Psychoneuroimmunology:
Inflammatory Cytokines and Brain

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Introduction

- In 1964 George F. Solomon coined the term *psychoimmunology* and published a landmark article: “Emotions, Immunity, and Disease: A Speculative Theoretical Integration”.

- Various aspects of behavioral influences on immune function have been reviewed elsewhere.

Duration of a Stressor: Implications for Immune Function and Health

- Acute laboratory stressors that typically last a half hour or less provoke transient immune changes.

- Both brief and longer term stressors are associated with declines in functional aspects of immunity; however, in contrast to the decrements in lymphocyte numbers associated with longer term naturalistic stressors, laboratory stressors appear to increase cell numbers in some lymphocyte subpopulations.

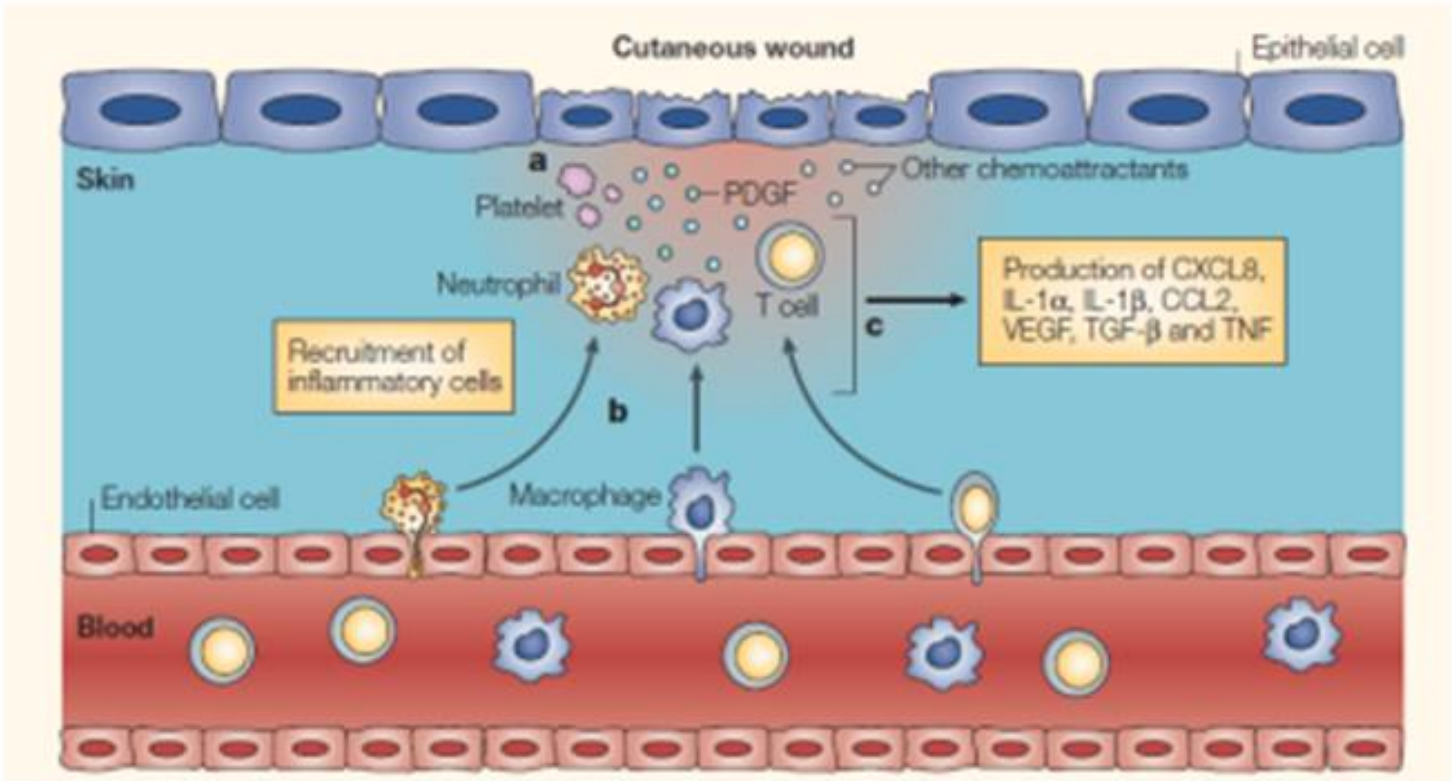
Duration of a Stressor: Implications for Immune Function and Health

- Most immune parameters return to resting levels within 1 hour after cessation of laboratory stressors.

- One possible mechanism may be the acute secretion of stress-responsive hormones, particularly catecholamines, which can alter a number of aspects of immune function.
- Both the duration and intensity of psychological stressors (as indexed by cardiovascular changes) are related to the breadth and magnitude of immune changes in laboratory studies.

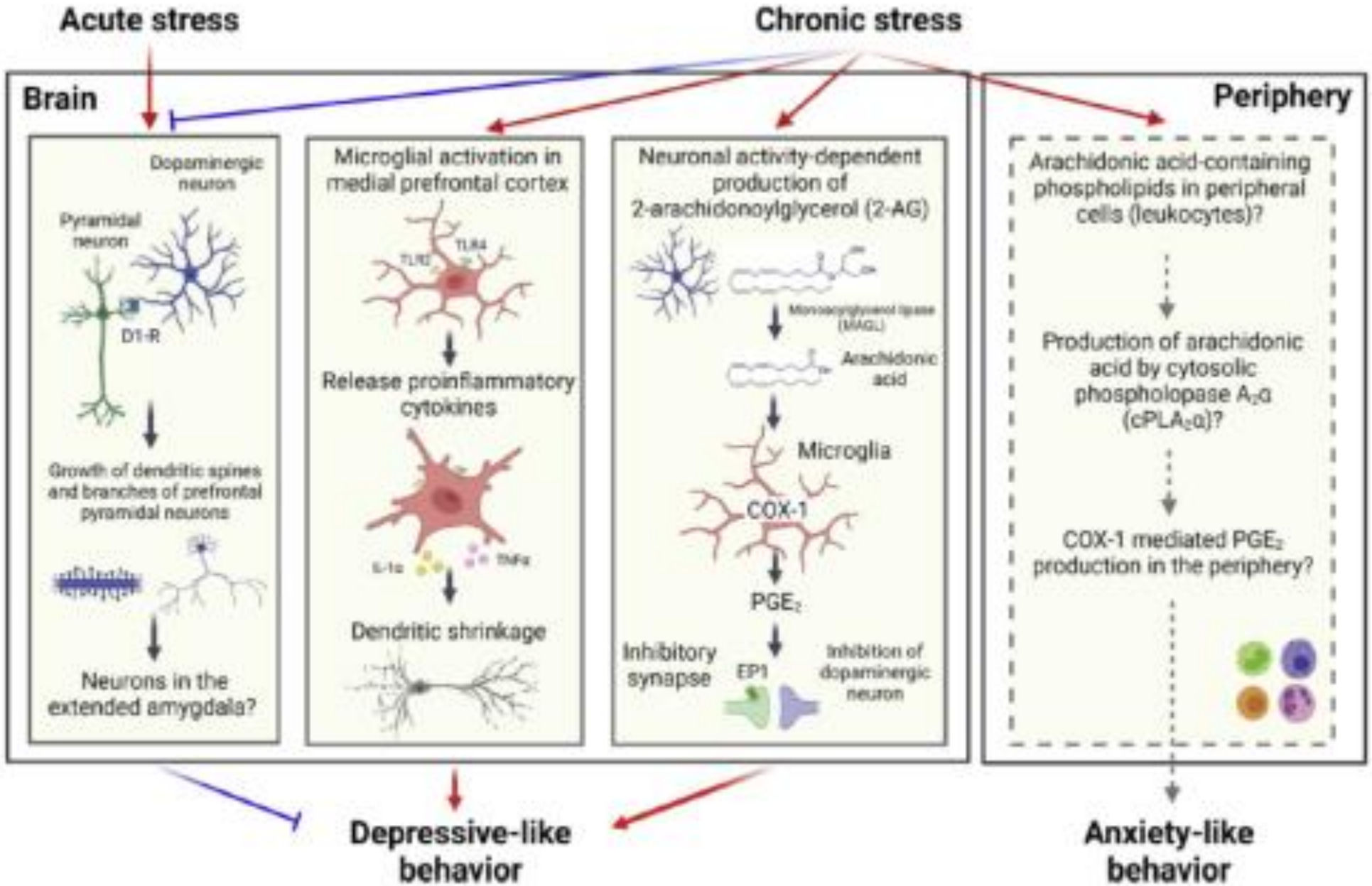
Short-Term or Acute Stressors

- A 10-year series of prospective studies of medical students' responses to examinations showed transient changes in multiple facets of the cellular immune response and its mediators; academic stress has also been widely used as a model by other laboratories.
- For example, stress influenced medical students' response to a series of three hepatitis B (Hep B) vaccinations.


Cutaneous wound
Epithelial cell
Skin
a
Platelet
PDGF
Other chemoattractants
Neutrophil
T cell
c
Production of CXCL8, IL-1α, IL-1β, CCL2, VEGF, TGF-β and TNF
Recruitment of inflammatory cells
b
Endothelial cell
Macrophage
Blood

Chronic Stress

- Stressors that are resistant to behavioral coping, particularly stressors perceived as unpredictable and uncontrollable, may continue to be associated with elevated stress hormones even after repeated exposure.
- For example, men and women who provide long-term care for a spouse or parent with Alzheimer’s disease typically report high levels of stress as they attempt to cope with the family member’s problematic behaviors, and this stressor has been associated with prolonged endocrine and immune dysregulation, as well as with health changes, including alterations in vaccine response and wound healing.


Acute stress
Chronic stress
Brain
Periphery
Dopaminergic neuron
Pyramidal neuron
D1-R
Growth of dendritic spines and branches of prefrontal pyramidal neurons
Neurons in the extended amygdala?
Microglial activation in medial prefrontal cortex
TLR2
TLR4
Release proinflammatory cytokines
IL-1α
TNFα
Dendritic shrinkage
Neuronal activity-dependent production of 2-arachidonoylglycerol (2-AG)
Monoacylglycerol lipase (MAGL)
Arachidonic acid
Microglia
COX-1
PGE2
Inhibitory synapse
EP1
Inhibition of dopaminergic neuron
Arachidonic acid-containing phospholipids in peripheral cells (leukocytes)?
Production of arachidonic acid by cytosolic phospholopase A2α (cPLA2α)?
COX-1 mediated PGE2 production in the periphery?
Depressive-like behavior
Anxiety-like behavior

Patients with Major Depression Show Increased Biomarkers of Inflammation

- Since the early reports of immune activation in major depression, a vast literature has reproduced these findings, and metaanalyses have revealed that peripheral blood elevations in the cytokines, interleukin (IL)-6, tumor necrosis factor (TNF)-a, and the acute-phase reactant, c-reactive protein (CRP) are some of the most reliable biomarkers of increased inflammation in depressed patients.

Cytokine Administration Induces Depressive Symptoms

- A second major body of data that has supported the notion that inflammation may have a role in depression is the findings that administration of inflammatory cytokines or cytokine inducers can induce a depressive-like behavior in both laboratory animals and humans.
- For example, acute administration of endotoxin and typhoid vaccination to humans leads to a host of behavioral changes, including depressed mood, fatigue, and cognitive dysfunction.

Cytokine Administration Induces Depressive Symptoms

- Chronic administration of the inflammatory cytokine, interferon-a (IFN-a) has also been found to induce depressive symptoms, with as many as 30–50% of IFN-a treated patients meeting the symptom criteria for major depression.

Stress Increases Inflammation

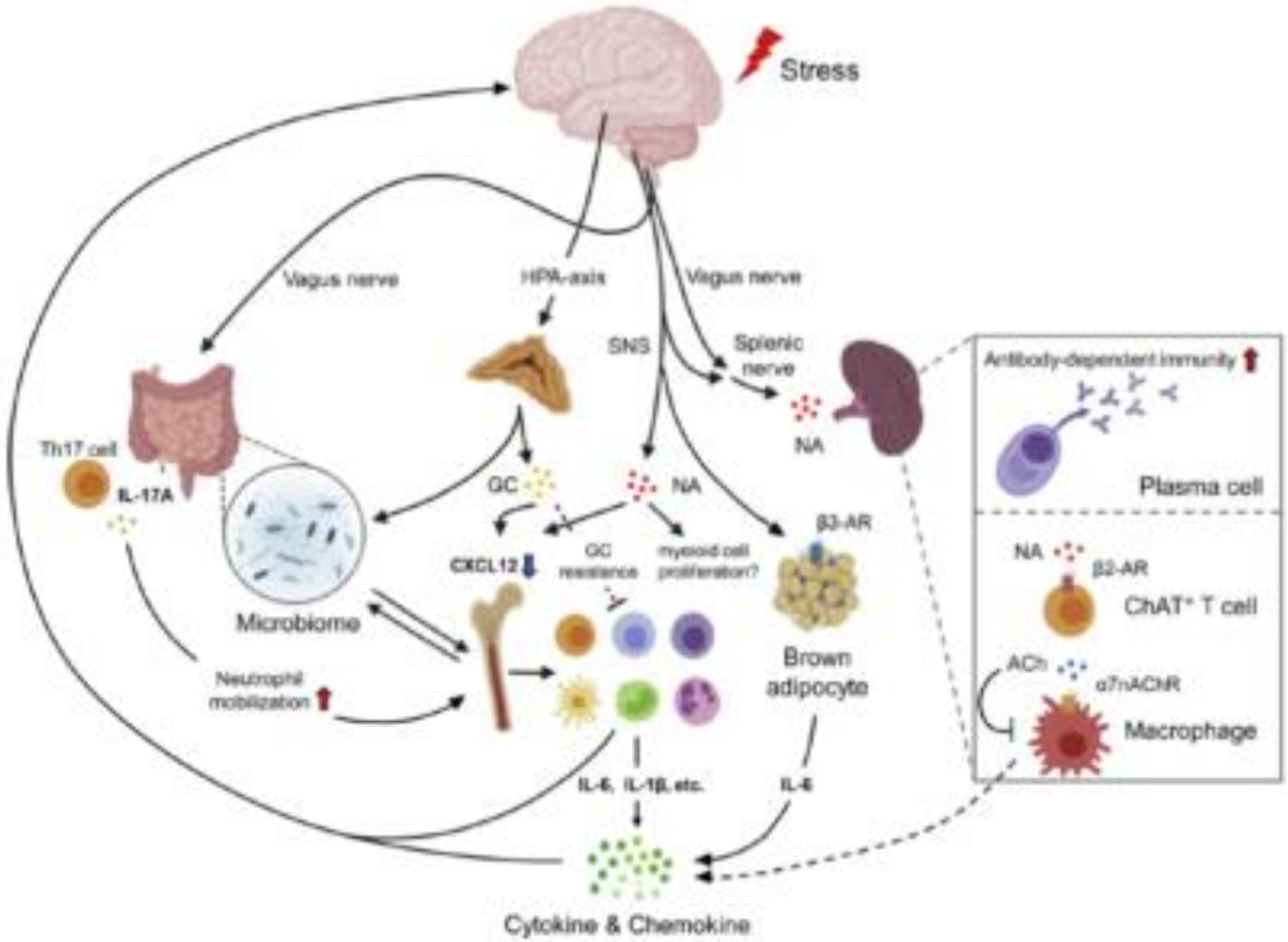
- One of the important early findings in this area was that exposure to the Trier Social Stress Test (TSST), a public speaking and mental arithmetic stressor, was associated with a significant increase in the DNA binding of the inflammatory transcription factor NF-kB in peripheral blood mononuclear cells (PBMCs) as measured by electromobility shift assay and compared with individuals who were spectators of the task.

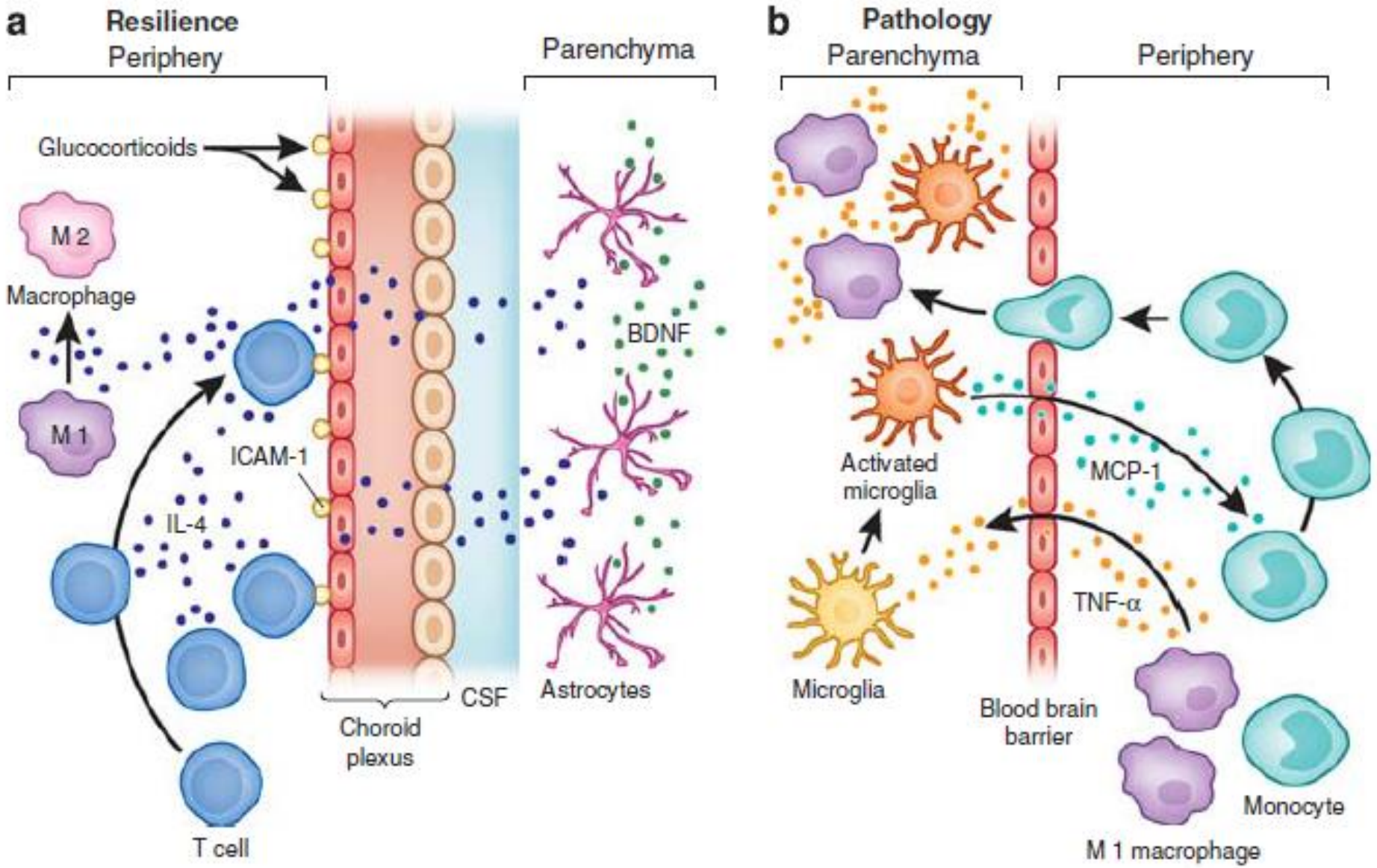
Stress Increases Inflammation

- In terms of the mechanisms by which stress activates the inflammatory response, attention has been focused on the sympathetic nervous system (SNS).
- For example, catecholamines acting through a- and b-adrenergic receptors have been shown to increase cytokine expression in both the brain and the periphery of rats, and a adrenergic antagonists were noted to block the increased peripheral blood concentrations of IL-6 induced by altitude stress in humans.

Stress Increases Inflammation

- Nevertheless, the impact of the SNS on the immune system is complex and involves both stimulatory and inhibitory aspects.
- It should be noted that there is an emerging literature that indicates that the parasympathetic nervous system is also involved in immune regulation.


Stress
Vagus nerve
HPA-axis
Vagus nerve
SNS
Splenic nerve
NA
Th17 cell
IL-17A
GC
NA
β3-AR
CXCL12
GC resistance
myeloid cell proliferation?
Microbiome
Brown adipocyte
Neutrophil mobilization
IL-6, IL-1β, etc.
IL-6
Cytokine & Chemokine
Antibody-dependent immunity
Plasma cell
NA
β2-AR
ChAT+ T cell
ACh
α7nAChR
Macrophage


a
Resilience
Periphery
Parenchyma
Glucocorticoids
M 2
Macrophage
M 1
ICAM-1
IL-4
BDNF
CSF
Choroid
plexus
Astrocytes
T cell
b
Pathology
Parenchyma
Periphery
Activated
microglia
MCP-1
TNF-α
Microglia
Blood brain
barrier
Monocyte
M 1 macrophage

Cytokines Alter Neurotransmitter Metabolism

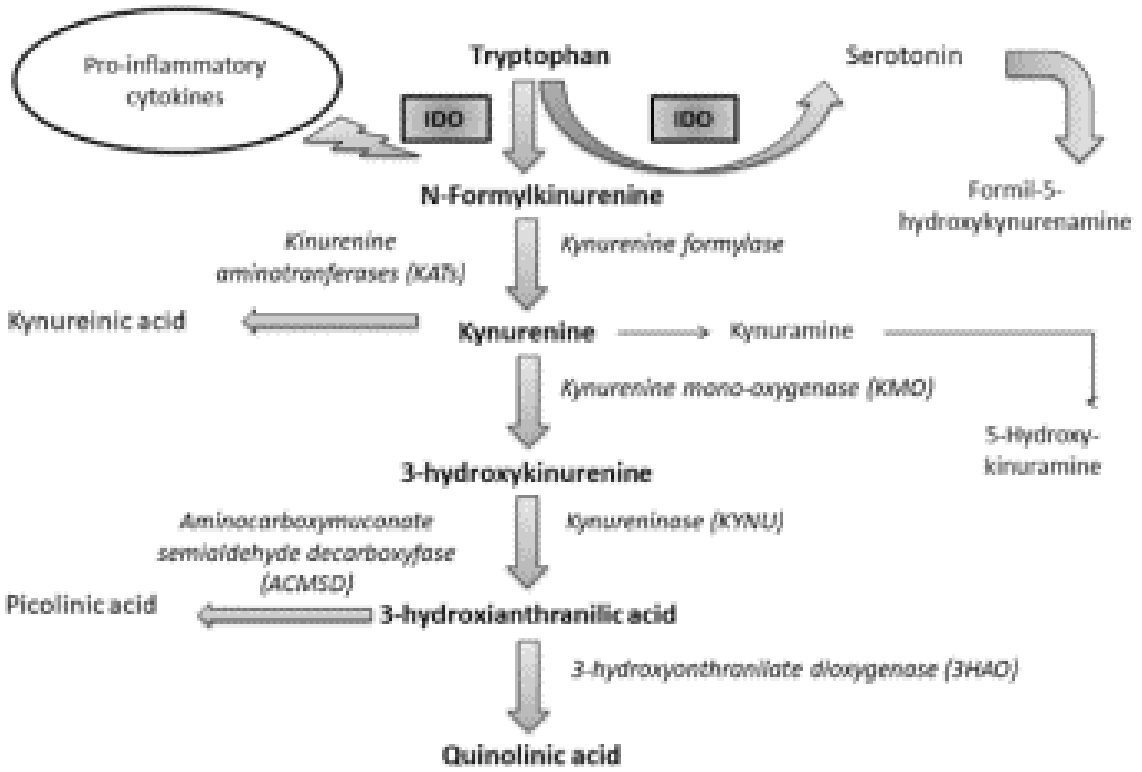
- Probably best studied of the mechanisms by which cytokines influence behavior is their effects on neurotransmitter metabolism.
- Numerous human and laboratory animal studies have demonstrated that multiple neurotransmitter systems are affected by acute and chronic administration of cytokines, including monoamines, serotonin, and dopamine, as well as glutamate.

Cytokine effects on monoamine metabolism

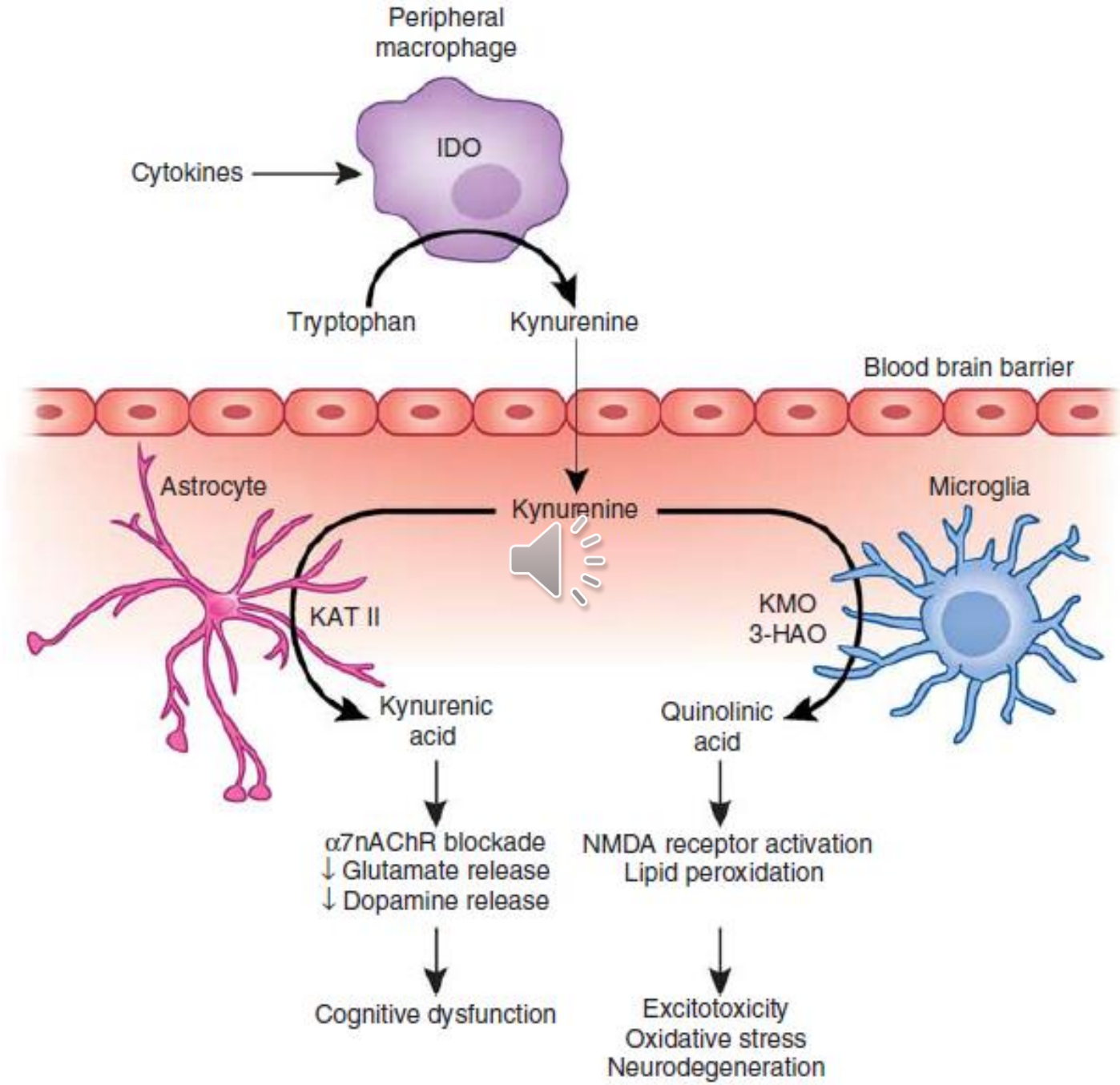
- Many studies have shown strong evidence that serotonin pathways are likely involved in the cytokine effects on behavior.
- In conjunction with these findings, data have suggested that cytokines have a significant impact on dopamine pathways as well.

Mechanisms by which cytokines affect monoamine metabolism

- Several mechanisms have received special attention regarding the impact of cytokines on monoamine metabolism that may ultimately serve as targets for pharmacologic intervention.
- Indoleamine-2,3-dioxygenase (IDO) is an enzyme expressed in multiple cell types, including macrophages, dendritic cells, microglia, astrocytes, and neurons.

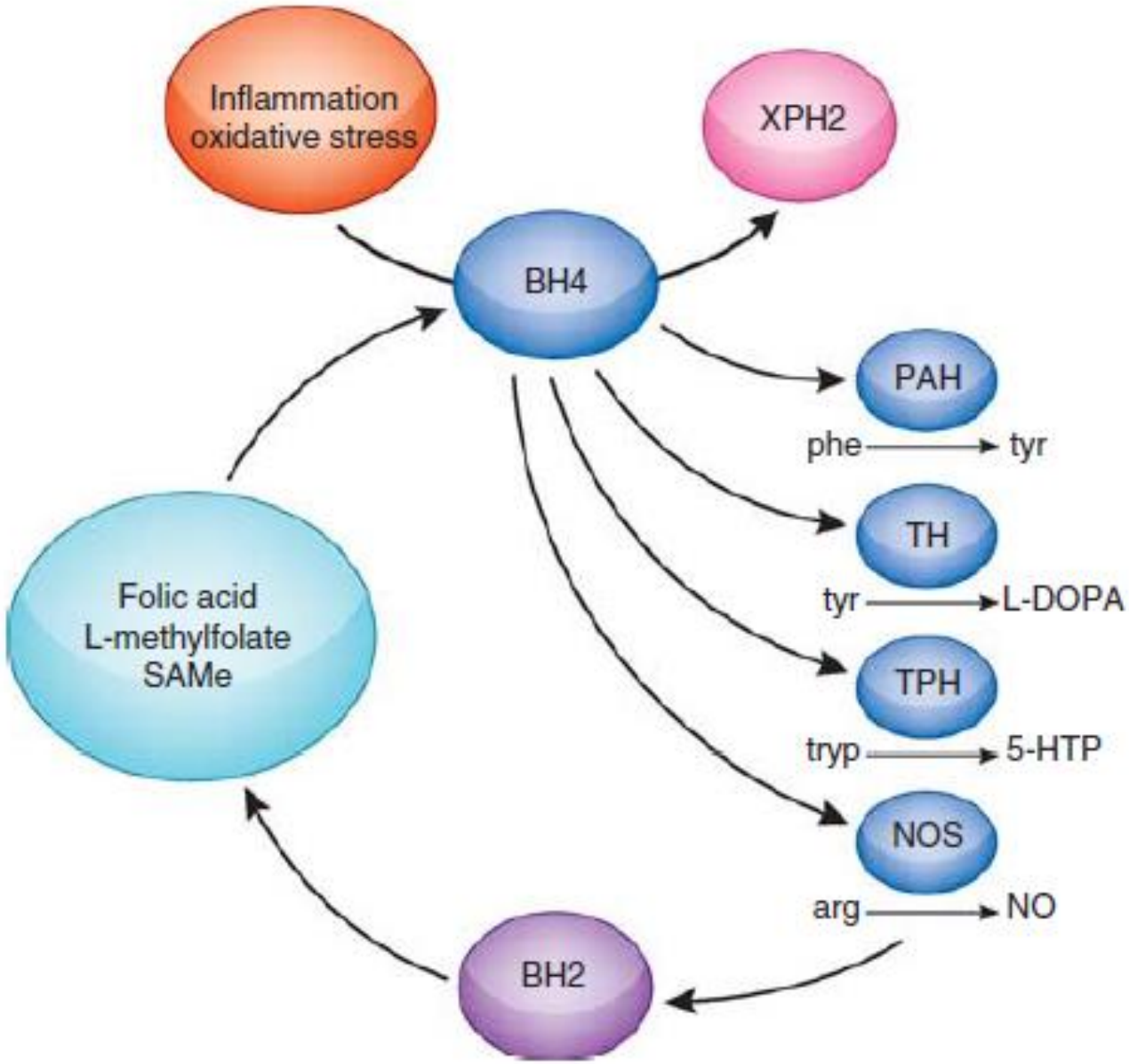


The degradation of serotonin by indolamine 2,3-deoxygenase, called kynurenine derivation, produces formyl-5-hydroxykynurenamine detected in brain of patients with major depressive disorder.


Peripheral macrophage
IDO
Cytokines
Tryptophan
Kynurenine
Blood brain barrier
Astrocyte
Kynurenine
Microglia
KAT II
KMO
3-HAO
Kynurenic acid
Quinolinic acid
α7nAChR blockade
↓ Glutamate release
↓ Dopamine release
NMDA receptor activation
Lipid peroxidation
Cognitive dysfunction
Excitotoxicity
Oxidative stress
Neurodegeneration

Mechanisms by which cytokines affect monoamine metabolism

- Another pathway that can influence monoamine metabolism is the cytokine signaling pathway, MAPK. Both in vitro and in vivo data have established that stimulation of p38 MAPK pathways can increase the expression and function of the SERT.
- For example, treatment of mouse midbrain and striatal synaptosomes with IL-1b and TNF-a was shown to lead to a dose- and time-dependent increase in serotonin reuptake, which was reversed by the p38 antagonist, SB203580.
- It should be noted that MAPK pathways have also been found to influence the dopamine transporter.


Inflammation
oxidative stress
XPH2
BH4
PAH
phe
tyr
TH
tyr
L-DOPA
TPH
tryp
5-HTP
NOS
arg
NO
Folic acid
L-methylfolate
SAMe
BH2

Cytokine effects on glutamate metabolism

- Aside from effects on monoamines, another neurotransmitter target of inflammation is glutamate. Cytokines have been shown to have profound effects on glutamate metabolism, including a rich literature demonstrating that cytokines can
- (1) decrease the expression of glutamate transporters on relevant glial elements and
- (2) increase the release of glutamate from astrocytes.

Cytokine Effects on Neurogenesis

- Chronic stress has been shown to inhibit neurogenesis, which in turn has been associated with the development of depressive-like behavior in laboratory animals.
- In terms of the role of cytokines in these findings, data have shown that stress-induced decreases in neurogenesis as well as the expression of relevant nerve growth factors, including BDNF, which support neurogenesis, can be reversed by the administration of an IL-1 receptor antagonist (IL-1ra) or transplantation of IL-1ra-secreting neural precursor cells into the hippocampus, or by the use of IL-1 receptor-knockout (KO) mice.

Cytokine Effects on Neuroendocrine Function

- Alterations in the hypothalamic–pituitary–adrenal (HPA) axis are some of the most reproducible findings in patients with major depression.
- Patients with major depression have been found to show increased concentrations of the HPA axis hormones, ACTH and cortisol, as well as increases in the CSF measures of the HPA axis-regulatory neuropeptide, corticotrophin-releasing hormone (CRH).
- Of relevance to inflammation, administration of inflammatory cytokines to laboratory animals has been shown to profoundly stimulate not only ACTH and cortisol but also the expression and release of CRH.

Cytokine Effects on Neuroendocrine Function

- It is generally believed that glucocorticoid resistance is a result of decreased expression and/or function of the receptor for glucocorticoids.
- Of relevance in this regard, there is a rich literature indicating that inflammatory cytokines can disrupt glucocorticoid receptor (GR) function while decreasing GR expression.

SOURCES OF PERIPHERAL INFLAMMATION IN DEPRESSION

CONCLUSION AND FUTURE DIRECTIONS

- Given the mounting data that the immune system may contribute both to the development of neuropsychiatric disease as well as the maintenance of neuronal integrity, there is an increasing need to
- (1) test neuropharmacologic strategies that target the immune system to treat neuropsychiatric disorders such as depression and
- (2) develop better biomarkers to measure the relative status of the immunologic response.

THANKS FOR YOUR ATTENTION

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