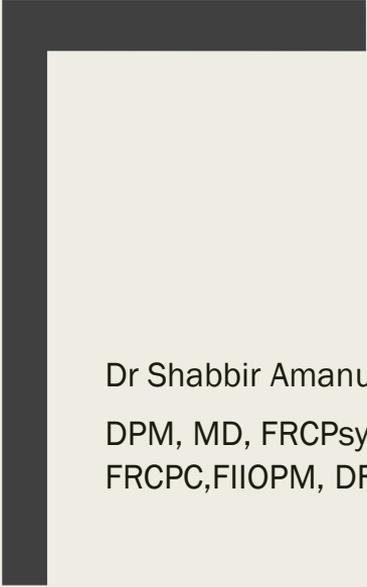


# DO CANNABINOIDS HAVE A ROLE IN DEMENTIA?-

*EUROPEAN ASSOCIATION OF GERIATRIC  
PSYCHIATRY JUNE 17<sup>TH</sup> 2021*



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# Acknowledgements

- Dr Bhaskar Mukherjee - A passionate and dedicated life long learner and well loved teacher and hard core molecular psychiatrist-  
dr.bhaskar.mukherjee78@gmail.com
- Dr R Jain- An incredible source of information and always happy to share information - rjain3@nhs.net
- Our patients – Who teach us everyday without charging us a cent



# DISCLOSURES

Lectures- Otsuka, Lundbeck, Sunovion, Esai,  
Jansen

Ad Boards- Esai, Otsuka,

Patent- I Applied for

Grants- Canadian Medical foundation

# Conflict of interest

- NIL

# Reading list

- There are some must reads but at the end of the paper I have mentioned a few so as not to overwhelm readers.
- They are very well written and will change your perception and understanding of neurodegenerative disorders
- List of references – please contact any one of us
- [Shabbir.amanullah@gmail.com](mailto:Shabbir.amanullah@gmail.com)
- [dr.bhaskar.mukherjee78@gmail.com](mailto:dr.bhaskar.mukherjee78@gmail.com)
- [rjain3@nhs.net](mailto:rjain3@nhs.net)

# Dementia

- Most prominent form- Alzheimer's
- Worldwide- 50 million people
- Alzheimer's and age related dementia- leading cause of disability in aged individuals
- Prevalence will increase to 68% in low and middle income countries by 2050
- 20-30% of early dementia AD patients show significant depressive and mood changes

# Evolutionary biology of cannabis

Original form of cannabis/hemp plant,-First discovered in Central Asia- 6000 years ago,  
Had a lower THC content.  
Was used in pain and cramps  
High THC containing cannabis plants were developed.

Human beings' have developed a very complex endocannabinoid system  
It has become infinitely more complex

This system is involved in  
Energy metabolism  
Gonadal function  
Neuroplasticity  
Others



MODULATION OF  
GUSTATORY AND  
OLFACTORY  
NEUROTRANSMISSION



GASTROINTESTINAL  
MOTILITY



MOTIVATION FOR  
PALATABLE FOOD

# Brain and other systems-

# Disease modifying

A-Beta

TAU-GSK-3 Beta  
inhibitor  
TAU-aggregation  
inhibitor  
(microtubule protein)

Neuroinflammation-COX  
-2/LOX - inhibitors

Neuroprotection-  
antineuroinflammatory  
agents

PDE 4 inhibitors

# Symptomatic treatments

Cholinergics- AChE  
Inhibitor/BuChE

NMDA- Memantine

G Protein coupled  
GPCRs CB1  
antagonist/  
Cannabinoids  
receptor- CB2 agonist

Oxidative damage –  
MAO A and B  
inhibitors

GPCRs, Histamine  
receptors-H3  
antagonist

# Any links to pain?

Einstein ageing  
study- 2019

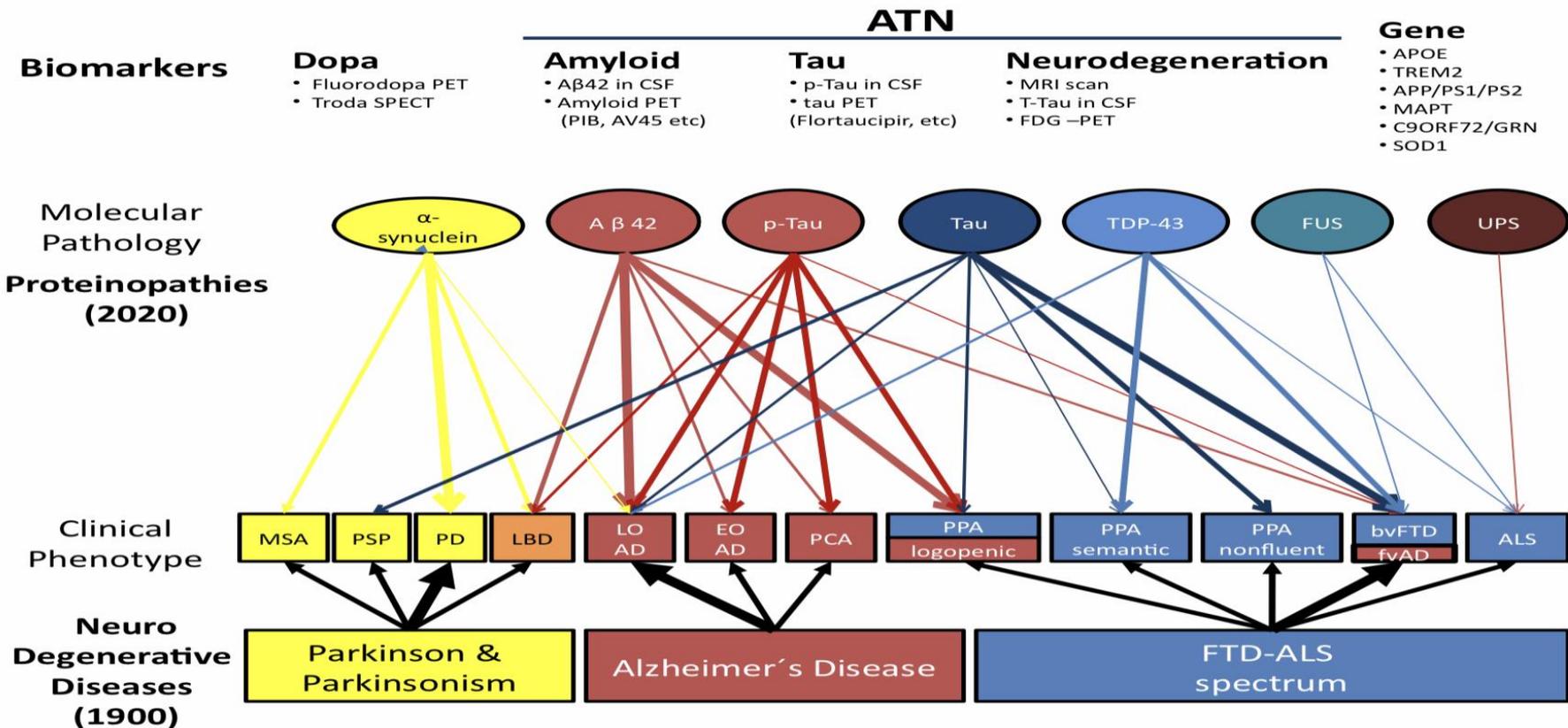
1114 participants

70 years or older

Higher levels of pain  
were correlated with  
higher possibility of  
dementia- Ezzat et  
al, Ikram et al

Dysfunction of LC-  
norepinephrine  
system was  
connected to chronic  
pain

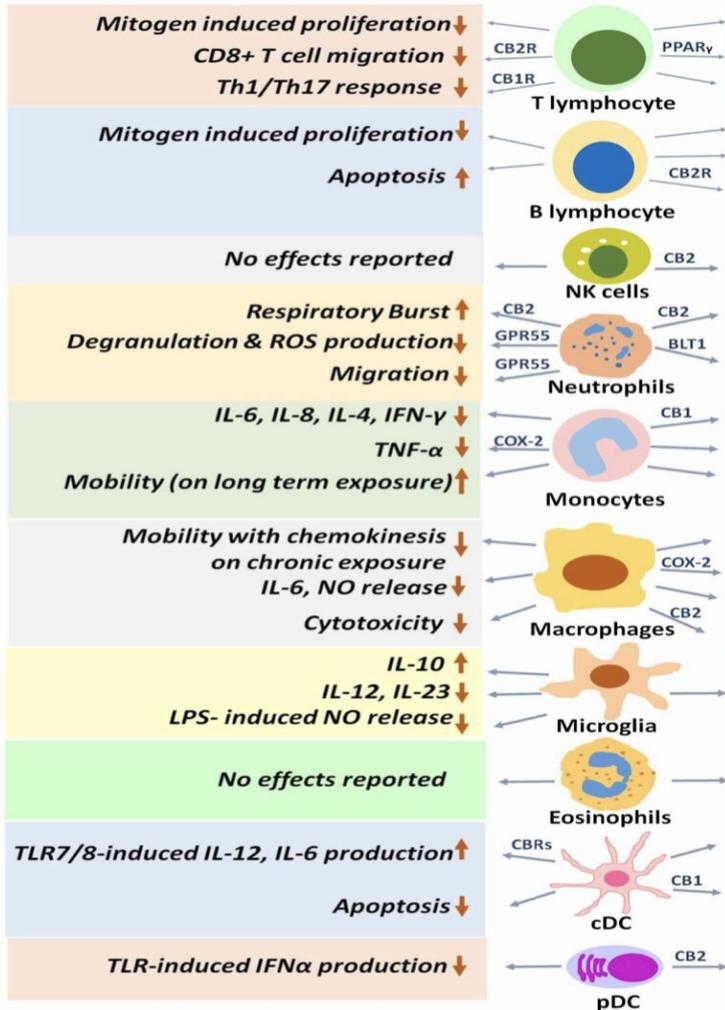
The Journey from dementia to proteinopathic neurodegeneration



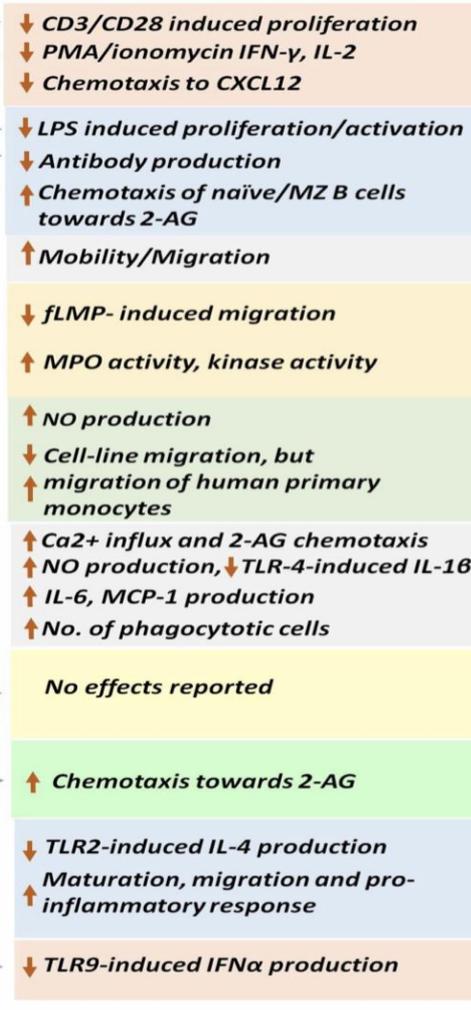
MSA: multi systemic atrophy; PSP: progressive supranuclear palsy; PD: Parkinson disease; LBD: Lewy Body dementia; LOAD: late onset Alzheimer; EOAD: early onset Alzheimer disease; PCA: posterior cortical atrophy; PPA: progressive primary aphasia; bvFTD: behavioral variant frontotemporal dementia; fvAD: frontal variant Alzheimer disease; ALS: amyotrophic lateral sclerosis; TDP-43: TAR DNA-binding protein 43; FUS: Fused-in Sarcoma protein; UPS: Ubiquitin proteasome;

APOE: apolipoprotein E; TREM2: triggering receptor expressed on myeloid cells 2; APP: amyloid precursor protein; PS1: presenilin 1; PS2: presenilin 2; MAPT: microtubule-associated protein tau; GRN: progranulin; SOD1: superoxide dismutase-1; ATN: amyloid, tau, neurodegeneration.

## Effects of Anandamide

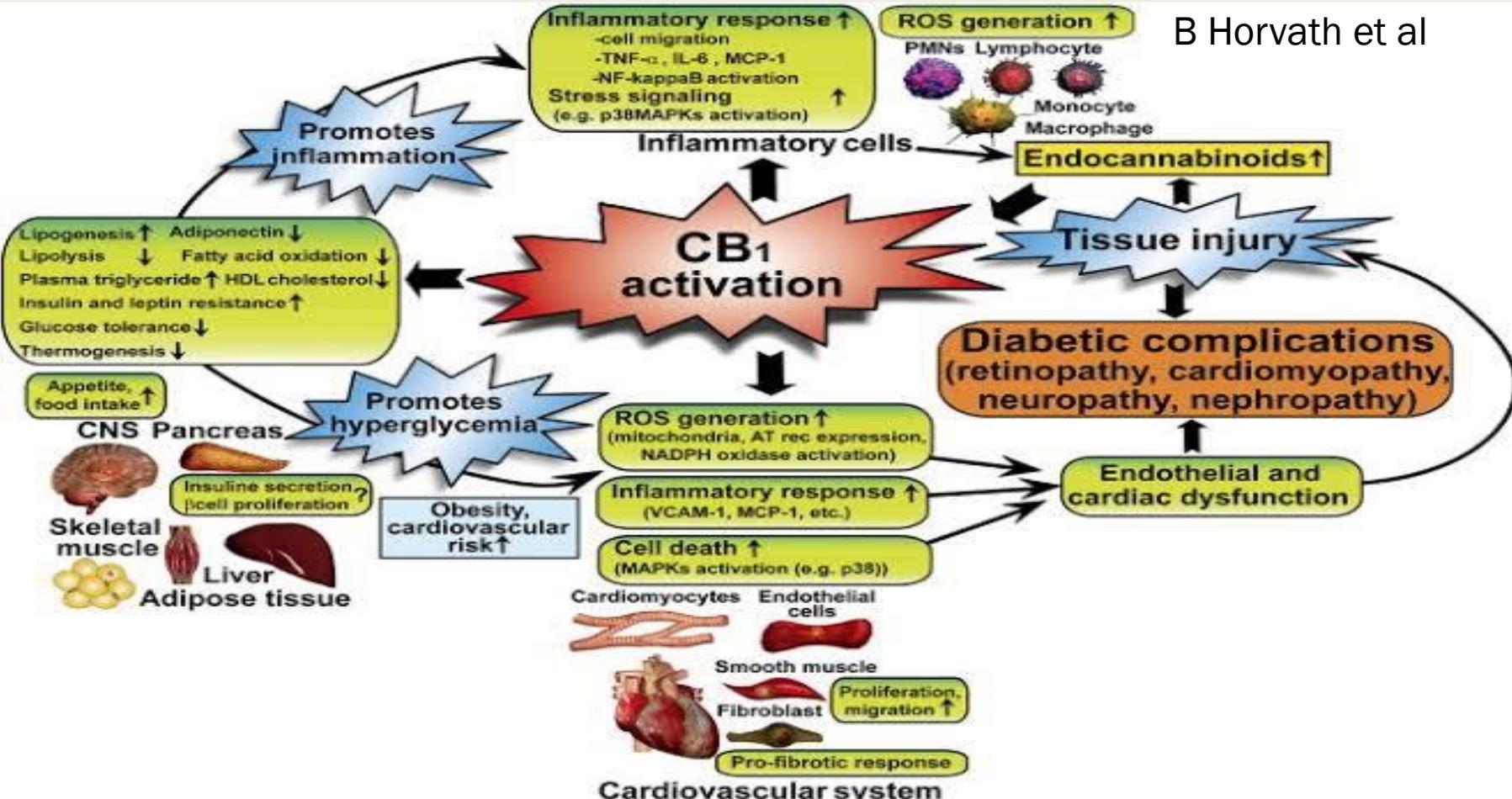


## Effects of 2-AG



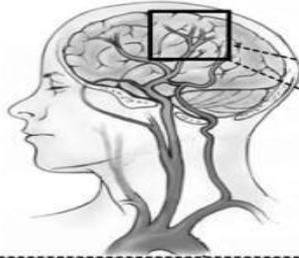
# INNATE IMMUNE SYSTEM-DIAGRAM-

O. RAHAMAN ET AL



Aso and Ferrer-  
2014

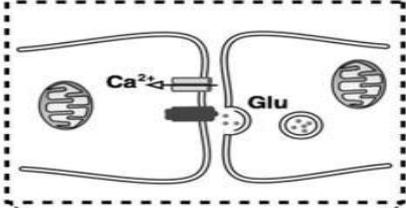
- Behavioral effects:**
- ↓ Agitation
  - ↓ Agressiveness
  - ↑ Food intake
  - Cognitive improvement (animals)



- Neurotransmission:**
- ↓ Excitotoxicity
  - ↓  $Ca^{2+}$  influx
  - ↓ AChE activity

- Vascular effects:**
- ↑ Vasodilation
  - ↑ Cerebral blood flow

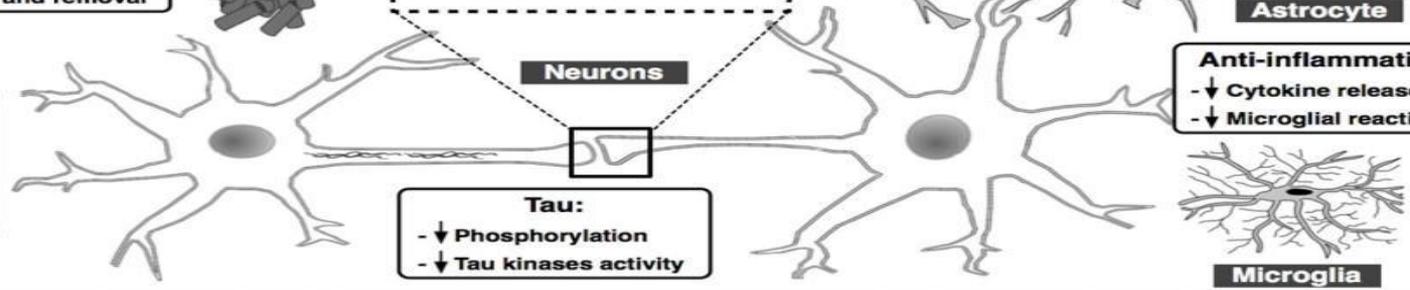
- Mitochondria:**
- ↓ ROS and NOS production
  - ↓  $O_2$  consumption
  - $Ca^{2+}$  homeostasis



- Anti-amyloid:**
- ↓ Neurotoxicity
  - ↑ Clearance and removal



- Others:**
- ↓ Apoptosis
  - ↑ Neurogenesis
  - ↑ Neurotrophin
  - ↑ Autophagy



- Tau:**
- ↓ Phosphorylation
  - ↓ Tau kinases activity

- Anti-inflammation:**
- ↓ Cytokine release
  - ↓ Microglial reactivity



What's the difference between street cannabis and medicinal cannabinoids

Synthetic Vs Medicinal

Effectiveness of medicinal cannabinoids in Dementia (Hypothetical) and its potential superiority over current anti-dementia medications

What can be done to target specific connectomes in the brain to achieve the desirable goal

- (1) Drug specific –extract the right molecules from right part of right plant
- (2) Patient specific

## Pharmacogenomics

Variations in metabolomics In normal individual

How an individual's genotype could affect their response to therapy, as well as how genetic polymorphisms in CYP450 and other enzymes are crucial in the metabolic profile of cannabinoids used for the treatment of Dementia.

Implementation of gene-focused pharmacotherapy has the potential to 'tailored' or signature interventions

Help us deliver select, more efficacious drugs and avoid unnecessary, polypharmacy-related adverse events in dementia.



Some CYP2C9 variants are associated with highly diminished THC metabolism,

Most of these patients carry genetic variants that may potentially predispose them to the development of psychosis and memory impairment.

Identification of these individuals will help in improving patient safety and empower individuals to make informed decisions about the therapeutic role of cannabinoids

It will also reduce if not eliminate possible/potential complications

# MUST READ ARTICLES

- Md Sahab Uddin et al. Emerging promise of Cannabinoids for the management of pain and associated neuropathological alterations in Alzheimer's disease. Frontiers in Pharmacology. Review 22 July 2020
- BELA HORVATH et al; The endocannabinoid system and plant derived Cannabinoids in Diabetes and Diabetic complications. The Am Journal of Path. Vol 180. NO 2 Feb 2012- **DIAGRAM 1**
- Amany Tawfik et al; Homocystein and age related central nervous system diseases:Role of inflammation; Int Journal of Molecular sci. 2021,22, 6259
- SPECIAL ISSUE- Masahiro Kawahara et al; Link between Aluminium and the pathogenesis of Alzheimer's disease:The integration of aluminium and the amyloid cascade hypotheses: Int Journal of Alzheimer's disease Vol 2011/ article 276393
- Ricardo Francisco Allegri: Moving from neurodegenerative dementia to cognitive proteinopathies,replacing "where" by "what"; Dement Neuropsychol 2020 Sept; 14(3): 237-242- **DIAGRAM 2**
- Aso and Ferrer (2014) **Diagram 3**

- Tiantian Guo et al; Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease. *Molecular degeneration* 2020. 14:40