neuroleptics

**Autonomic nervous system:**

Dry mouth, constipation, difficulty urinating - block mAch receptors
Orthostatic hypotension, failure to ejaculate - block $\alpha$-AR

**CNS:**

Parkinson’s syndrome - block DA receptors in substantia nigra
Toxic confusional state - muscarinic block

**Endocrine system:**

Amenorrhea-galactorrhea, infertility - DA block resulting in hyperprolacinemia
Therapeutic sites of action
Dopamine receptor Antagonists

Chlorpromazine (Thorazine)

- Derivative of phenothiazine (anti-emetic)
- Very sedating at first but tolerance builds
- Some anti cholinergic activity (dry mouth, blurred vision)
- Actively metabolized (Half life of 30hrs)

**Side effects:** Tardive Dyskinesia
Haloperidol (Haldol)

Potent dopamine antagonist
Uses - non drug-compliant patients
- acute psychotic episodes

Long time in the body 3 week half life.
Only 60% excreted in the first week.

Side effects: dry mouth, dystonia, sedation, depression, tardive Dyskinesia
Clozapine (Clozaril)

Active at DA and 5-HT receptors

Treats positive and negative symptoms

Half Life of 12 hrs

Limited to treatment resistant patients

Strong risk of seizures

**Side effects:** Anticholinergic, adrenolytic, antihistaminic and antiserotonergic activity.
Cannabinoids
& CNS Function
CANNABIS HISTORY

In use since 2,800 BC

Knowledge in Europe

First ban in Europe
CANNABIS HISTORY

First scientific research

Medicinal use
Cannabis sativa is **STILL** a plant of medicinal and economic value

Most used recreational drug prevalent in young males (NACD, 2004)

$\Delta^9$-Tetrahydrocannabinol ($\Delta^9$- THC)
main psychoactive component

Psychoactive effects are mediated through the CB$_1$ receptor
G protein-coupled
THC can be obtained from:

a) Leaves
b) Stem
c) Resin from flower head
THE CANNABIS HIGH

Δ⁹-Tetrahydrocannabinol (Δ⁹-THC)

Cannabis Vapour

Vapour

Heart/Brain

Alveoli enlarged
THE CANNABIS HIGH

* THC is highly lipophilic
* THC half-life is 7 days
* THC metabolised in liver (11-OH-THC) **psychoactive metabolite
Numerous preparations of cannabis

<table>
<thead>
<tr>
<th>Preparation type</th>
<th>Source</th>
<th>Approx. $\Delta^9$-THC content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis (herbal)</td>
<td>Cigarette of dried leaves/flowers etc., from plants cultivated in the 1960s and 1970s</td>
<td>1 - 3% $\Delta^9$-THC (10 mg/cigarette)</td>
</tr>
<tr>
<td></td>
<td>Modern cannabis cigarette using more potent material or plant strains (sinsemilla, skunk, white widow et al.)</td>
<td>6 - 20% $\Delta^9$-THC (60 - 150 mg/cigarette)</td>
</tr>
<tr>
<td>Cannabis resin (Hashish)</td>
<td>Resin secreted in the flower heads</td>
<td>10 - 20% $\Delta^9$-THC</td>
</tr>
<tr>
<td>Hashish oil</td>
<td>Product of extraction by organic solvents</td>
<td>15 - 30% $\Delta^9$-THC (sometimes up to 65%)</td>
</tr>
</tbody>
</table>

$\Delta^9$-THC concentrations in different preparations

Adapted from Ashton, 1999.
Behavioural effects

* Euphoria followed by sedation

* Altered time perception

* Dissociations of ideas

* Impaired cognitive performance
  
  - Slow reaction time
  - Motor disturbances
  - Short-term memory deficits
CANNABIS USE TODAY

Table 2.2.2  Lifetime, last-year and last-month prevalence of cannabis in Ireland, 2002/2003

<table>
<thead>
<tr>
<th>Ever used cannabis</th>
<th>Adults</th>
<th>Males 15-64 yrs</th>
<th>Female 15-64 yrs</th>
<th>Young adults 15-34 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Lifetime</td>
<td>17.4</td>
<td>22.4</td>
<td>12.3</td>
<td>24</td>
</tr>
<tr>
<td>Last year</td>
<td>5</td>
<td>7.2</td>
<td>2.9</td>
<td>8.6</td>
</tr>
<tr>
<td>Last month</td>
<td>2.6</td>
<td>3.4</td>
<td>1.7</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Adapted from: National Advisory Committee on Drugs and Drug and Alcohol Information and Research Unit, 2005.

* Tolerance with moderate cannabis doses

* Dependence?
The cannabis plant contains a family of approximately 60 related compounds, which are termed "cannabinoids".

Cannabidiol, (CBD)  
Cannabinol, (CBN)

No psychoactivity
Cannabinoid receptors - CBRs

* The psychoactive effects of $\Delta^9$-THC were believed to be as a consequence of its interaction with the plasma membrane

![Diagram showing passive diffusion and membrane disturbance]
Cannabinoid receptors

7 transmembrane domains

CB₁ – CB₂ homology
- 68% sequence homology in transmembrane
- 44% throughout entire protein
CB1R is one of the most abundantly expressed neuronal receptors
   a) Cerebellum
   b) Hippocampus
   c) Cortex

CB₁ expression in periphery
Cannabinoid receptors

- $G_i \& G_o$
- inhibit voltage-dependent Na$^+$ channels
- inhibition of adenylyl cyclase
- inhibition of Ca channels
- activation of K channels
- activation of MAP kinases (context dep.)
- expression consistent with psy. Effects
- pre-synaptic localisation (axon terminals)
- Neurotransmission
  (inhibits cholinergic, glutamatergic, dopaminergic, adrenergic)
Periphery

$\text{CB}_2R$

Almost exclusively restricted to cells and organs of the immune system

$\text{CB}_1$ and $\text{CB}_2$ (existence of other isoforms)
CB₂ expression is almost exclusively restricted to cells and organs of the immune system.

Identification and Functional Characterization of Brainstem Cannabinoid CB₂ Receptors

Marja D. Van Sickle,¹* Marnie Duncan,¹* Philip J. Kingsley,² Abdeslam Mouihate,¹ Paolo Urbani,³ Ken Mackie,⁴ Nephi Stella,⁵ Alexandros Makriyannis,⁶ Daniele Piomelli,⁷ Joseph S. Davison,¹ Lawrence J. Marnett,² Vincenzo Di Marzo,³ Quentin J. Pittman,¹ Kamala D. Patel,¹ Keith A. Sharkey¹†


Note the lack of immunoreactive cell bodies in the knockout mouse (n = 3 per group). Scale bar, 50 μm. (D) Immunoreactivity for the neuronal nuclear marker NeuN (left, green) and CB₂ receptor immunoreactivity (center, red) in neurons of the dorsal motor nucleus of the vagus of the ferret and rat, as indicated. Overlay (right) of NeuN and CB₂ receptor illustrates that CB₂ receptor immunoreactivity is present in neurons of both the ferret and rat (n = 4), where it is localized on the cell membrane and in the cytoplasm of the neurons. Scale bars, 20 μm.
Discovery of the Presence and Functional Expression of Cannabinoid CB2 Receptors in Brain

EMMANUEL S. ONAIVI,a,b HIROKI ISHIGURO,c JIAN-PING GONG,b SEJAL PATEL,a ALEX PERCHUK,a PAUL A. MEZZOZI,a Lester MYERS,a Zoila MORA,a Patricia TAGLIAFerro,a Eileen GARDNER,a Alicia BRUSCO,d Babatunde E. AKINSHOLA,e Qing-Rong LIU,b Bruce HOPE,f Shinya IWASAKI,c Tadao ARINAMI,c Lindsey TeasenFITZ,a and George R. UHLb


CB2 receptors in the brain: role in central immune function
G A Cabral, E S Raborn, L Griffin, J Dennis & F Marciano-Cabral

The Cannabinoid CB2 Receptor as a Target for Inflammation-Dependent Neurodegeneration

John C. Ashton1 and Michelle Glass2

1Department of Pharmacology & Toxicology, University of Otago, New Zealand; 2Department of Pharmacology, University of Auckland, New Zealand
The Body’s Own cannabis - Endocannabinoids (eCBs)

why should we have receptors for a plant derived substance such as \( \Delta^9 \)-THC?

The presence of CBRs suggested the presence of an endogenous ligand

eCBs exist as precursors in the cell membrane

Unsaturated fatty acid derivatives

Produced in response to specific stimuli

depolarization

Differ in pharmacology

(2-AG more efficacious)

Guzman et al., 2003, Nature Reviews Cancer 3, 745-755
Role of endogenous cannabinoids

* Precise physiological role unknown

* Inhibit memory consolidation

* Inhibit neurotransmission

* Regulation of JNK, ERK, p38, PKB, adenylate cyclase
ECB biosynthesis

• Derived from unsaturated FA arachidonic acid (FA found in phospholipids in cell membranes)

• Not stored in vesicles but are produced ‘on demand’

• Biosynthesis increases upon nerve cell activation

ECB degradation

2-AG

Monoacyl glycerol lipase (MAGL)

Glycerol + arachidonic acid

AEA

Fatty acid amide Hydrolase (FAAH)

Ethanolamine + arachidonic acid

Retrograde signalling

Activation of pre-synaptic CB$_1$ decreases neurotransmitter release

Since ECBs are synthesised during neuronal activity - presCB$_1$ forms a sort of feedback inhibition

Serves to attenuate or enhance excitability, depending on the type of transmitter released

Man-made synthetic cannabinoids

Synthetic analogues of THC

\[
\text{HU 210}
\]

\[
\text{CP55,940}
\]

\[
\text{WIN 55212-2}
\]

\[
\text{Cesamet}
\]
Man-made synthetic cannabinoids

Specific CB2 agonist

JWH 133

Receptor antagonists

CB1

CB2
Endocannabinoid system

Endogenous Ligands

Metabolic enzymes

CNS

CB₁R

FAAH

Anandamide (AEA)

Novel ligands

2-arachidonoyl Glycerol (2-AG)

MAGL

Periphery

CB₂R

Interaction with other receptor types

Novel receptors
Endocannabinoid system

Fear & Pain

CNS development and plasticity

Cell Fate

Appetite control & metabolism

Immune system

Reproduction

Bone metabolism
Cannabinoids and Cell Fate

Toxic
- Glioma cells, Sanchez et al., 1998
- Hp neurones, Chan et al., 1998

Protective
- Ischaemia, Louw et al., 2000
- Excitotoxicity, Gilbert et al., 2007

Neurodengeneration

THC → apoptosis
- THC → Lysosomal leakage
  - Gowran and Campbell, 2008

Cyt-c
- Downer et al., 2003, 2001

JNK1
- P
- p53

THC

Cannabinoids and Cell Fate

THC → apoptosis
- THC → Lysosomal leakage
  - Gowran and Campbell, 2008

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- Downer et al., 2003, 2001

JNK1
- P
- p53

THC

Tetrahydrocannabinol-induced neurotoxicity depends on CB$_1$ receptor-mediated c-Jun N-terminal kinase activation in cultured cortical neurons

Eric J. Downer, Marie P. Fogarty & Veronica A. Campbell

Department of Physiology, Trinity College, Trinity College Institute of Neuroscience, Dublin 2, Ireland

The tumour suppressor protein, p53, is involved in the activation of the apoptotic cascade by Δ$_9$-tetrahydrocannabinol in cultured cortical neurons

Eric J. Downer, Aoife Gowran, Áine C. Murphy, Veronica A. Campbell

Department of Physiology and Trinity College Institute of Neuroscience, Trinity College, Dublin 2, Ireland

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A role for p53 in the regulation of lysosomal permeability by Δ$_9$-tetrahydrocannabinol in rat cortical neurones: implications for neurodegeneration

Aoife Gowran and Veronica A. Campbell

Department of Physiology and Trinity College Institute of Neuroscience, Trinity College, Dublin, Ireland
Research Report

A comparison of the apoptotic effect of Δ⁹-tetrahydrocannabinol in the neonatal and adult rat cerebral cortex

Eric J. Downer, Aoife Gowran, Veronica A. Campbell

Department of Physiology and Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin 2, Ireland
eCB signalling in CNS development

Tunes neuronal specification programs

CB₁R activation on neural progenitors promotes gliosis

Interacts with other signalling pathways e.g., Neurotrophins

Induces the migration of late-gestational GABAergic interneurones

Shapes neuronal connectivity
  growth cone navigation
  axonal elongation
  synaptogenesis
The emerging functions of endocannabinoid signaling during CNS development


Endocannabinoid functions controlling neuronal specification during brain development

Tibor Harkany\textsuperscript{a,b,*}, Erik Keimpema\textsuperscript{a}, Klaudia Barabás\textsuperscript{a}, Jan Mulder\textsuperscript{a}

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\textsuperscript{b} Division of Molecular Neurobiology, Department of Medical Biochemistry & Biophysics, Karolinska Institutet, SE-17177 Stockholm, Sweden
IS CANNABIS TOXIC?

Cigarette smoking

Low birth weight
Small head size

Cannabis exposure during pregnancy

Prenatal study
Fried et al.
Effects of prenatal marijuana on visuospatial working memory:
An fMRI study in young adults

Prenatal Exposure to the CB1 Receptor Agonist WIN 55,212-2 Causes Learning Disruption Associated with Impaired Cortical NMDA Receptor Function and Emotional Reactivity Changes in Rat Offspring

Prenatal exposure to a cannabinoid agonist produces memory deficits linked to dysfunction in hippocampal long-term potentiation and glutamate release
Cannabis exposure during pregnancy

Deficits in executive function & Visuospatial working memory

Persists into adulthood

Animal studies - CB receptor agonists decreases glutamatergic Transmission

Abnormal activation of these pathways by exogenous CB’s may lead to cognitive impairments in later life
CANNABIS AS MEDICINE

Cannabinol, CBN

Cannabidiol, CBD

Downregulation of inflammation etc.

Reverses Tau hyperphosphorylation

CB₁ independent signalling
no psychoactive activity
Cannabinoid system and Neurodegeneration

Chronic recreational use of cannabis is linked with morphological changes in brain structures
- frontal white matter volume decreased
- reduced grey matter

Could be related to alterations in the control of neurogenesis, synaptogenesis and wiring.
Cannabinoid system and AD

Drobinol (solution of THC) improves disturbed behaviour and stimulates appetite in AD patients

Increased expression of CB receptors on microglia within plaques

FAAH is upregulated in plaques - increased AEA metabolites increases PGs & increases pro-inflammatory molecules

2-AG is increased during Aβ exposure - local neuroprotection

Drugs that augment eCB tone - potential treatment of AD

THC reduces Aβ aggregation
Cannabinoids and MS


Cannabinoid system modulating drugs

Marinol
(dronabinol)
THC
Anti-nausea
Appetite stimulant

Acomplia
(rimonabant)
Anti-obesity

Sativex
Pain relief in MS

Cesamet
(nabilone)
THC analogue
anti-emetic
in cancer therapy
The AAPS Journal 2005; 7 (3) Article 64 (http://www.aapsj.org).

Themed Issue: Drug Addiction - From Basic Research to Therapies
Guest Editors - Rao Rapaka and Wolfgang Sadée

The Therapeutic Potential of Drugs That Target Cannabinoid Receptors or Modulate the Tissue Levels or Actions of Endocannabinoids
Submitted: May 31, 2005; Accepted: July 21, 2005; Published: October 24, 2005

Roger G. Pertwee

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