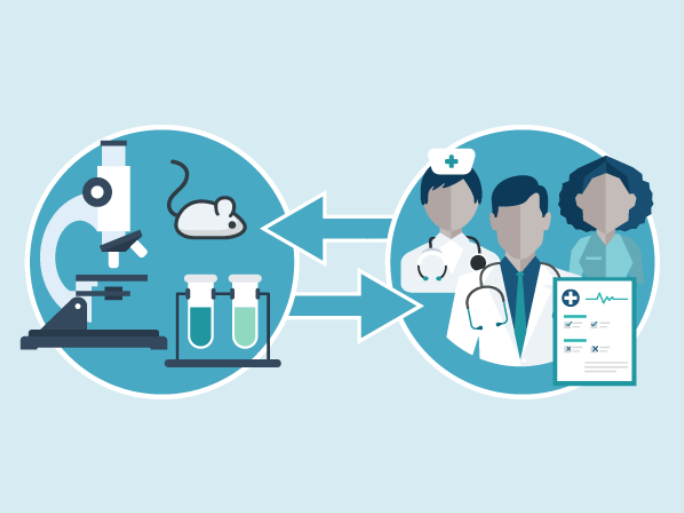
THE INFLAMMATION HYPOTHESIS OF MAJOR DEPRESSION: THIRTY YEARS OF PROGRESS FROM THE BENCH TO CLINIC



Dr Vikas Menon
Additional Professor of Psychiatry
JIPMER, Puducherry

Overview of presentation

- Brief historical overview
- Evidence base for inflammation in depression
- Mechanistic pathways explaining the association
- Translational implications
- Evidence for anti-inflammatory treatments in MDD
- An integrated approach to practice

Introduction

Late 19th century

Sir William Osler

Progressive Septicemia – marked mental prostration and apathy

1970's-80's

Robert Ader – Psychoneuroim-munology

Benjamin Hart - Sickness Behavior

2014

Immunopsychiatry

Bullmore & Lynall (Biol Psychiatry)

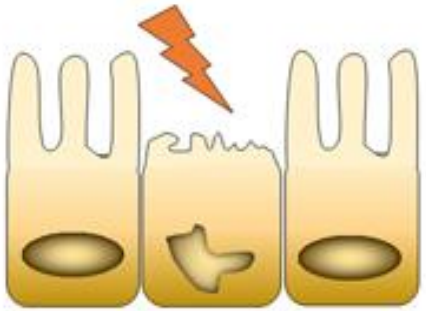
Novel treatments targeting immune systems can be used to manage psychiatric disorders

Introduction

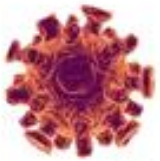
- Functions - Brain development, neuronal integrity, neurogenesis, and synaptic remodelling
- Evidence for a contributory role in pathobiology of major mental illness

(Felger and Lotrich., 2013)

INDUCERS

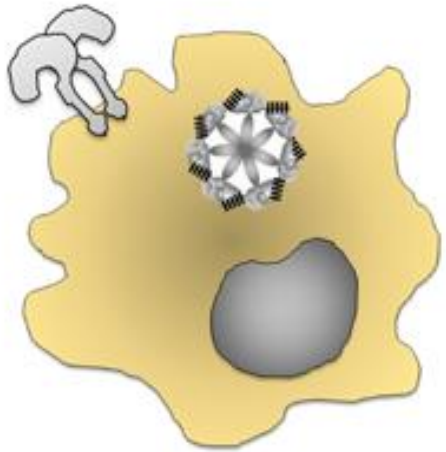


Tissue damage
(DAMPs)



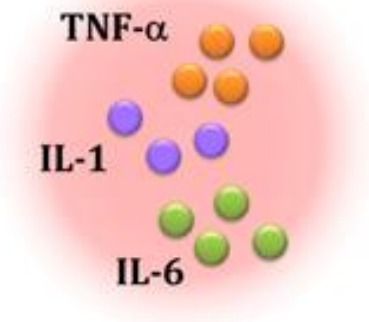
Infections
(PAMPs)

SENSORS

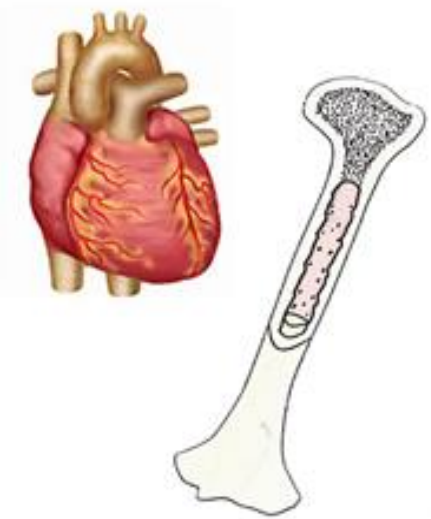


Membrane and intracellular sensing receptors

MEDIATORS



TARGET TISSUES

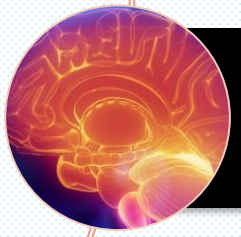


Evidence base for immuno-inflammation in major depression

Levels of Evidence for immuno-inflammation in depression

MOLECULAR

PERIPHERAL BLOOD



CNS

CLINICAL

Evidence for immuno-inflammation in depression

Level of evidence	Research findings
Molecular	• ↑ expression and polymorphisms of immune-related genes (IL-1, TNFalpha, and CRP) • ↑ activation of intracellular pathways (MAPK and NF-kB) • ↑ activated sensors (TLRs and inflammasome) • ↑ telomere length

Evidence for immuno- inflammation in depression

Level of evidence	Research findings
Peripheral blood	• ↑ proinflammatory cytokines • ↑ endothelial cell activation markers • ↑ adipokines • ↑ acute phase proteins (e.g., CRP) • ↑ oxidative stress markers

Evidence for immuno-inflammation in depression

Level of evidence	Research findings
CNS	

Evidence for immuno-inflammation in depression

Level of evidence	Research findings
Clinical	• ↑ prevalence of autoimmune diseases • ↑ prevalence of diseases with a proinflammatory status • 'Depressogenic' effects of immunotherapy with cytokines such as interferon alpha

Evidence for inflammation in depression

A Meta-Analysis of Cytokines in Major Depression

Yekta Dowlati, Nathan Herrmann, Walter Swardfager, Helena Liu, Lauren Sham, Elyse K. Reim, and Krista L. Lanctôt

BIOL PSYCHIATRY 2010;67:446–457

24 studies (pooled N > 1200)
8 cytokines analysed
TNFα (WMD – 3.97pg/ml) and IL-6 (WMD – 1.78pg/ml) higher in MDD subjects vs controls

Is Depression an Inflammatory Disease? Findings from a Cross-sectional Study at a Tertiary Care Center

Indian J Psychol Med 2016;38:114-9.

Avin Muthuramalingam, Vikas Menon, Ravi Philip Rajkumar, Vir Singh Negi[1]

Significantly raised levels of TNFα and IL-6 but not TGFβ

Evidence for inflammation in depression

Original Investigation

Association of Serum Interleukin 6 and C-Reactive Protein in Childhood With Depression and Psychosis in Young Adult Life

A Population-Based Longitudinal Study

Golam M. Khandaker, PhD; Rebecca M. Pearson, PhD; Stanley Zammit, PhD; Glyn Lewis, PhD; Peter B. Jones, PhD

JAMA Psychiatry. 2014;71(10):1121-1128. doi:10.1001/jamapsychiatry.2014.1332

Measured serum IL-6 at 9 years
Assessed subjects for depression at 18 years (n=4500)
After adjusting for confounders, those with raised IL-6 at 9 years more likely to be depressed at 18y (OR – 1.6, 95% CI – 1.1-2.1)

Evidence for inflammation in depression

Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls

Emanuele F. Osimo[a,b,c,1], Toby Pillinger[a,d,1], Ir… Mateos Rodriguez[e,1], Golam M. Khandaker[b,c], Carmine M. Pariante[d,f,g], Oliver D. Howes[a,d]

…n, Behavior, and Immunity 87 (2020) 901–909

107 studies and …06 immune

Levels of CRP, I… IL… …her in cases vs controls

Findings persiste…

More severe, chronic, treatment resistant depression associated with dysregulated inflammation

…per

…matory profiles of severe treatment-resistant depression

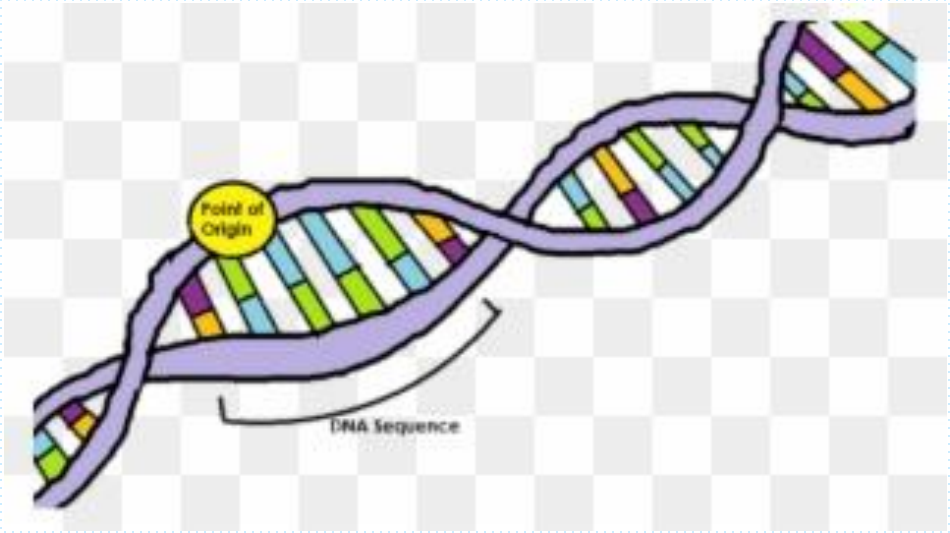
…Strawbridge[a,*], John Hodsoll[b], Timothy R. Powell[c], Matthew Hotopf[a,d], …hani L. Hatch[a], Gerome Breen[c], Anthony J. Cleare[a,d]

Journal of Affective Disorders 246 (2019) 42–51

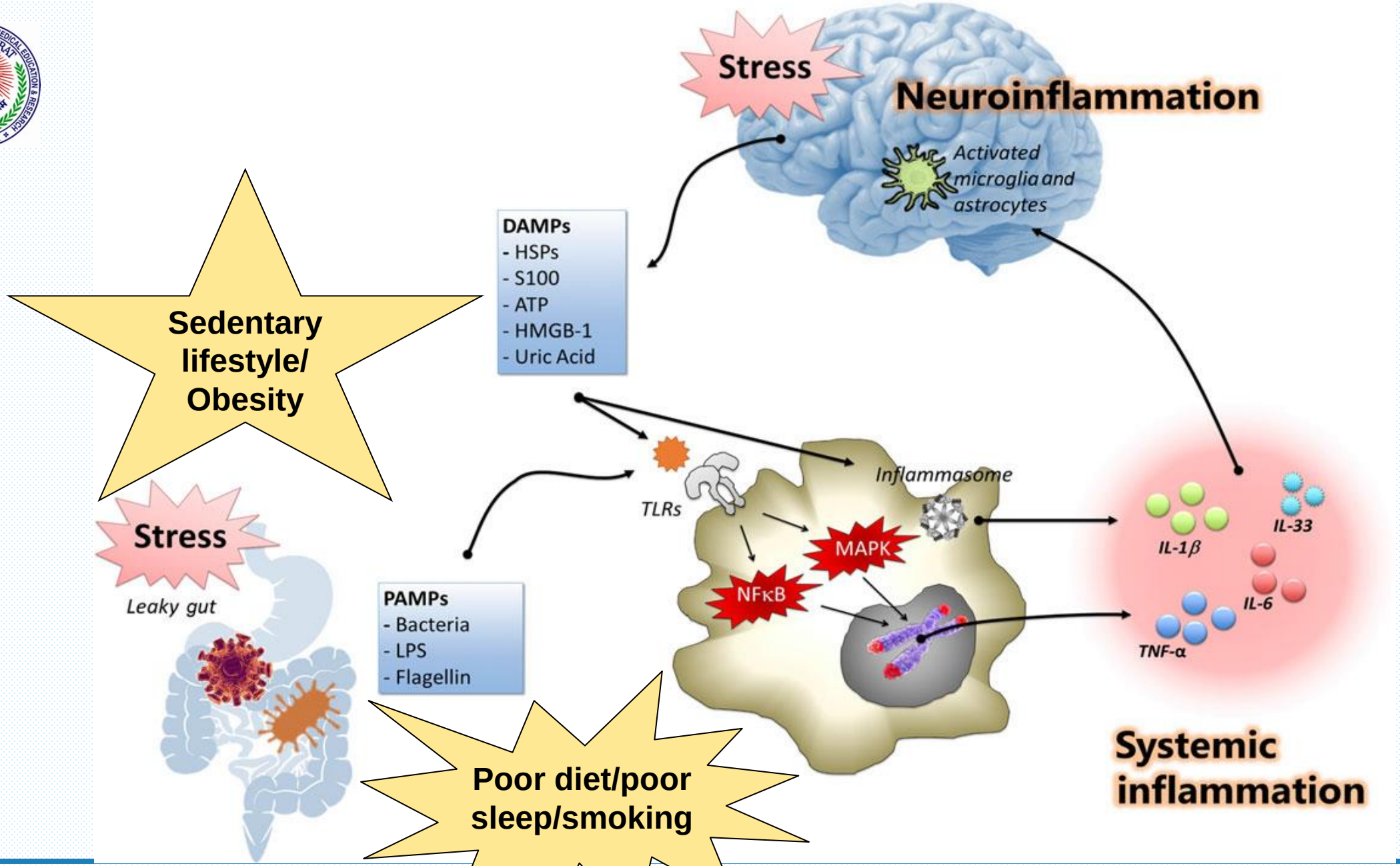
↑IL-6,IL-8, TNFα, CRP associated with poor treatment response

Some proteins increased during treatment

Potential to develop predictors of response for personalized care



Sources of inflammation in medically healthy individuals


Stress
Neuroinflammation
Activated microglia and astrocytes
DAMPs
- HSPs
- S100
- ATP
- HMGB-1
- Uric Acid
Sedentary lifestyle/ Obesity
Stress
Leaky gut
PAMPs
- Bacteria
- LPS
- Flagellin
TLRs
Inflammasome
MAPK
NFκB
IL-1β
IL-33
IL-6
TNF-α
Systemic inflammation
Poor diet/poor sleep/smoking

Access to brain and activation of inflammatory networks

Peripheral Inflammation

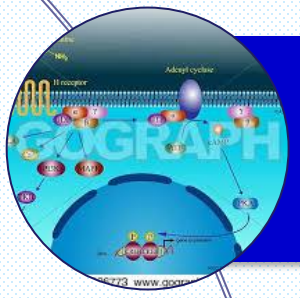
Humoral route

- Leaky BBB at circumventricular organs
- Active uptake across BBB

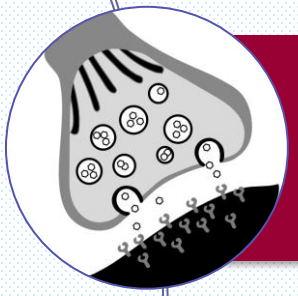
Neural route

Action at peripheral VNA that relay signals to regions like NTS

Mechanistic pathways linking inflammation and mental illness

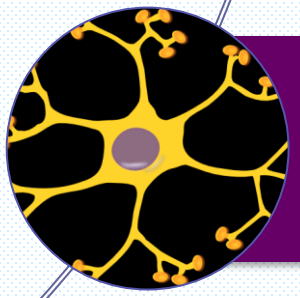


Activation of IDO pathway



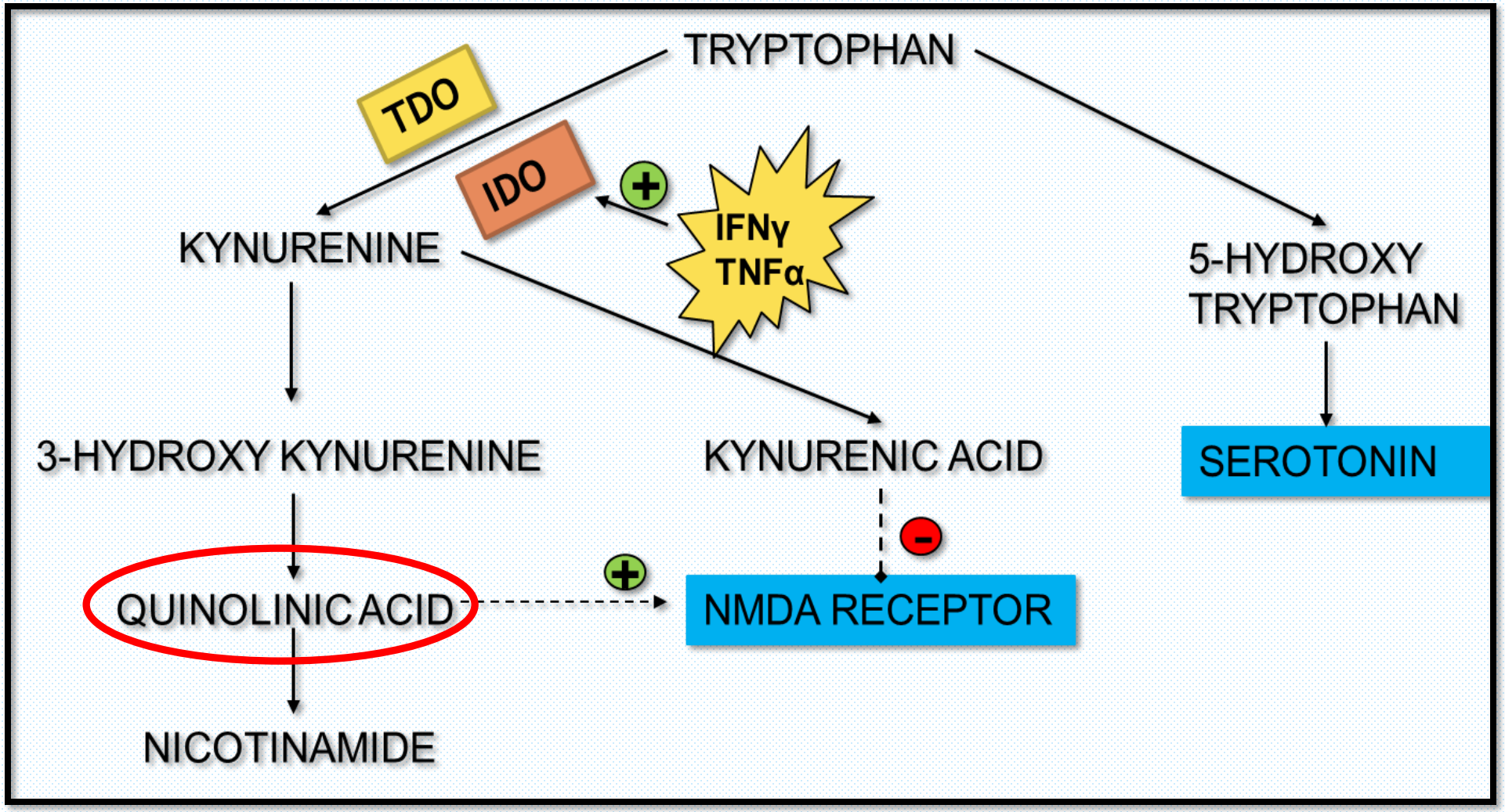
Alters metabolism, production and transport of neurotransmitters

Effects on HPA Axis

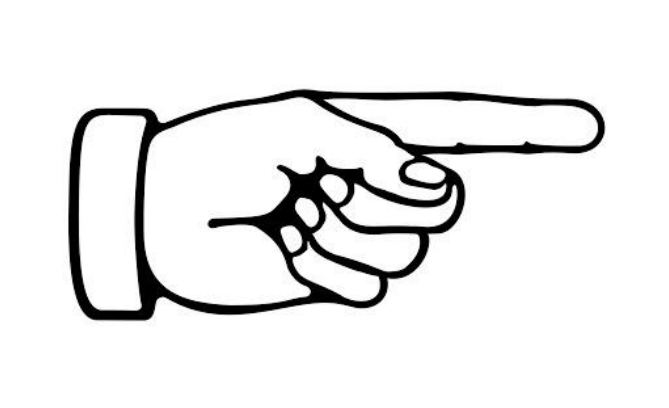


Effects on neurotrophic/growth factors

Effect of inflammation on IDO pathway



Effect of inflammation on serotonin

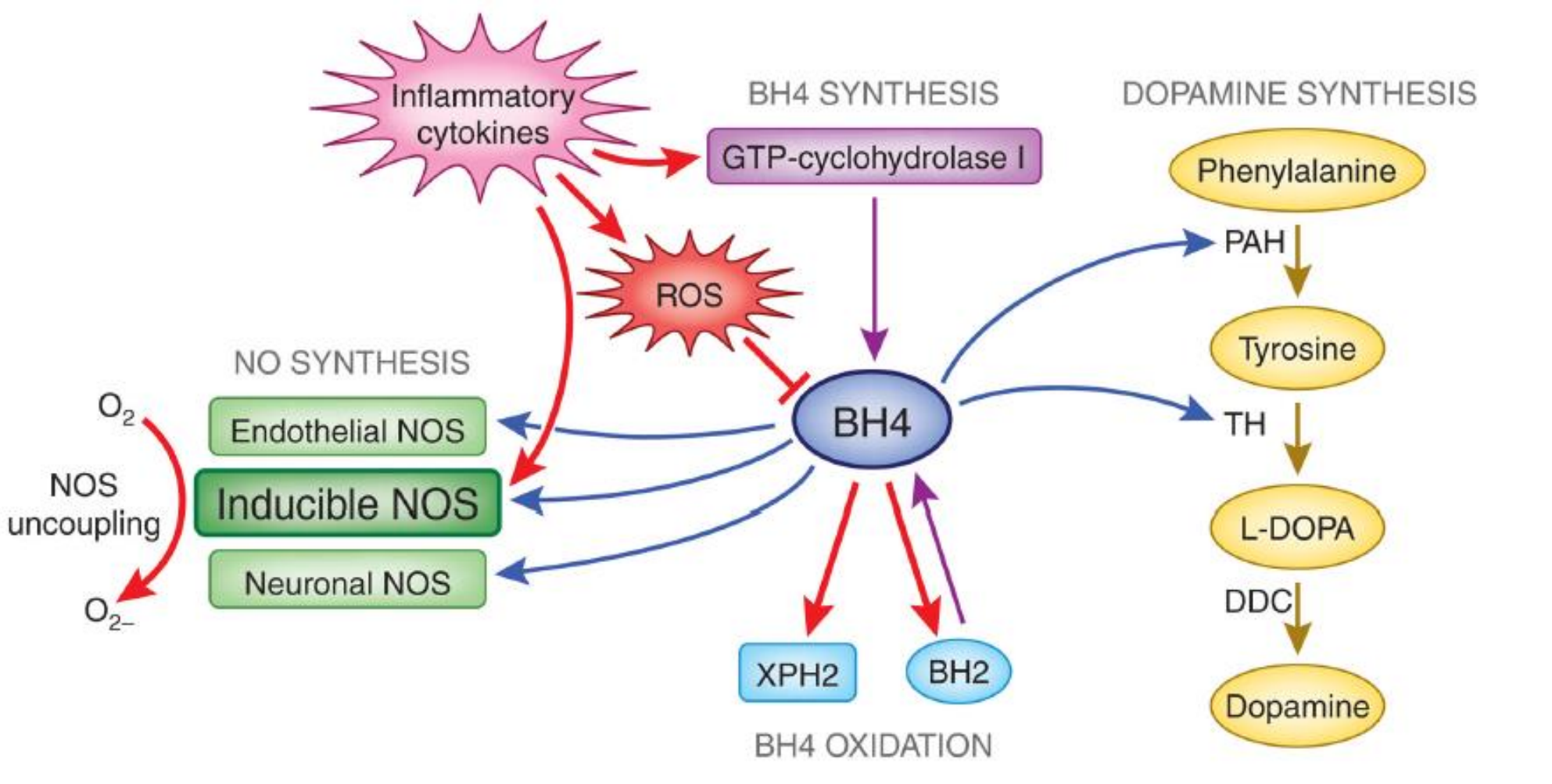


- Increase expression and activity of neuronal 5HTT
- Induction of p38 mitogen-activated protein kinase (MAPK), both in vitro and in vivo

(Zhu et al., 2005)

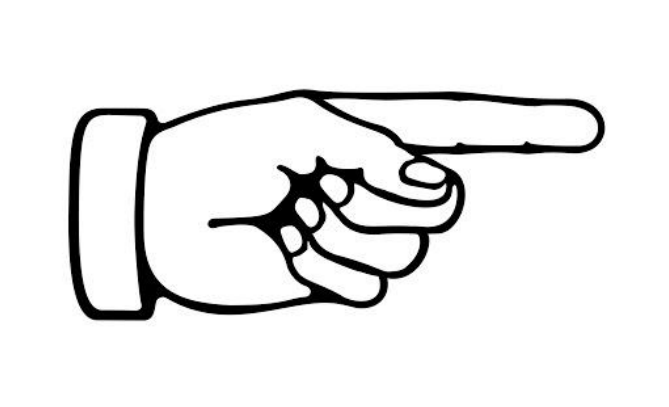
- Interact with genetic vulnerability - influence 5-HT levels

Effect on dopamine - synthesis

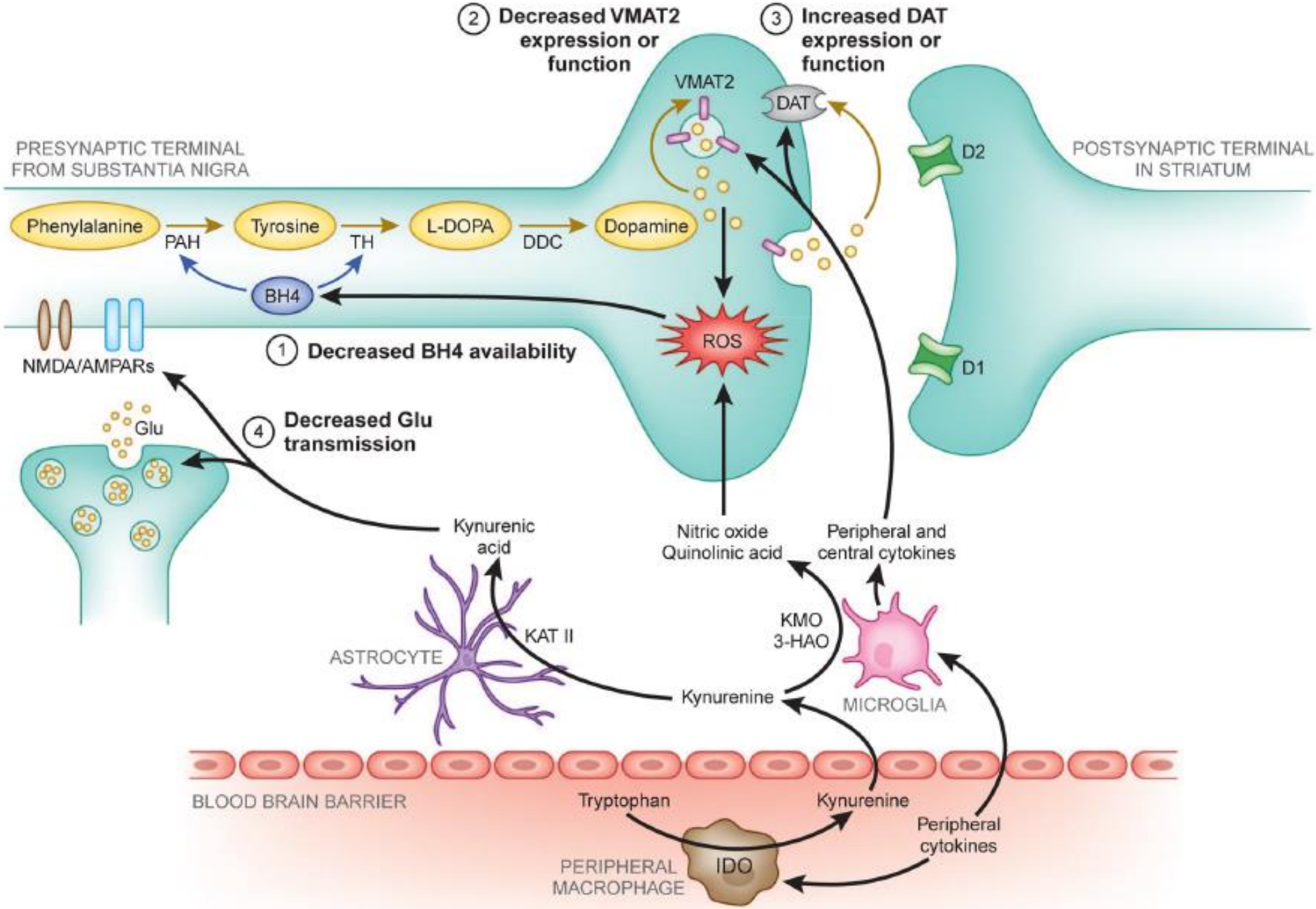


Felger JC & Miller AH. Front. Neuroendocrinol 2012

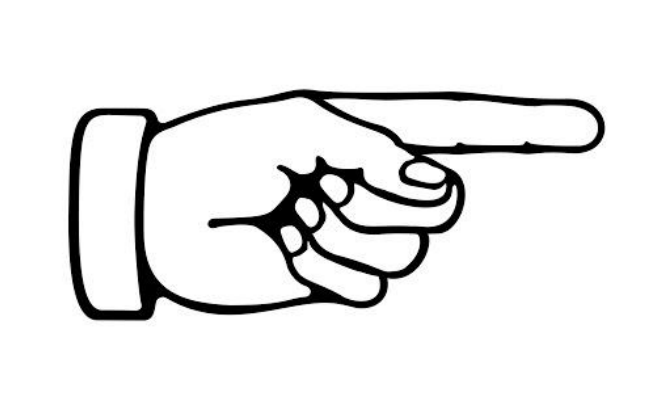
Effect on dopamine – packaging/reuptake



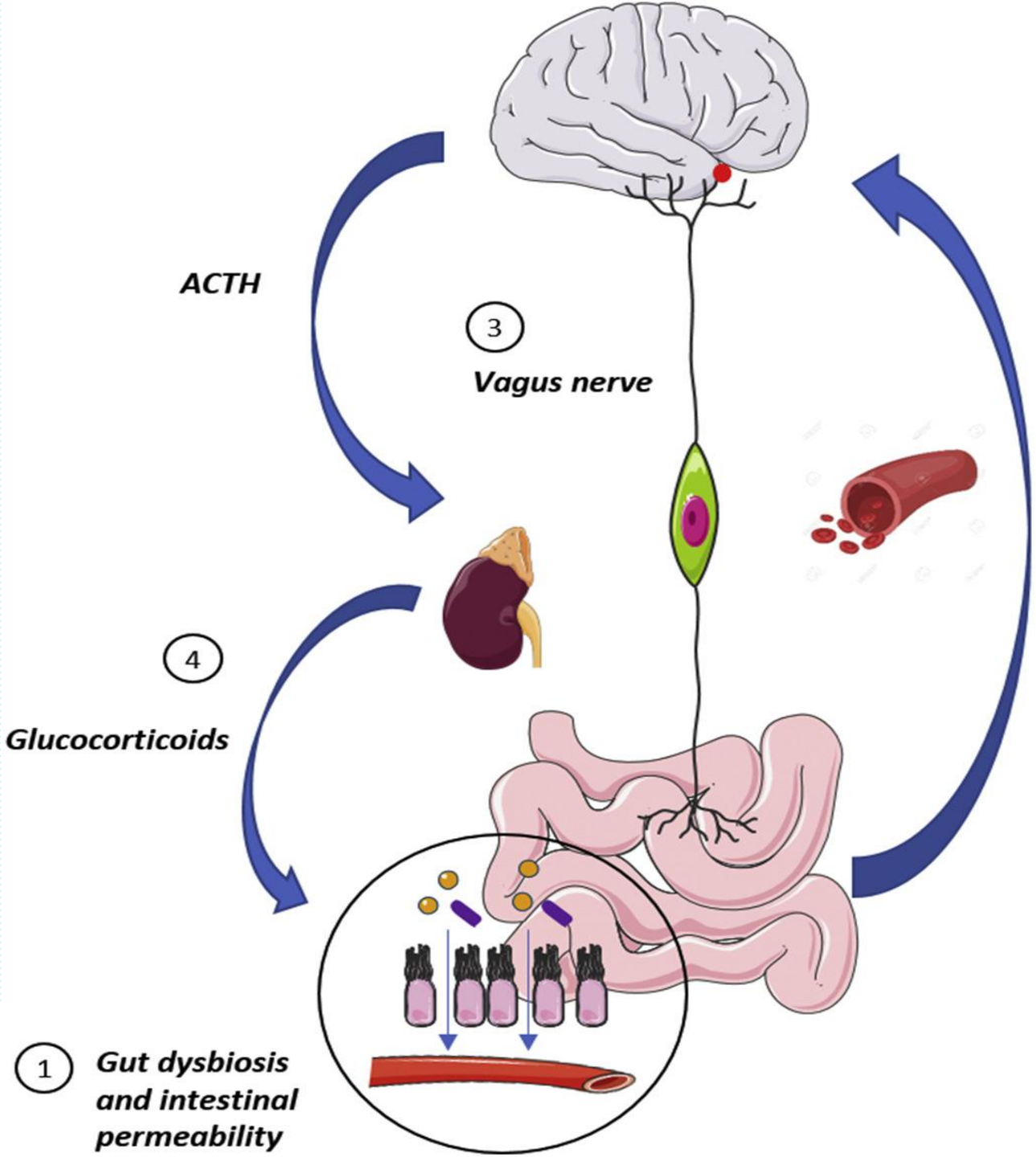
- Negatively affect the expression and function of VMAT2
- Preclinical evidence for ↑DAT function and expression
- ↑KA – reduces Glu transmission and ↓Glu-evoked DA release


2 Decreased VMAT2 expression or function
3 Increased DAT expression or function
VMAT2
DAT
PRESYNAPTIC TERMINAL FROM SUBSTANTIA NIGRA
POSTSYNAPTIC TERMINAL IN STRIATUM
D2
D1
Phenylalanine
PAH
Tyrosine
TH
L-DOPA
DDC
Dopamine
BH4
ROS
NMDA/AMPARs
1 Decreased BH4 availability
Glu
4 Decreased Glu transmission
Kynurenic acid
Nitric oxide
Quinolinic acid
Peripheral and central cytokines
KMO
3-HAO
KAT II
ASTROCYTE
Kynurenine
MICROGLIA
BLOOD BRAIN BARRIER
Tryptophan
Kynurenine
Peripheral cytokines
PERIPHERAL MACROPHAGE
IDO

Effect on glutamate



- QUIN - directly activate NMDA receptor to induce release of Glu
- ↓astrocytic expression of Glu transporters/↑ release of Glutamate
- Extrasynaptic NMDA receptors - ↓ production of BDNF



2

Pro-inflammatory cytokines (e.g., IL-1, IL-6 and TNF-α)

Small bioactive molecules

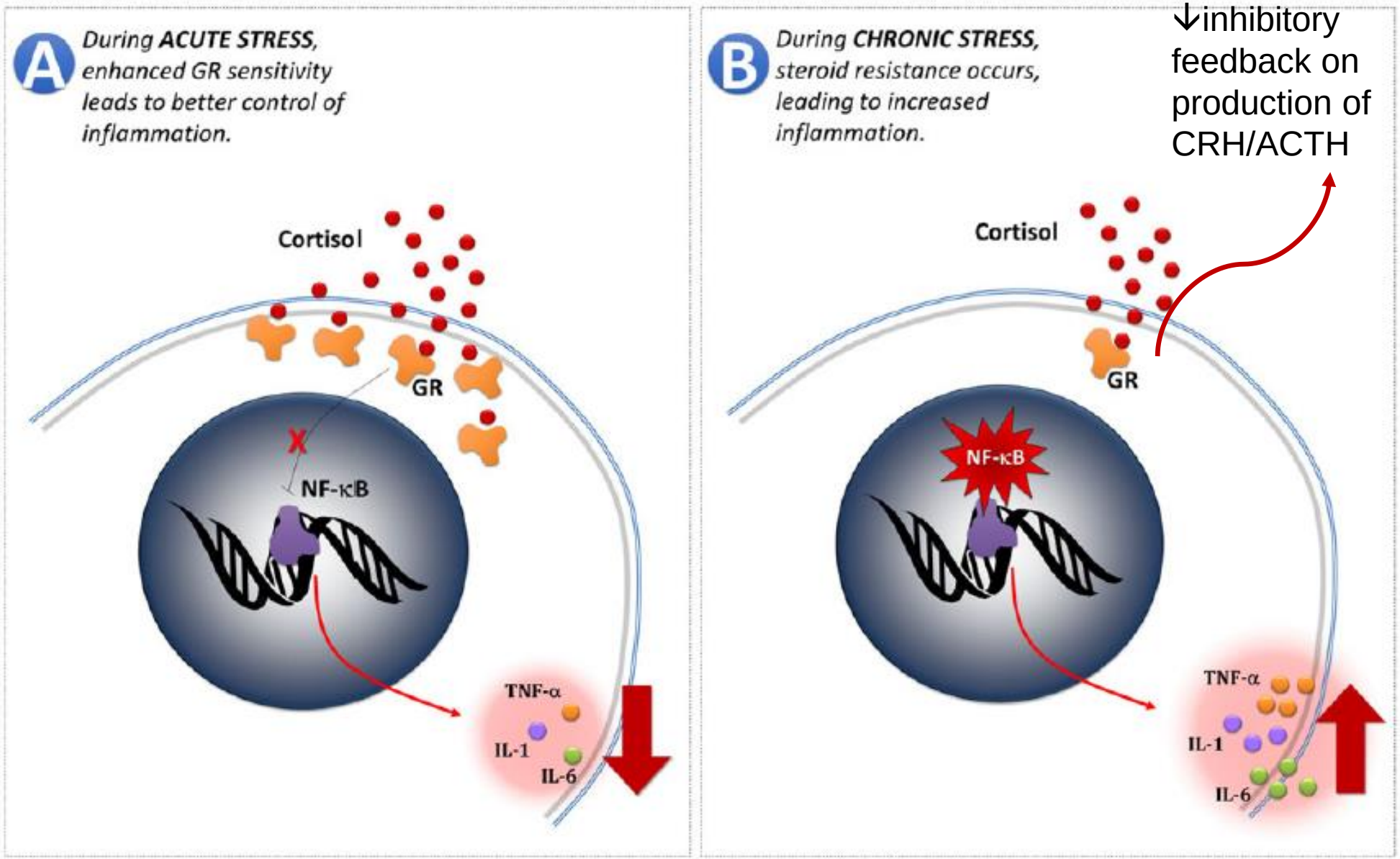
Prostaglandins

Microbial antigens (e.g., ClpB and LPS)

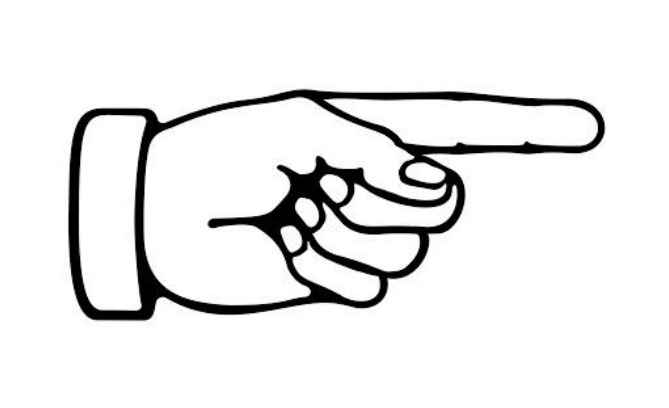
Stem, progenitor and immune cells

SCFAs

Ileal corticosterone

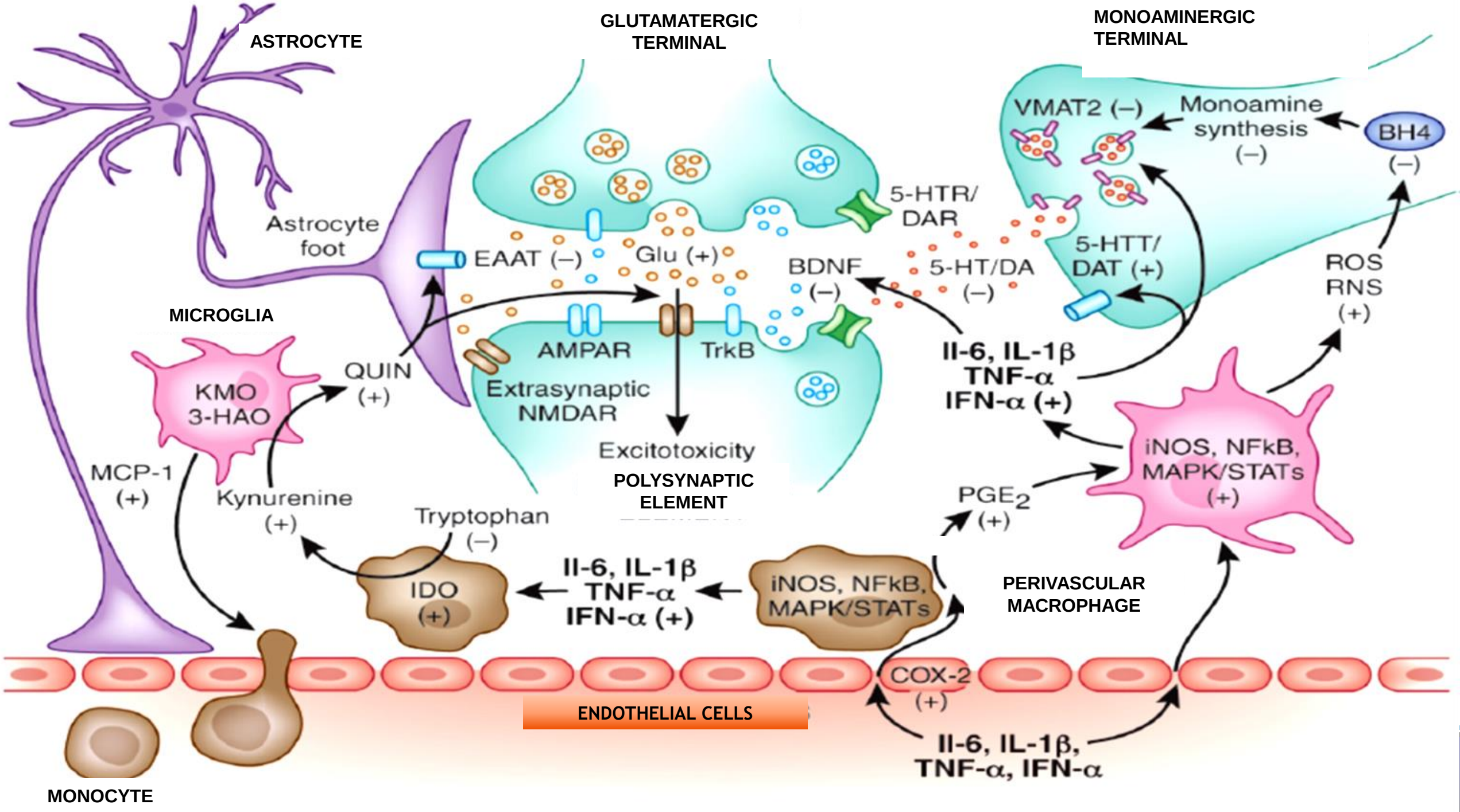

A
During ACUTE STRESS, enhanced GR sensitivity leads to better control of inflammation.
Cortisol
GR
X
NF-κB
TNF-α
IL-1
IL-6
B
During CHRONIC STRESS, steroid resistance occurs, leading to increased inflammation.
↓inhibitory feedback on production of CRH/ACTH
Cortisol
GR
NF-κB
TNF-α
IL-1
IL-6

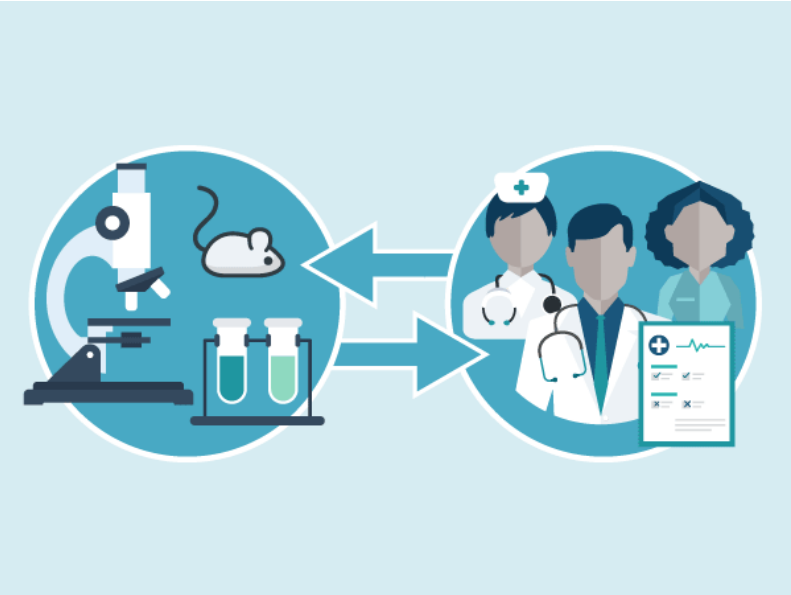
Effects on neuropeptides and growth factors



- ↑ glucocorticoid exposure - decline in BDNF expression in hippocampal and cortical regions
- Influence BDNF receptor (TrkB) phosphorylation, thereby further interfering with BDNF signaling

(Anacker et al., 2013; Cortese et al., 2011)

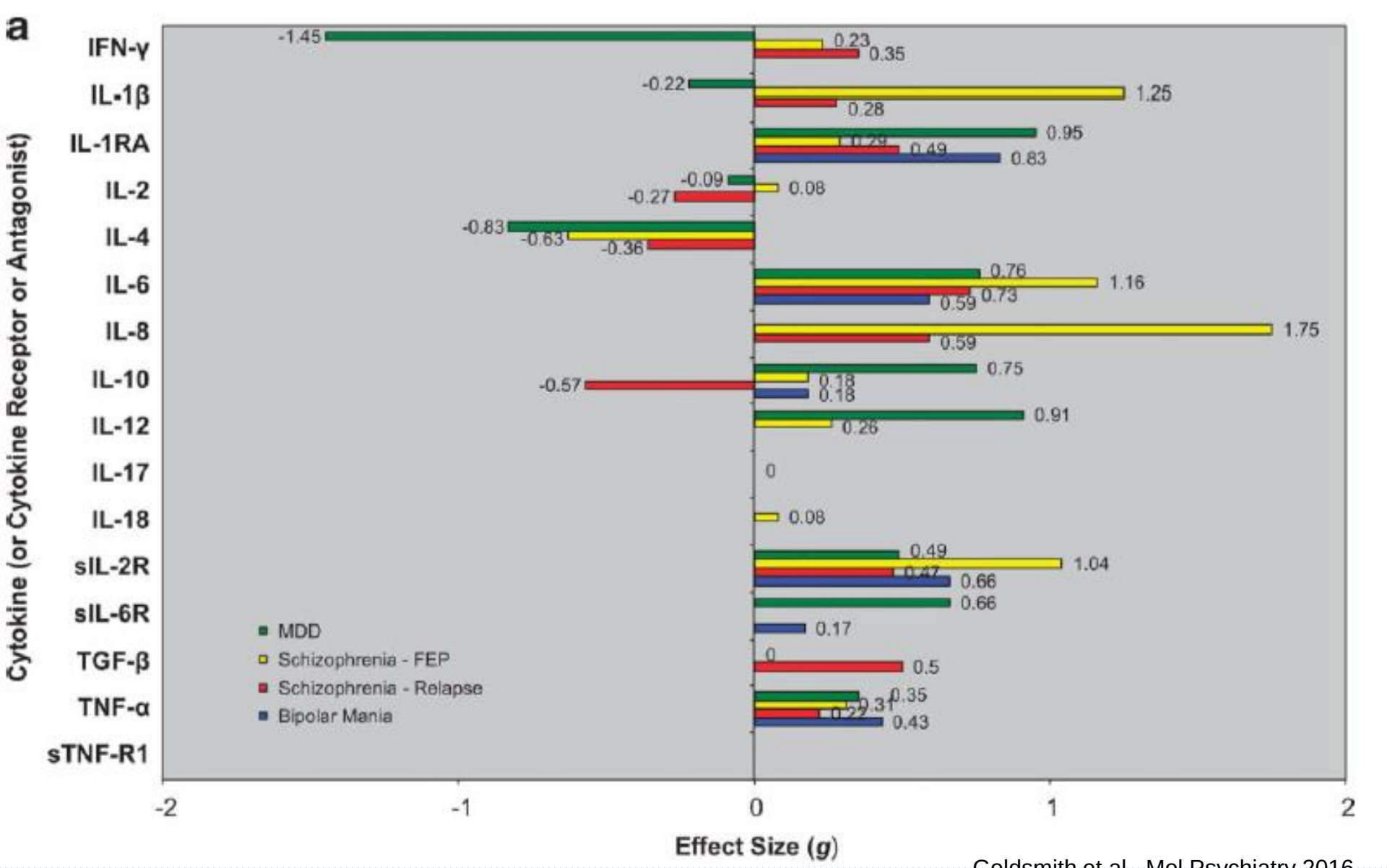

ASTROCYTE
GLUTAMATERGIC TERMINAL
MONOAMINERGIC TERMINAL
Astrocyte foot
EAAT (–)
Glu (+)
5-HTR/ DAR
VMAT2 (–)
Monoamine synthesis (–)
BH4 (–)
5-HTT/ DAT (+)
5-HT/DA (–)
BDNF (–)
ROS RNS (+)
MICROGLIA
AMPAR
TrkB
Extrasynaptic NMDAR
Excitotoxicity
POLYSYNAPTIC ELEMENT
KMO 3-HAO
QUIN (+)
Il-6, IL-1β TNF-α IFN-α (+)
iNOS, NFkB, MAPK/STATs (+)
MCP-1 (+)
Kynurenine (+)
Tryptophan (–)
PGE2 (+)
IDO (+)
Il-6, IL-1β TNF-α IFN-α (+)
iNOS, NFkB, MAPK/STATs
PERIVASCULAR MACROPHAGE
COX-2 (+)
ENDOTHELIAL CELLS
Il-6, IL-1β, TNF-α, IFN-α
MONOCYTE



Translational implications

Translational implications

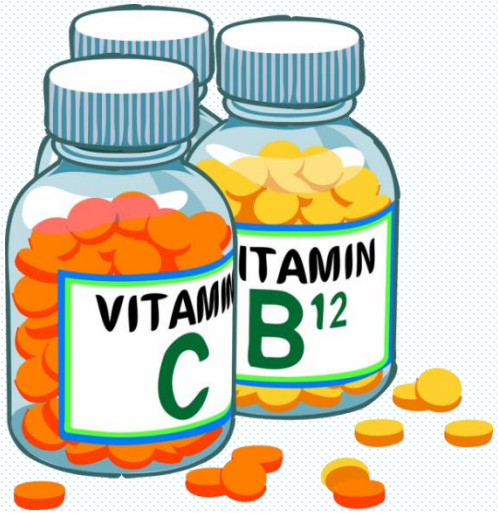
Research finding	Translational implications
↑ Levels of inflammatory markers in TRD	**Can potentially identify treatment resistant sub-group**
Some markers decrease with AD treatment whereas others do not	**Can be used as markers of treatment prognosis**
Machine learning algorithm approaches using longitudinal EMR data – predictive relationship between↑ inflammation and lifetime MDD	**Specific inflammatory markers may predict first MDD onset**
Interferon-γ-induced protein 10 predicted dysthymic disorder (Dysthymia > Depression > Controls)	**MDD spectrum conditions may have specific immune signatures**



Goldsmith et al., Mol Psychiatry 2016

Translational implications

Research finding	Translational implications
Higher CRP levels were associated with a better response to nortriptyline > escitalopram	**Inflammatory biomarkers may be used to guide treatment response**
Infliximab alleviated dep. symptoms in TRD compared to placebo - only in those with hsCRP >5 mg/L	**Trials of anti-inflammatory agents need to enrich themselves for inflammatory sub-type of patients**
Effect sizes for statistically significant findings/differences were small	**Not clinically significant or immune disequilibrium occurs in a minority**



Anti-inflammatory treatments for depression

Potential anti-inflammatory treatments for mental illness

- Why do we need new treatments for mental illness?
  - ➔High rates of treatment resistance across disorders
  - ➔Our relatively limited psychopharmacologic repertoire

RESEARCH PAPER

Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder: a systematic review and meta-analysis of randomised controlled trials

Shuang Bai,[1] Wenliang Guo,[2] Yangyang Feng,[1] Hong Deng,[1] Gaigai Li,[1] Hao Nie,[1] Guangyu Guo,[1] Haihan Yu,[1] Yang Ma,[1] Jiahui Wang,[1] Shiling Chen,[1] Jie Jing,[1] Jingfei Yang,[1] Yingxin Tang,[1] Zhouping Tang [1]

Bai S, *et al*. *J Neurol Neurosurg Psychiatry* 2019;**0**:1–12. doi:10.1136/jnnp-2019-320912

Pooled analysis of 26 RCTs - >1600 participants
NSAIDs/Omega-3FA/Statins/Minocycline/Modafanil/NAC

Evidence for monotherapy in depression

Study or Subgroup	Anti-inflammatory agents Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year	Std. Mean Difference IV, Random, 95% CI
1.1.1 Monotherapy of anti-inflammatory agents										
Marangell 2003	-8.1	7.7	18	-5.8	8.6	17	3.4%	-0.28 [-0.94, 0.39]	2003	
Su 2008	-12.4	4.69	17	-7.7	4.42	16	3.2%	-1.01 [-1.74, -0.28]	2008	
Rees 2008	-11.8	4.96	13	-9.3	4.52	13	3.0%	-0.51 [-1.29, 0.27]	2008	
Freeman 2008	-6.04	4.8	28	-7.52	4.11	23	3.8%	0.32 [-0.23, 0.88]	2008	
Rondanelli 2010	-4.5	3.93	22	-0.8	4.94	24	3.6%	-0.81 [-1.41, -0.21]	2010	
Mischoulon EPA 2015	-10.34	4.8	60	-9.49	4.69	29	4.3%	-0.18 [-0.62, 0.27]	2015	
Mischoulon DHA 2015	-9.26	4.72	58	-9.49	4.69	30	4.3%	0.05 [-0.39, 0.49]	2015	
Rapaport DHA 2016	-9.61	4.07	51	-9.79	3.97	26	4.2%	0.04 [-0.43, 0.52]	2016	
Rapaport EPA 2016	-10.14	4.11	52	-9.79	3.97	26	4.2%	-0.09 [-0.56, 0.39]	2016	
Emadi-Kouchak 2016	-5.83	1.92	25	-1.65	2.12	25	3.6%	-1.66 [-1.66, -0.44]	2016	
Subtotal (95% CI)			**342**			**227**	**37.6%**	**-0.30 [-0.58, -0.02]**		

Heterogeneity: Tau² = 0.12; Chi² = 22.30, df = 9 (P = 0.008); I² = 60%

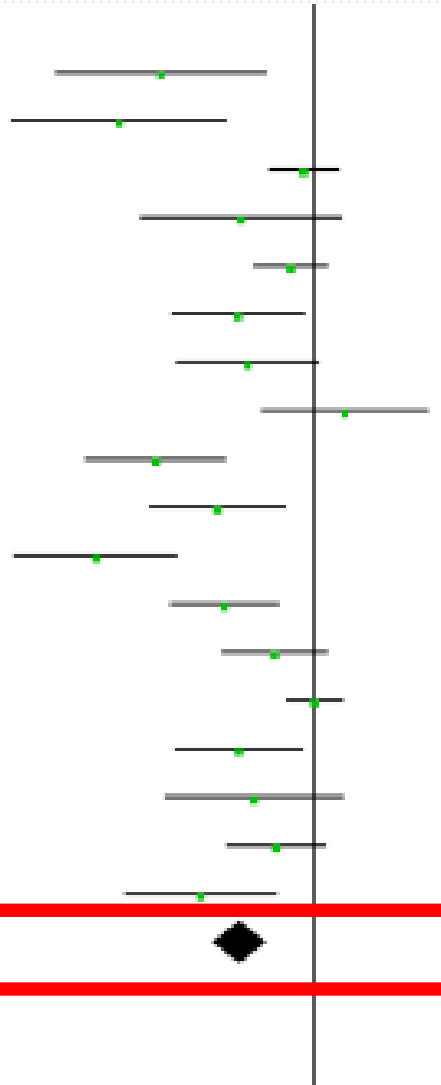
Test for overall effect: Z = 2.14 (P = 0.03)

Evidence for adjunctive anti-inflammatory treatments in depression

1.1.2 Adjuctive anti-inflammatory agents									
Nemets 2002	-12.4	6.72	10	-1.6	7.35	10	2.3%	-1.47 [-2.48, -0.46]	2002
Su 2003	-13.6	3.8	12	-6.4	3.6	10	2.2%	-1.87 [-2.90, -0.83]	2003
DeBattista 2003	-6.1	4.62	68	-5.57	5.73	67	4.7%	-0.10 [-0.44, 0.24]	2003
Müller 2006	-17.5	6.17	10	-12.5	7.4	8	2.4%	-0.71 [-1.67, 0.26]	2006
Carney 2009	-11.5	6.1	62	-10.1	6.06	60	4.7%	-0.23 [-0.58, 0.13]	2009
Akhondzadeh 2009	-13.2	4.26	20	-10.2	3.77	20	3.5%	-0.73 [-1.37, -0.09]	2009
Mischoulon 2009	-7.7	7.9	16	-3	6.5	19	3.3%	-0.64 [-1.32, 0.04]	2009
Bot 2010	-12.3	8.91	12	-14.8	7.63	12	2.9%	0.29 [-0.51, 1.10]	2010
Abolfazli 2011	-14.04	2.49	22	-10.04	2.69	22	3.4%	-1.52 [-2.19, -0.84]	2011
Abbasi 2012	-13.4	3.88	20	-10.05	3.15	20	3.4%	-0.93 [-1.58, -0.27]	2012
Sepanjnia 2012	-16.7	1.55	20	-13.4	1.55	20	3.0%	-2.09 [-2.87, -1.30]	2012
Ghanizadeh 2013	-12.84	6.36	31	-8.2	4.02	31	4.0%	-0.86 [-1.38, -0.34]	2013
Haghighi 2014	-13.7	3.65	30	-12.27	3.69	30	4.0%	-0.38 [-0.90, 0.13]	2014
Berk 2014	-5.8	7.96	108	-5.8	8.31	99	5.0%	0.00 [-0.27, 0.27]	2014
Gougol 2015	-18.5	7.1	22	-13.68	5.89	22	3.6%	-0.73 [-1.34, -0.11]	2015
Majd 2015	-18.3	3.4	14	-15.8	5.2	9	2.7%	-0.58 [-1.43, 0.28]	2015
Dean 2017	-15.2	9.21	36	-11.9	8.53	35	4.2%	-0.37 [-0.84, 0.10]	2017
Hussain 2017	-18.2	16.1	16	-9.2	16.1	18	2.2%	-1.00 [-1.82, -0.18]	2017
Subtotal (95% CI)			**529**			**512**	**62.4%**	**-0.70 [-0.97, -0.43]**	

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 66.25$, df = 17 ($P < 0.00001$); $I^2 = 74\%$

Test for overall effect: $Z = 5.12$ ($P < 0.00001$)



Evidence - anti-inflammatory therapies in depression

- Sub-group analysis - NSAIDs/Minocycline/Statins and Omega-3 FA – significant anti-depressant effects
- Gastrointestinal AE's - different between groups – only for statins/NAC

Evidence - anti-inflammatory therapies in depression

Systematic Review / Meta-analysis

Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials

Acta Psychiatr Scand 2019: 139: 404–419

DOI: 10.1111/acps.13016

36 RCTs (N ~ 9000)
NSAIDs(n=13)/**Cytokine** inhibitors(n=9)/**Statin**s(n=7)/**Minocycline**(n=3)/Pioglitazone(n=2)/**Glucocorticoids** (n=2)
Pooled effects as monotherapy – SMD = 0.41
Pooled effects as add-on – SMD = 0.64
No increased risk for GI or CVS events
Non-significant increased risk of infections

Potential anti-inflammatory treatments

Intervention	Evidence	Comments
Celecoxib and other NSAIDs	• May be useful as a monotherapy • Or in combination with antidepressant medication	Patients with higher initial inflammation experienced greater benefit from celecoxib than those with lower inflammation

Potential anti-inflammatory treatments

Intervention	Evidence	Comments
Cytokine inhibitors (e.g., infliximab)	• Reduced depressive symptoms in people with psoriasis • Lessened fatigue during cancer treatment • Resolved MDD in Crohn's disease	Patients with high baseline CRP levels had substantially greater reductions in depressive symptoms than those with low CRP levels

Potential anti-inflammatory treatments

Intervention	Evidence	Comments
Prebiotics and probiotics	2 Meta-analysis 10 trials (n=1349) Probiotics – NS – (d = -0.13) 34 trials Prebiotics – NS (d = -0.08) Probiotics – Sig (d = -0.24)	Larger ES noted for clinical/medical samples (d=-0.45, p<0.001)

Liu et al., Neurosci Behav Rev 2019; Ng et al., J Affect Dis 2018

Potential anti-inflammatory treatments

Intervention	Evidence	Comments
Healthy diets (e.g., Mediterranean diet)	Review of 6 RCT's - 3 found fewer recurrences of depression - 2 found higher BDNF levels (MeDi + nuts)	• Few side effects • Wide variability in dietary components • Applicability to Indian culture • Disadv – motivation

Altun et al., Neurol Psy Brain Res 2019

Potential anti-inflammatory treatments

Intervention	Evidence	Comments
Exercise	• 23 RCT's (n=977) ➢ Vs no intervention (g=1.24) ➢ Vs psychotherapy (g=0.22) ➢ Vs anti-deps (g=0.08) ➢ As adjunct to anti-deps (g=0.50)	Best used as an adjunct to anti-deps (g=0.50, sig trend) Advantages vs Disadvantages Kvam et al., J Affect Disord 2016

Potential anti-inflammatory treatments

Intervention	Evidence	Comments
Integrative medicine Interventions – yoga/breathing /meditation	• May modulate stress immune response • Positive ES vs placebo • Comparable ES vs standard interventions • Mixed evidence for add-on to A/D medication	• Limited no of RCT's with lot of variability in results • Risk of bias unclear

(Cramer et al., J Affect Disord 2017)

Potential new therapeutic targets

- CBT - Can address multiple behaviors leading to inflammation and have lasting effects

(Su et al., 2014; Gazal et al., 2013)

- Lopresti AL (ANZJP, 2019)
  - ➔23 trials
  - ➔14 studies showed reduction in ≥1 marker, ↑ in 3 studies and no change in 6 studies
  - ➔Poorer treatment response in those with higher pre-morbid inflammation (n=3)

Unanswered questions…

Do changes in cytokine levels parallel treatment response in depression

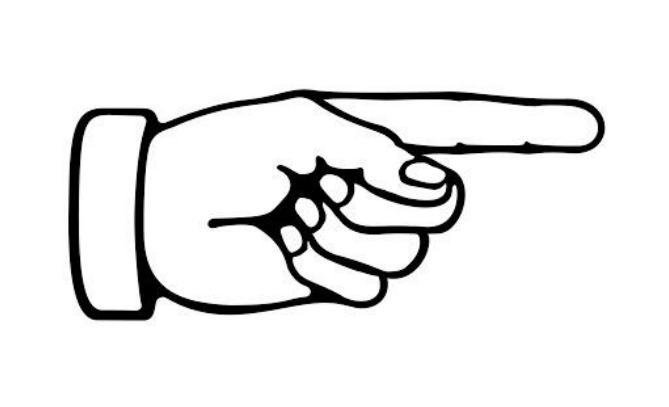
Do specific depressive symptoms predict better response to treatment?

How long to give anti-inflammatory treatments?

How to identify sub-groups that may optimally benefit from add-on Rx?

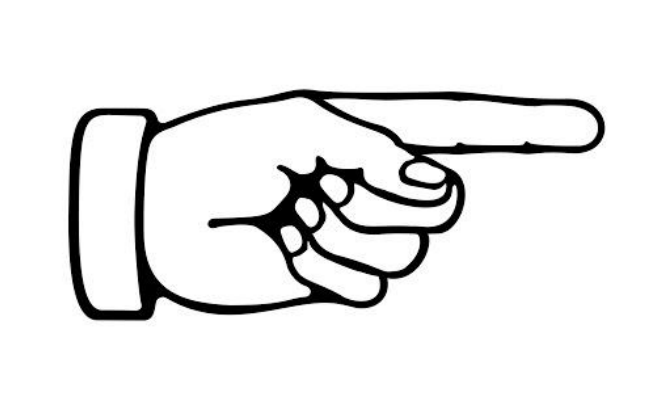
An integrated approach to practice

What can clinicians do? – An integrated approach to practice



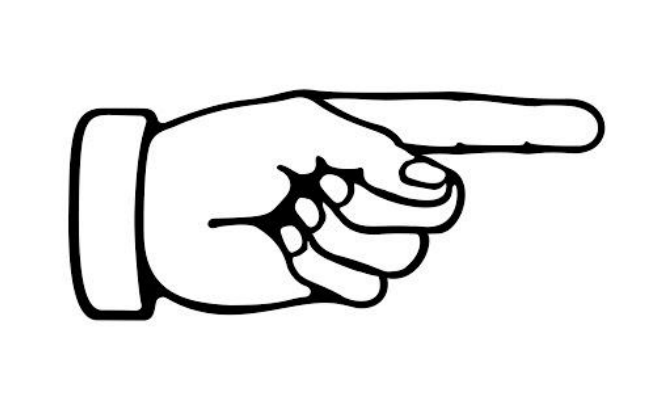
- Obtain a detailed history – obesity/sedentary lifestyle/early life adversity/smoking/f/h of immune disorders/gluten sensitivity/IBD
- Explore symptoms – omega-3 FA/Vit C/Vit E/FA

What can clinicians do? – An integrated approach to practice



- Incorporate these into diagnostic formulation
- Advice low cost non-pharmacological interventions
- Manage co-morbid alcohol/smoking

What can clinicians do? – An integrated approach to practice



- If non-response or inadequate response – CRP
- Choose from evidence based options
- Keep abreast of the emerging literature in the field of anti-inflammatory therapeutics

Conclusion

- Mounting evidence for inflammation in the pathogenesis of depression
- Mechanistic links include monoamines, glutamate, neuropeptide, HPA axis and growth factors
- Some promise noted in trials with anti-inflammatory agents but as trials get longer and more robust, efficacy is more modest
- Field is very exciting – personalized medicine
- Key question – Inflammation in whom?

Future needs

- Efficacy and safety of drugs that have less off-target effects
- Examine the extent of inflammatory change and relate it to changes in depressive symptoms
- Defining a reliable biomarker signature – at-risk patients that may benefit from immune therapies

References

- Cortese GP, Barrientos RM, Maier SF, Patterson SL. Aging and a peripheral immune challenge interact to reduce mature brain-derived neurotrophic factor and activation of TrkB, PLCgamma1, and ERK in hippocampal synaptoneurosomes. Journal of Neuroscience. 2011; 31:4274–4279
- Felger JC, Lotrich FE. Inflammatory Cytokines in Depression: Neurobiological Mechanisms and Therapeutic ImplicationsNeuroscience. 2013; 246: 199–229
- Bauer ME, Teixeira AL. Inflammation in psychiatric disorders: what comes first? Ann. N.Y. Acad. Sci. 2018;1–11
- Kiecolt-Glaser JK, Derry HM, M.A, Fagundes CP. Inflammation: Depression Fans the Flames and Feasts on the Heat. Am J Psychiatry 2015;172:11
- Menon V, Ameen S. Immunoinflammatory Therapies in Psychiatry: Current Evidence Base. Indian J Psychol Med 2017 Nov-Dec;39(6):721-726
- Muthuramalingam A, Menon V, Rajkumar RP, Negi VS. Effect of Fluoxetine on Inflammatory Cytokines in Drug-Naive Major Depression: A Short-Term Prospective Study from South India. J Clin Psychopharmacol. 2016 Dec;36(6):726-728

References

- Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008; 9(1): 46–56
- Capuron L, Ravaud A, Miller AH, Dantzer R. Baseline mood and psychosocial characteristics of patients developing depressive symptoms during interleukin-2 and/or interferon-alpha cancer therapy. Brain Behav Immun. 2004; 18:205–213.
- Uher R, Tansey KE, Dew T, et al: An inflammatory biomarker as a differential predictor of outcome of depression treatment with escitalopram and nortriptyline. AmJ Psychiatry 2014; 171:1278–1286
- Felger JC, Cole SW, Pace TW, Hu F, Woolwine BJ, Doho GH, Raison CL, Miller AH. Molecular signatures of peripheral blood mononuclear cells during chronic interferon-alpha treatment: relationship with depression and fatigue. Psychol Med. 2012a; 42:1591–1603.
- Gazal M, Souza LD, Fucolo BA, et al: The impact of cognitive behavioral therapy on IL-6 levels in unmedicated women experiencing the first episode of depression: a pilot study. Psychiatry Res 2013; 209:742–745
- Miller AH, Raison CL: Are anti-inflammatory therapies viable treatments for psychiatric disorders? Where the rubber meets the road. JAMA Psychiatry 2015; 72:527–528

References

- Köhler O, Benros ME, Nordentoft M, et al: Effect of antiinflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatry 2014; 71:1381–1391
- Molendijk ML, Bus BA, Spinhoven P, Penninx BW, Kenis G, Prickaerts J, Voshaar RC, Elzinga BM. Serum levels of brain-derived neurotrophic factor in major depressive disorder: state-trait issues, clinical features and pharmacological treatment. Mol Psychiatry. 2011; 16:1088–1095
- Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, Haroon E, Miller AH. A Randomized Controlled Trial of the Tumor Necrosis Factor Antagonist Infliximab for Treatment- Resistant Depression: The Role of Baseline Inflammatory Biomarkers. Arch Gen Psychiatry 2012:1–11.
- Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. Neuropsychopharmacology. 2000; 22:370–379.
- Frommberger UH, Bauer J, Haselbauer P, Fraulin A, Riemann D, Berger M. Interleukin-6-(IL-6) plasma levels in depression and schizophrenia: comparison between the acute state and after remission. Eur Arch Psychiatry Clin Neurosci. 1997; 247:228–233.
- Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polyorphism in the 5-HTT gene. Science. 2003; 301:386–389.

THANK YOU FOR A PATIENT LISTENING

Contact: drvmenon@gmail.com

Website:

http://www.jipmer.puducherry.gov.in/department/psychiatry/general-info