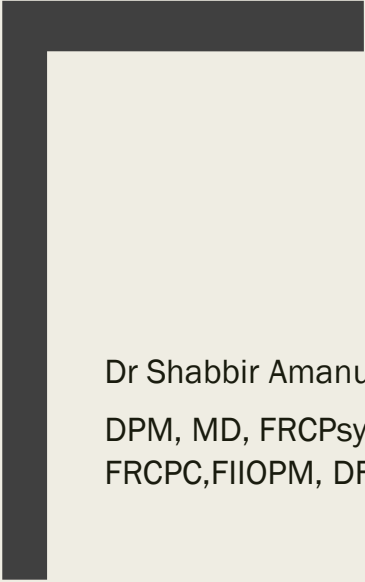



DO CANNABINOIDS HAVE A ROLE IN DEMENTIA?-

*EUROPEAN ASSOCIATION OF GERIATRIC
PSYCHIATRY JUNE 17TH 2021*



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- 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
- dr.bhaskar.mukherjee78@gmail.com
- 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

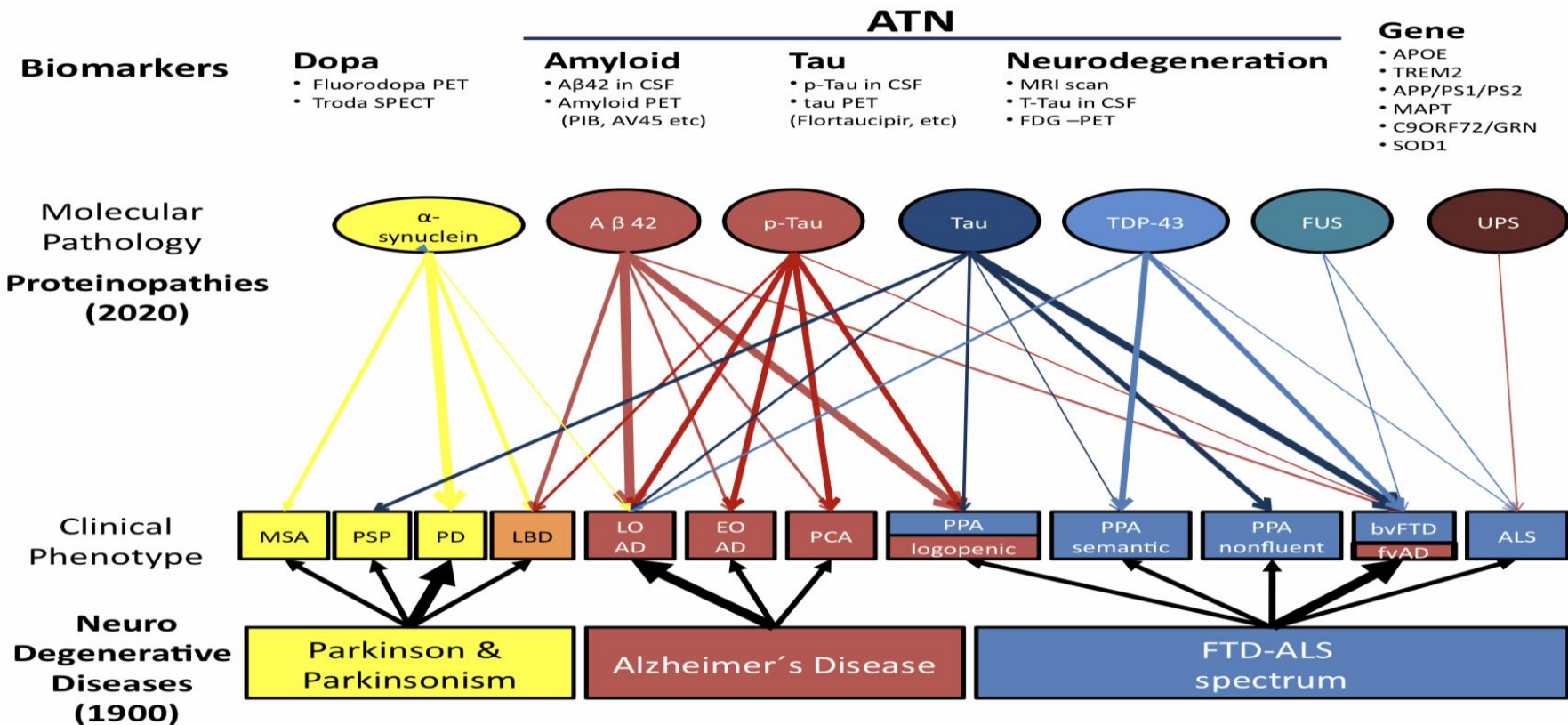
1114 participants

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

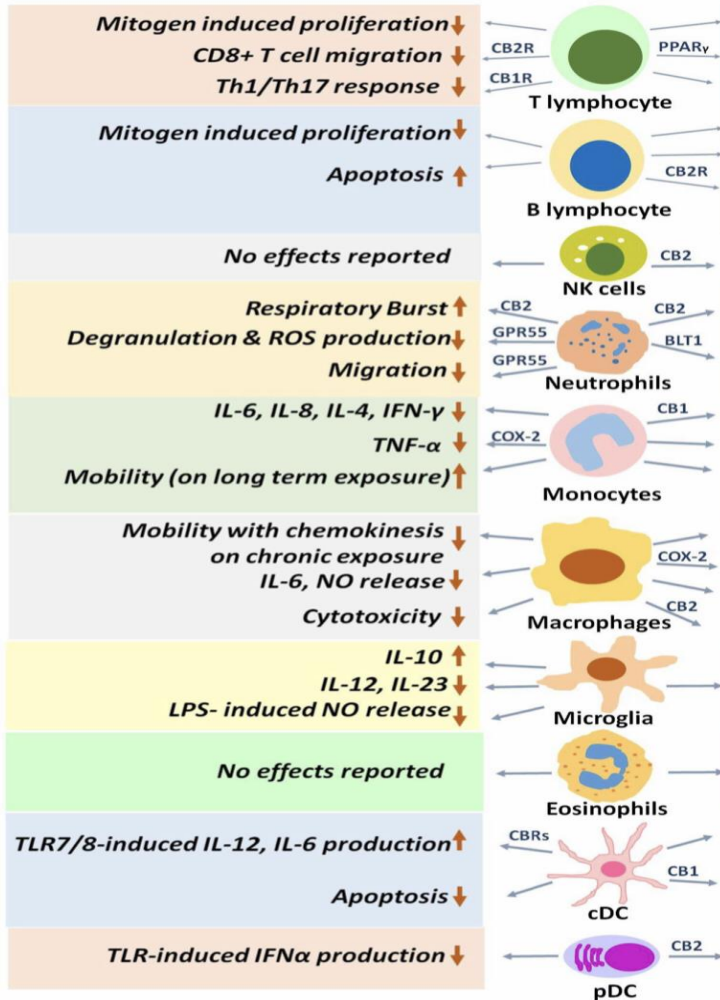
The Journey from dementia to proteinopathic neurodegeneration



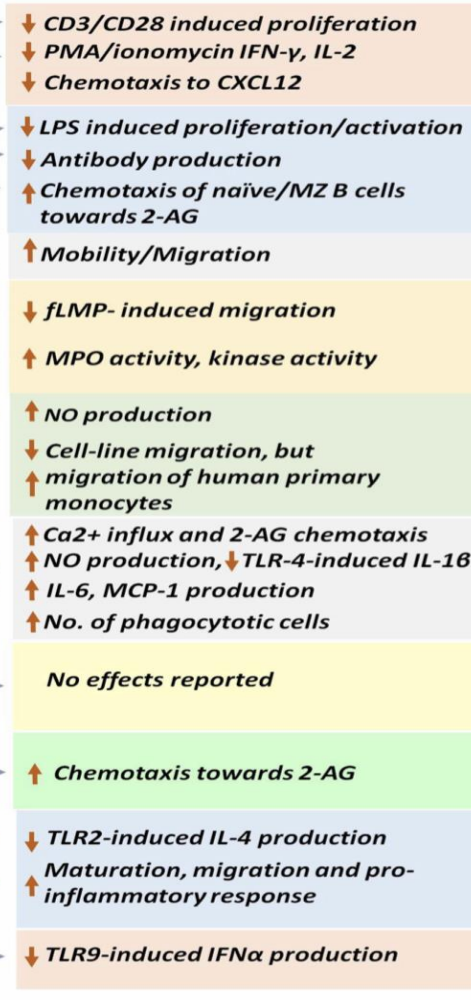
MSA: multi systemic atrophy; PSP: progressive supranuclear palsy; PD: Parkinson disease; LBD: Lewy Body dementia; LOAD: late onset Alzheimer; EOAD: early onset Alzheimer disease; PCA: posterior cortical atrophy; PPA: progressive primary aphasia; bvFTD: behavioral variant frontotemporal dementia; fvAD: 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

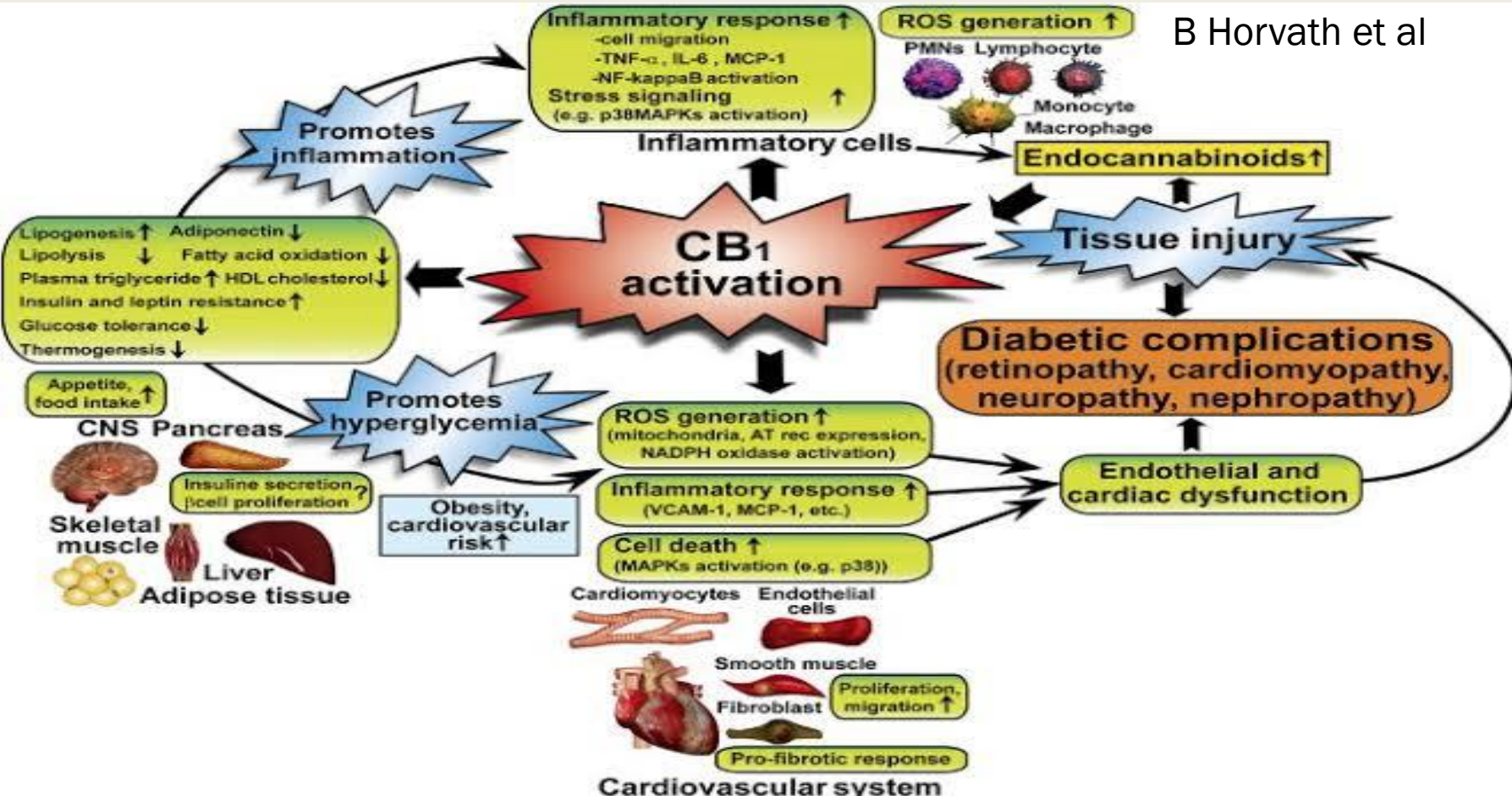


Effects of 2-AG



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

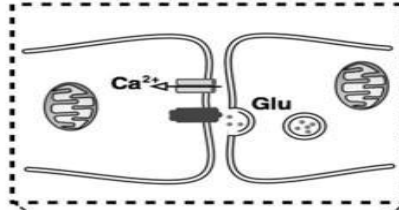
Anti-amyloid:

- ↓ Neurotoxicity
- ↑ Clearance and removal



Others:

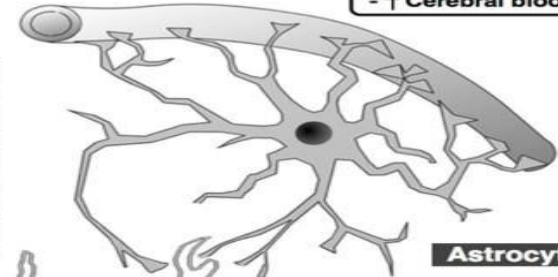
- ↓ Apoptosis
- ↑ Neurogenesis
- ↑ Neurotrophin
- ↑ Autophagy



Neurons

Tau:

- ↓ Phosphorylation
- ↓ Tau kinases activity



Astrocyte

Anti-inflammation:

- ↓ Cytokine release
- ↓ Microglial reactivity



Microglia



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