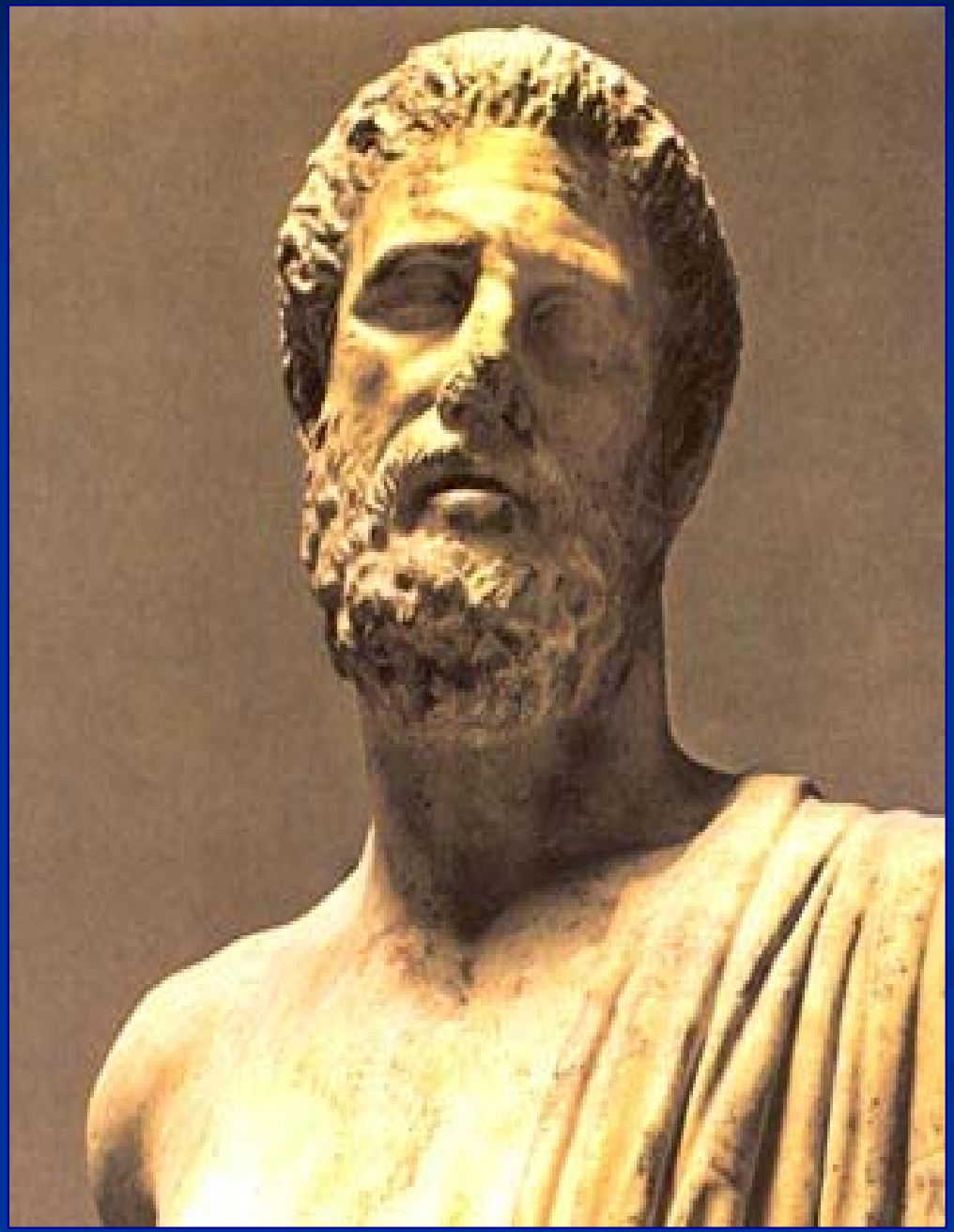
Psychoimmunology and Psychiatry.

Brian E. Leonard,

Galway, Munich, Maastricht.

Hippokrates (5th century BC)



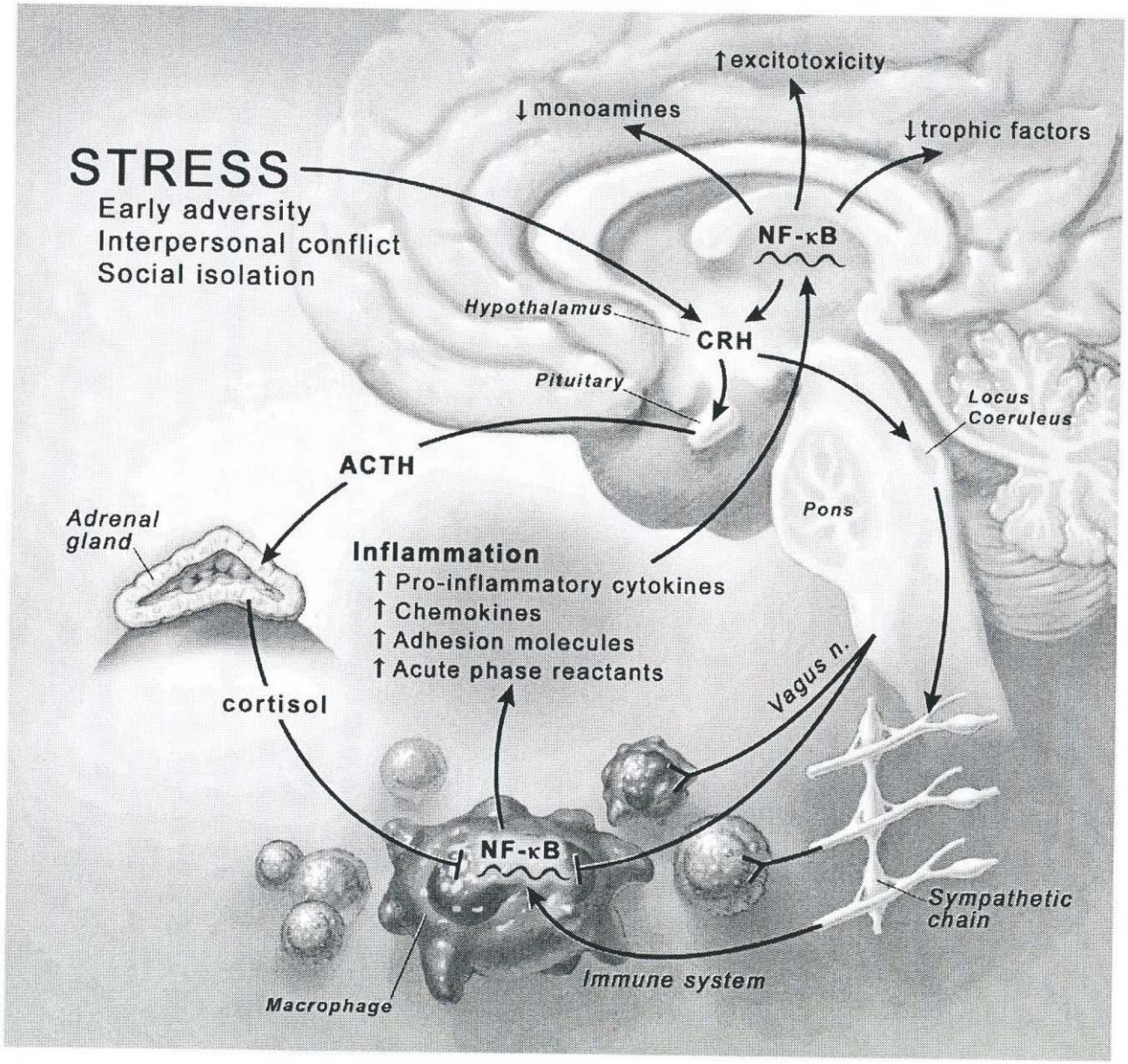
The hygiene hypothesis and psychiatric disorders.

- Chronic inflammatory disorders [allergies, IBS, autoimmune disorders] are increasing in developed countries because of a changing microbial environment has disrupted immunoregulatory circuits which normally terminate inflammatory responses.
- Depression and anxiety disorders are increasing in industrialised countries and in urban areas.
- Stress related markers of ongoing inflammation occur in patients with depression and anxiety in absence of accompanying inflammatory disorder.
- [Rook and Lowry,Trends Immunol.29,150,2008;Bach. N.Eng.J.Med. 347,911,2002].

Depression as a whole body disorder

- Endocrine changes.
- Immune changes.
- Cardiovascular changes.
- Cancer.
- Diabetes mellitus type 2.
- Autoimmune diseases.
- FREQUENCY INCREASES IN PATIENTS WITH MAJOR DEPRESSION.

Stress, the ANS and Inflammation



Trauma, Stress and Depression-1.

- Stress activates the Hypothalamic-Pituitary-Adrenal Axis.
- Increase in synthesis and release of glucocorticoids.
- Activation of macrophages and microglia to release pro-inflammatory cytokines [TNF alpha and IL-6]
- Glucocorticoids inhibit synthesis of nerve growth factors [BDNF,IGF-1,VEGF etc.]

Trauma, Stress and Depression-2.

- Nerve growth factors are responsible for repair to damaged neurons, synaptic plasticity and neurotransmitter synthesis.
- Stress and depression reduce the synthesis of these growth factors (possibly via release of glucocorticoids).
- Thus damaged neuronal networks remain ;apoptosis increased and key brain regions decrease in volume (hippocampus ,frontal cortex, amygdala).

Immune changes in depression.

- Depression as an inflammatory disorder:-
- Over 40 different immune markers (most of them inflammatory markers!) related to depression (Zorrilla et al,2000)
- Increased peripheral and central pro-inflammatory cytokines associated with depression (IL-1, IL-6, TNF,IFN). Rise in acute phase proteins.
- Epidemiological studies show increase in inflammatory diseases [such as rheumatoid arthritis, psoriasis and autoimmune diseases] in patients with depression.

Immune changes in major depression-1..

- Macrophage theory of Smith [1991]suggested that the major symptoms of depression [anhedonia, sleep disturbance, anorexia, cognitive dysfunction, loss of libido etc.] were the result of chronic low grade inflammation.
- Evidence: increase in pro-inflammatory cytokines [IL-1 and 6,interferon gamma, tumour necrosis factor alpha etc] and a reduction in anti-inflammatory cytokines [IL-4,IL-10,IL-13 etc] in depressed patients.
- : pro-inflammatory cytokines, such as interferon alpha, used therapeutically [eg.in hepatitis and MS] cause severe depressive symptoms in about 40% of otherwise non-depressed patients.

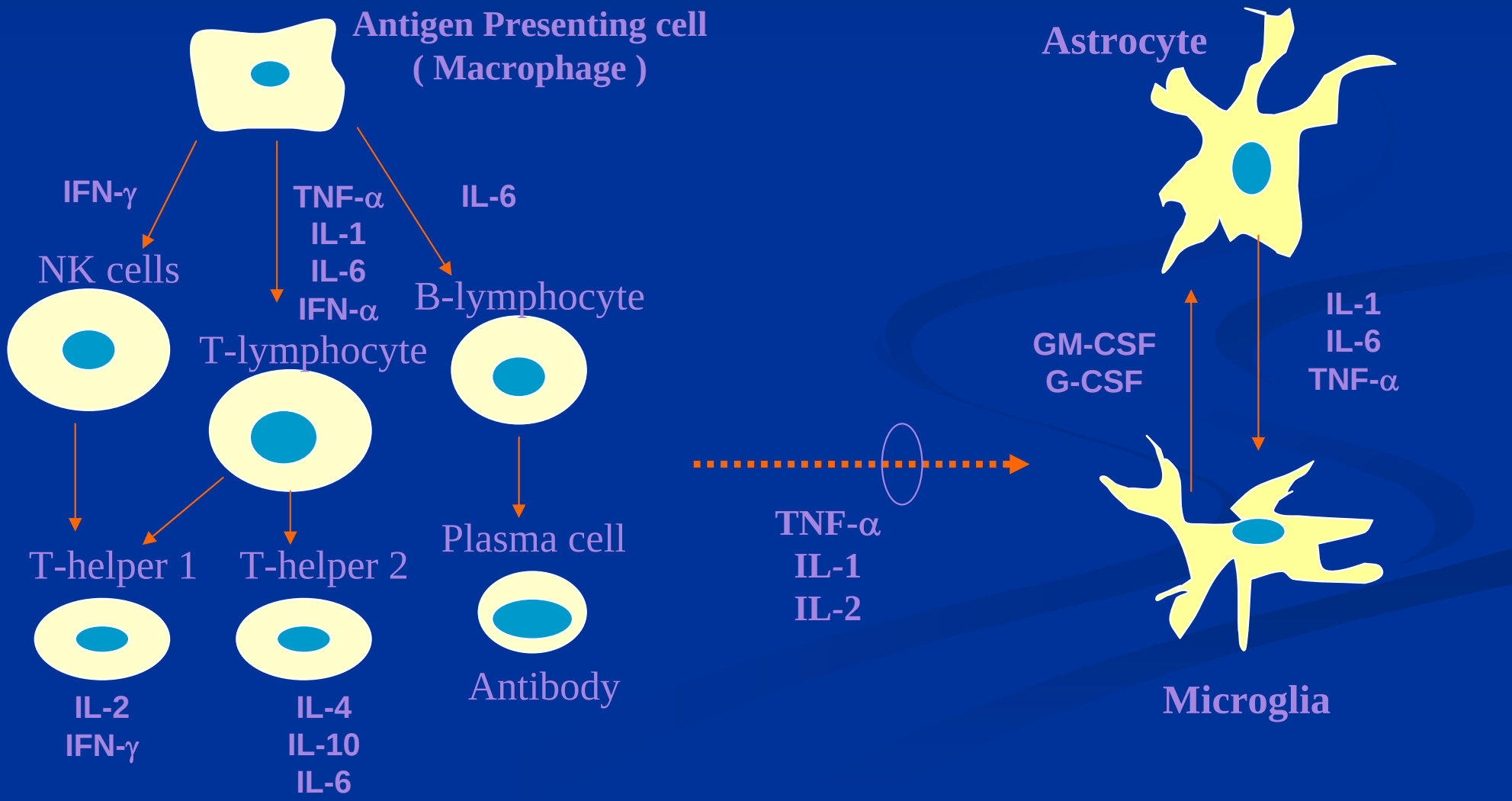
Immune changes in depression-2.

- Depression-like symptoms are initiated by LPS, bacterial and viral infections. These include: anhedonia, anorexia, lethargy, sleep disturbance, loss of libido, memory deficit, cognitive dysfunction).
- Effective antidepressant treatment reduces these changes.

CYTOKINE NETWORK

Peripheral immune system

Central nervous system



Are small immune changes of biological importance?

- Small, diurnal changes in TNF and IL-1 in blood and CSF regulate the normal sleep-wake cycle.

- In control subjects, low doses of endotoxins (LPS, Salmonella vaccine etc.) double the blood pro-inflammatory cytokines and NREM sleep without causing a change in heart rate, temperature or cortisol.

- Kapsimarko et al. Curr.Opin.Pulm.Med. 11,481, 2005; Wright et al. Brain Behav. Immun. 19,345,2005.

Pro-inflammatory cytokines in depression.

- Meta-Analysis of 22 studies for period 1995-2010 by Hannestad et al.(2011).
- TNF-alpha,IL-6 and IL-1 beta raised in untreated patients.
- Effective antidepressant treatment reduced depressive symptoms but not TNF.
- Antidepressants, SSRI's, reduced IL-1 and IL-6.
- Thus inflammatory cytokines may contribute to symptoms of depression, but do not necessarily block all their effects.

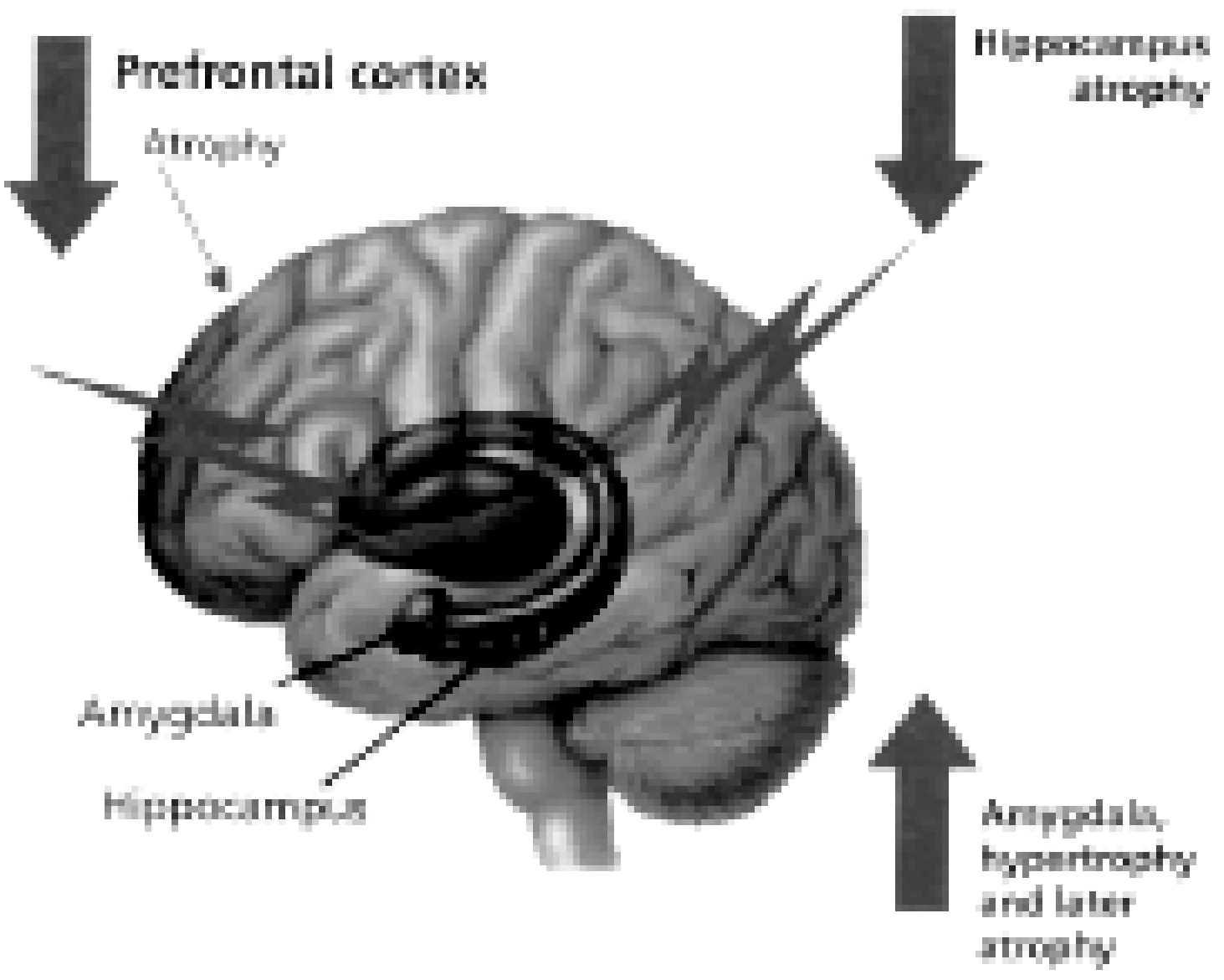
Anti-inflammatory treatments and depression.

- Anti-TNF antibodies in Crohn's disease and psoriasis attenuate depressive symptoms before improvement in physical symptoms of the disease.
- Cyclo-oxygenase inhibitors enhance the efficacy of standard antidepressants in depressed patients.
- Cyclo-oxygenase inhibitors have anti-depressant effects in chronic rodent models of depression.
- Some antidepressants have anti-inflammatory activity .
- [see Mueller et al. Mol.Psychiat.11,680,2006]

Link between inflammation and neurodegeneration in depression.

- Chronic inflammation increases neurotoxins that, together with cytokines and glucocorticoids increase apoptosis.

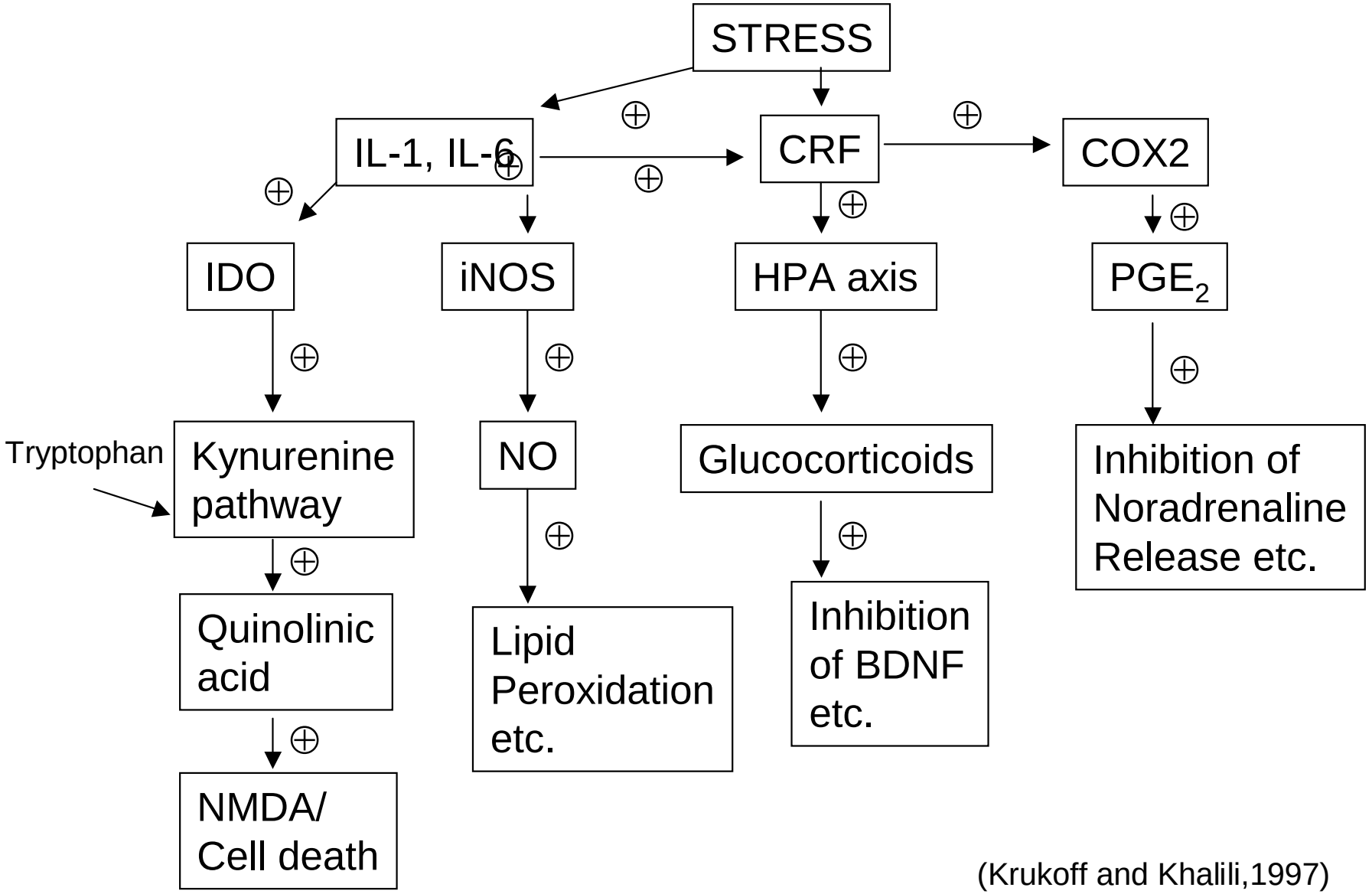
The brain under stress: structural remoceling



Neurodegeneration in depression-evidence.

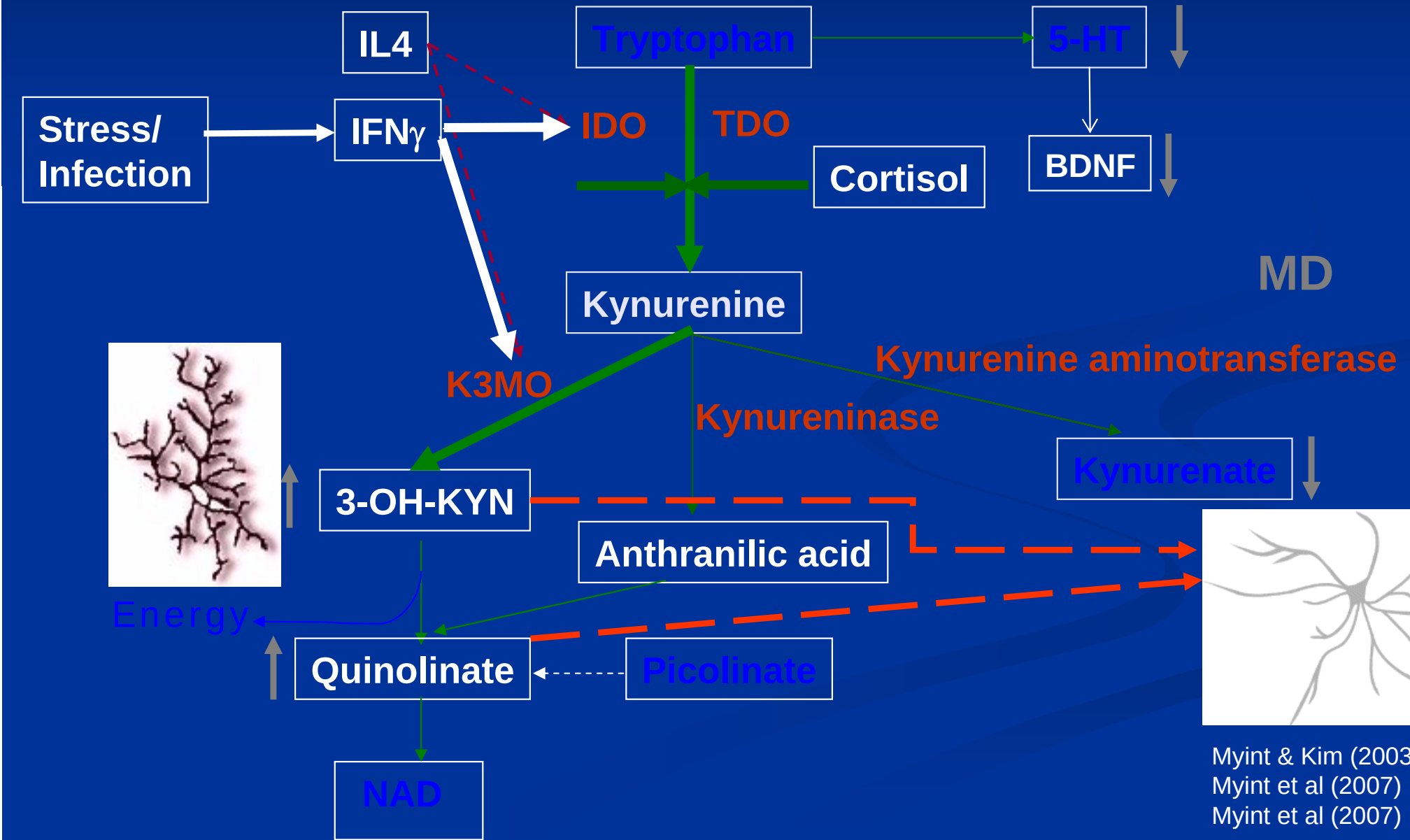
- Reduced volume of gray matter in hippocampus (Sheline et al. Am.J.Psychiat.2003)
- Decreased hippocampal neuropil (Stockmeier et al. Biol. Psychiat.2003)
- Loss of prefrontal cortical astroglia and neurons (Rajkowska et al. Biol. Psychiat.1999).
- Reduced amygdala volume.

Possible Mechanisms of Neurodegeneration



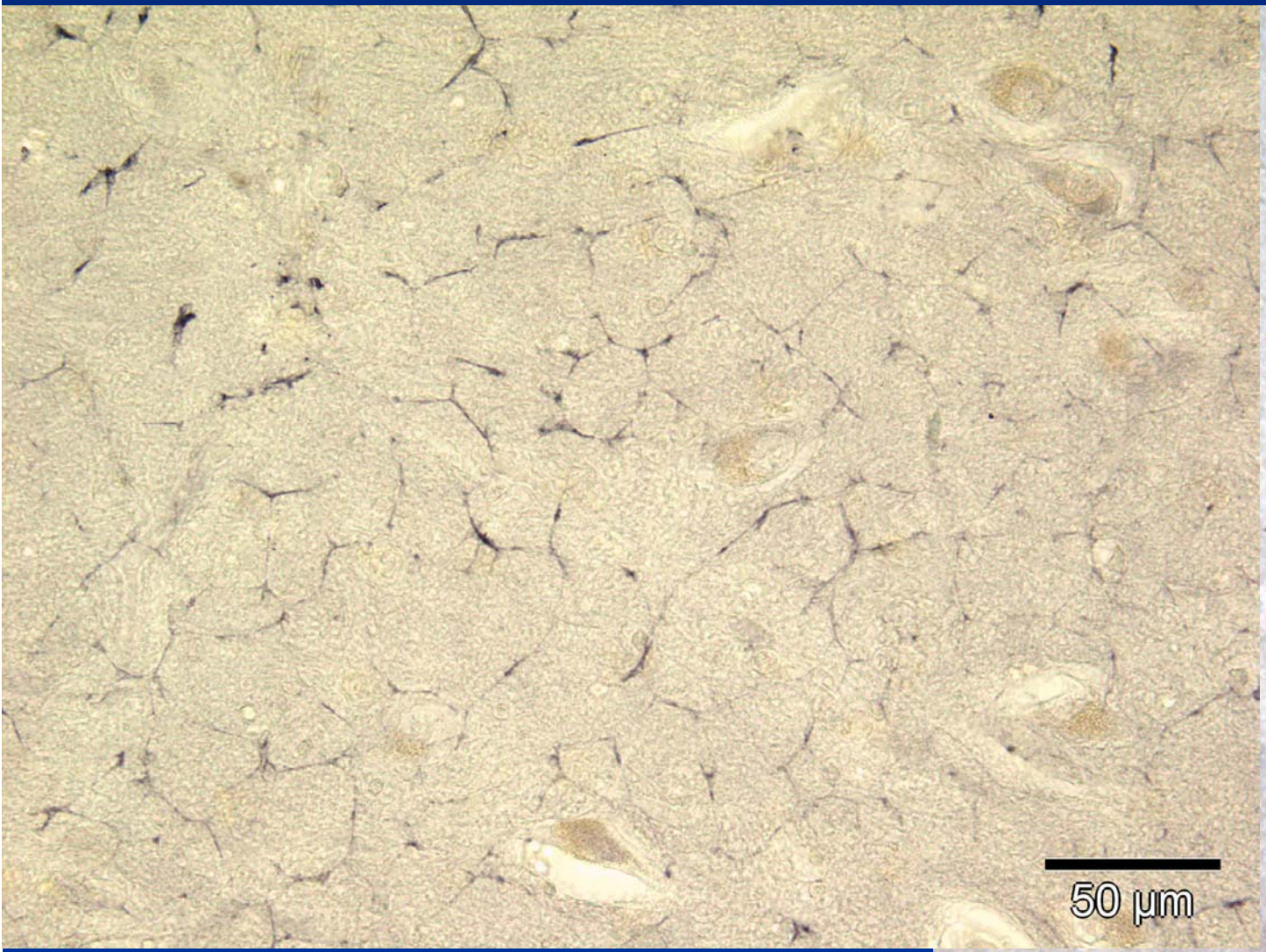
(Krukoff and Khalili,1997)
(Dawson and Dawson, 1995)

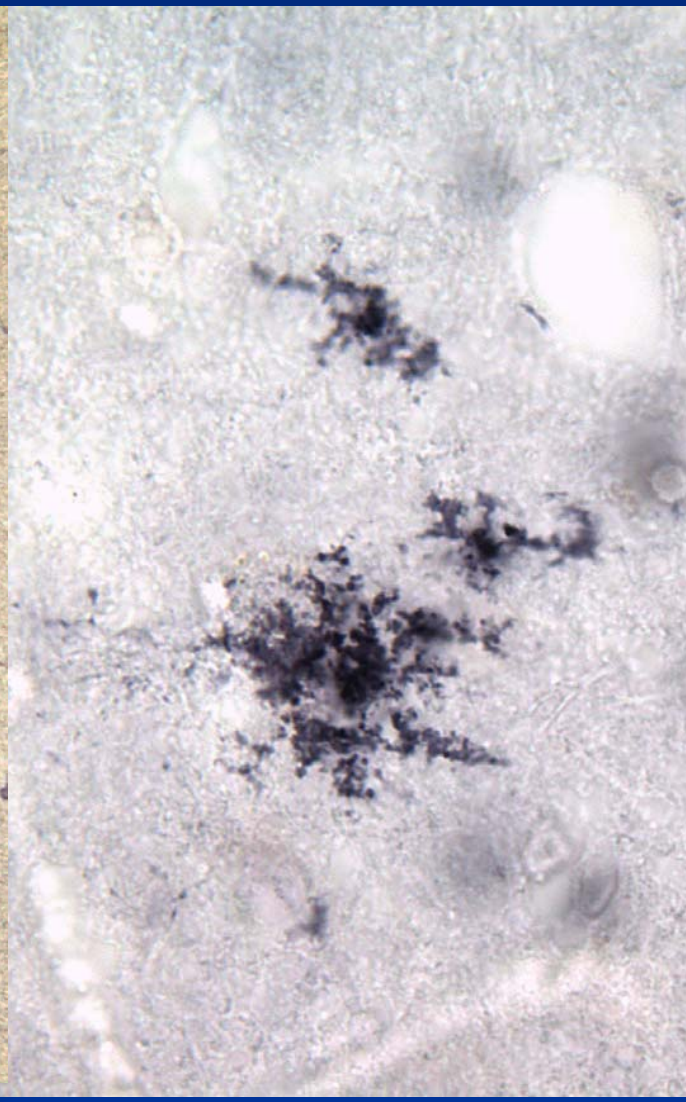
Possible Mechanisms



Myint & Kim (2003)
Myint et al (2007)
Myint et al (2007)

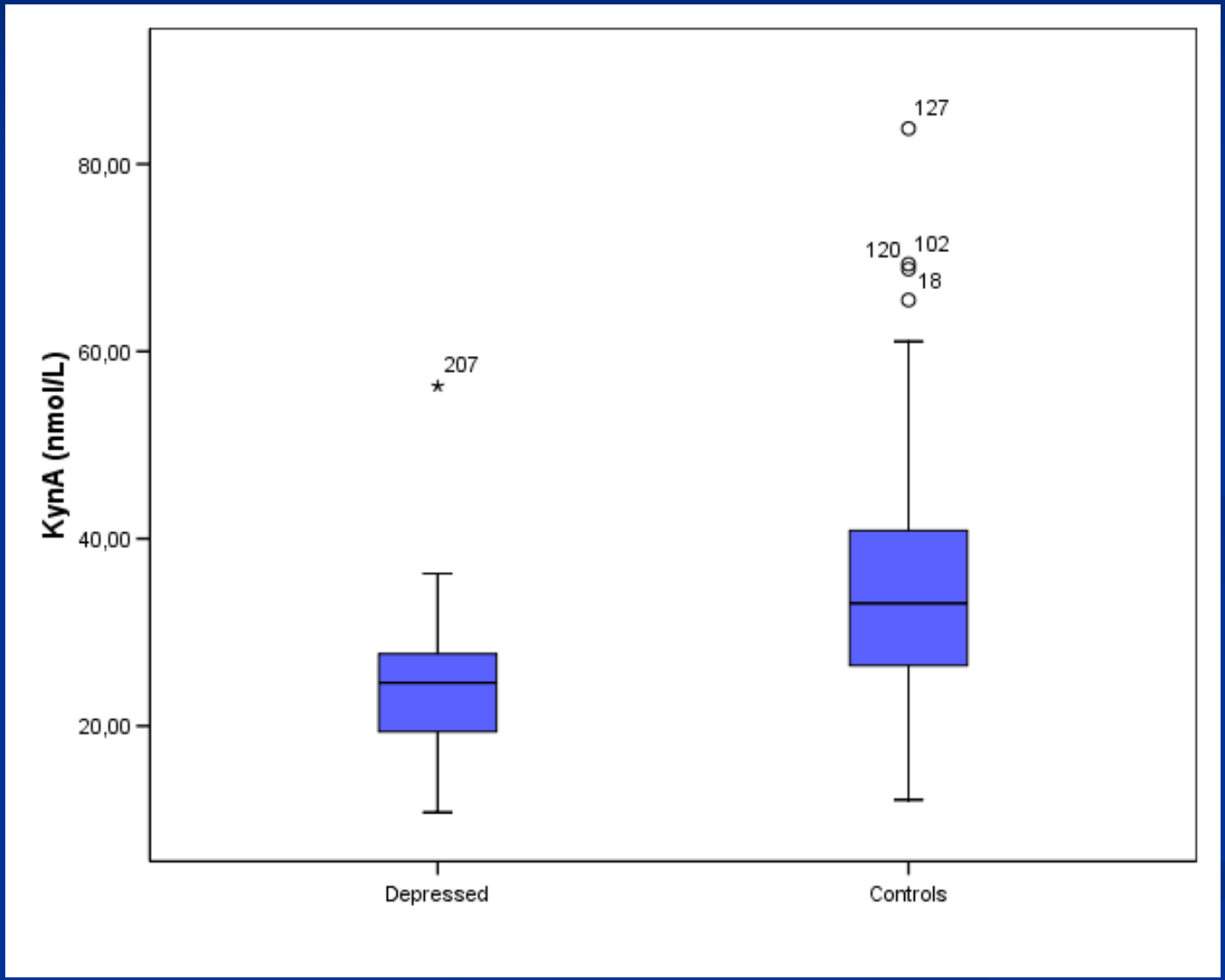
Kynurenine pathway in the brain (depressed patients) III





(Steiner, Myint, Guillemin et al, *paper under preparation*)

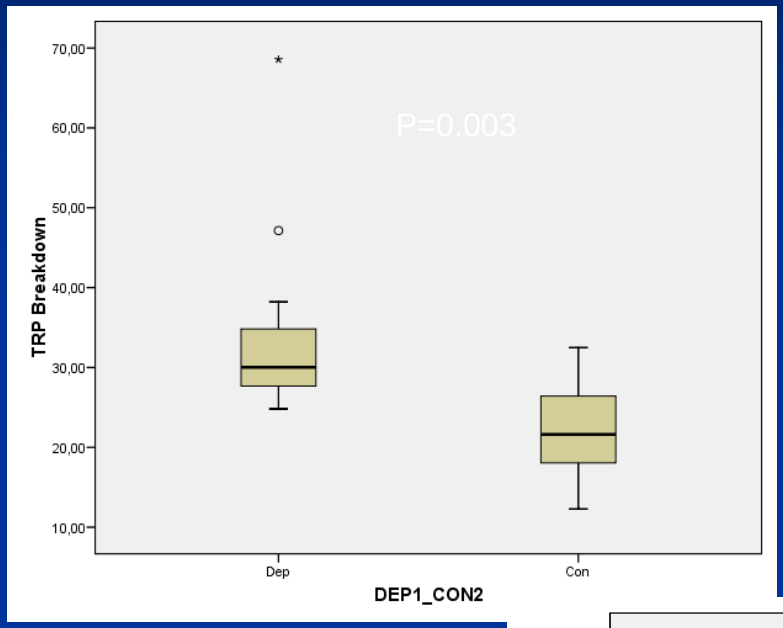
Kynurenine pathway (depressed patients)

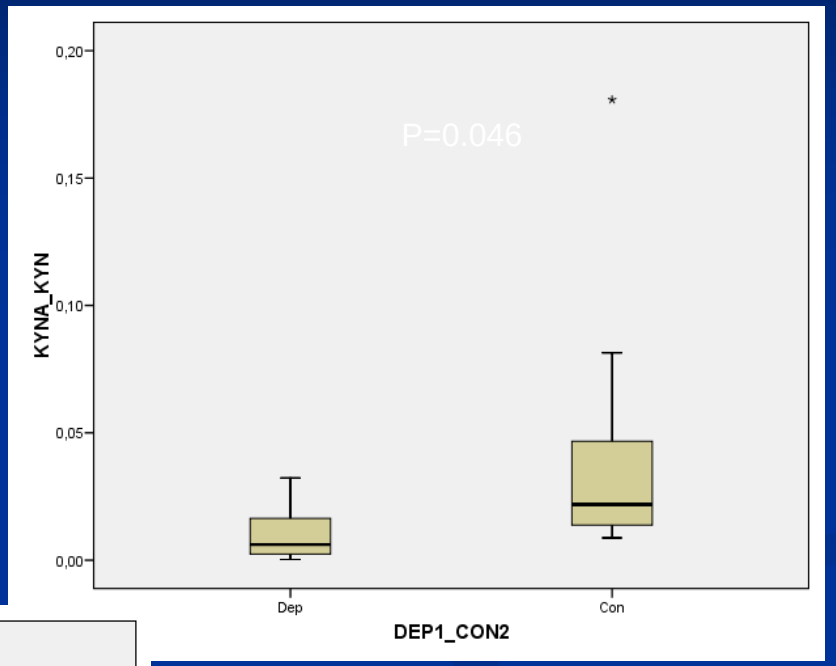


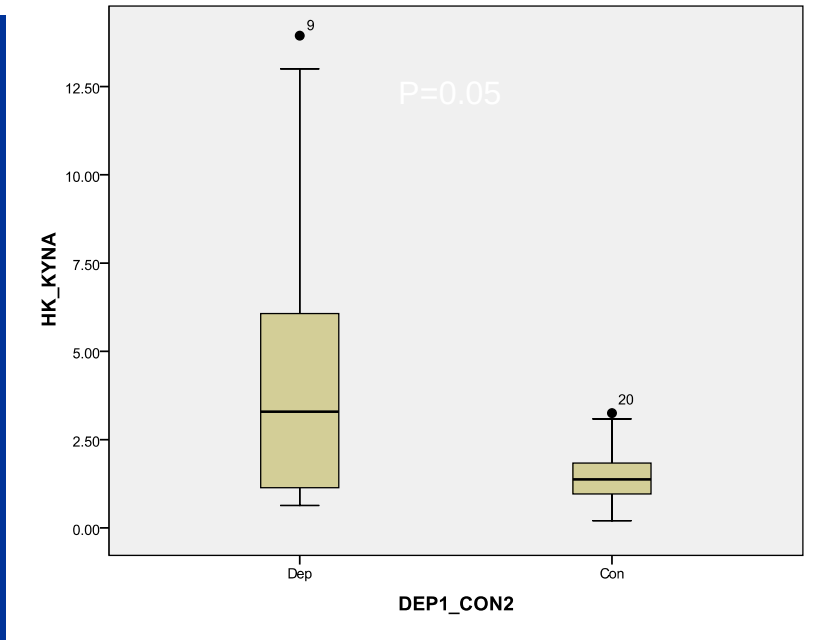
N = 58 depressed, 189 controls

(Myint et al, *JAD* 2007)

Kynurenine pathway (depressed patients) II

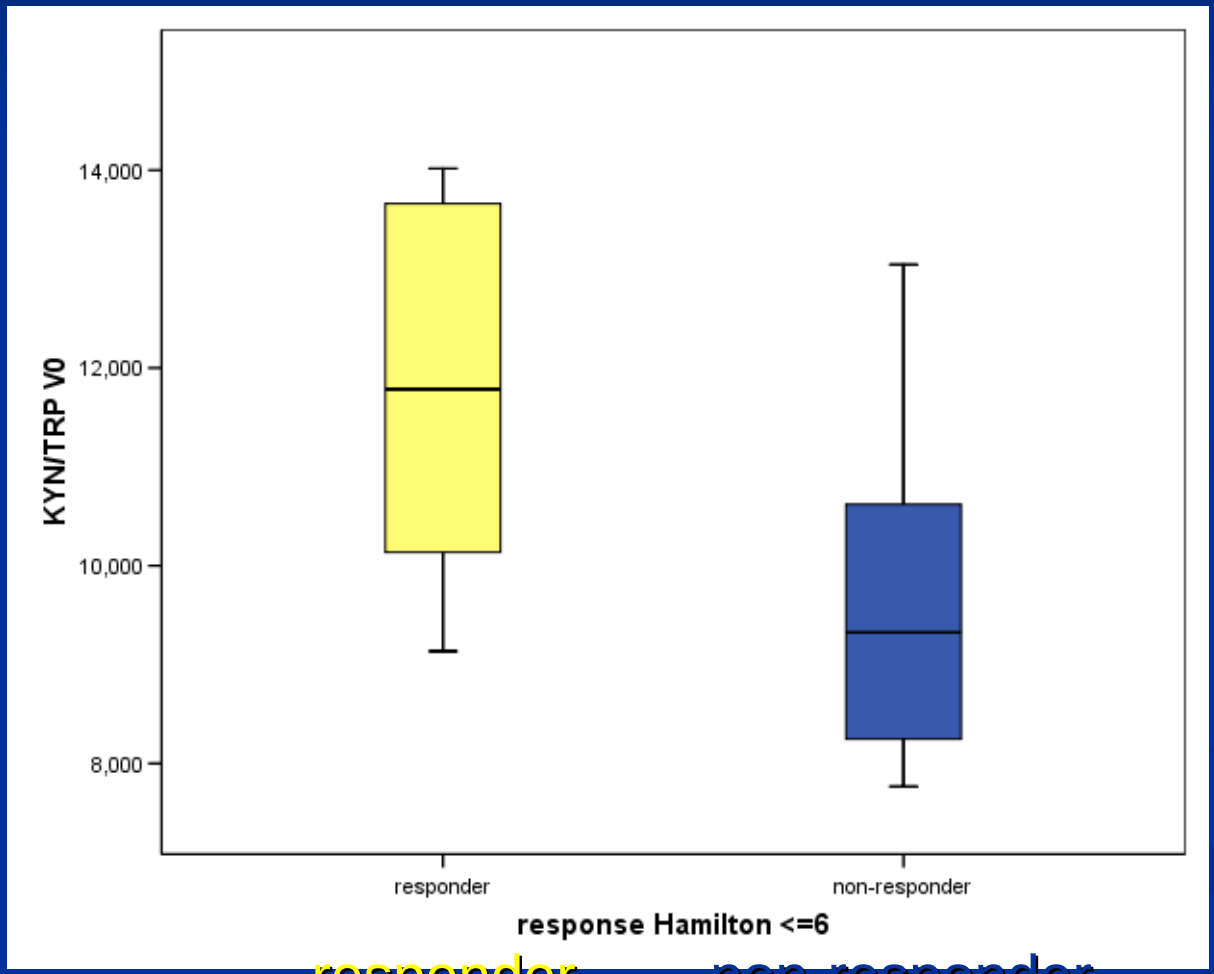






(Myint , Schwarz, Riedel, *unpublished new data*)

KYN/TRP ratio in COX-2 inhibitor treatment in MDD



responder non-responder

T = 2.344; p = .034

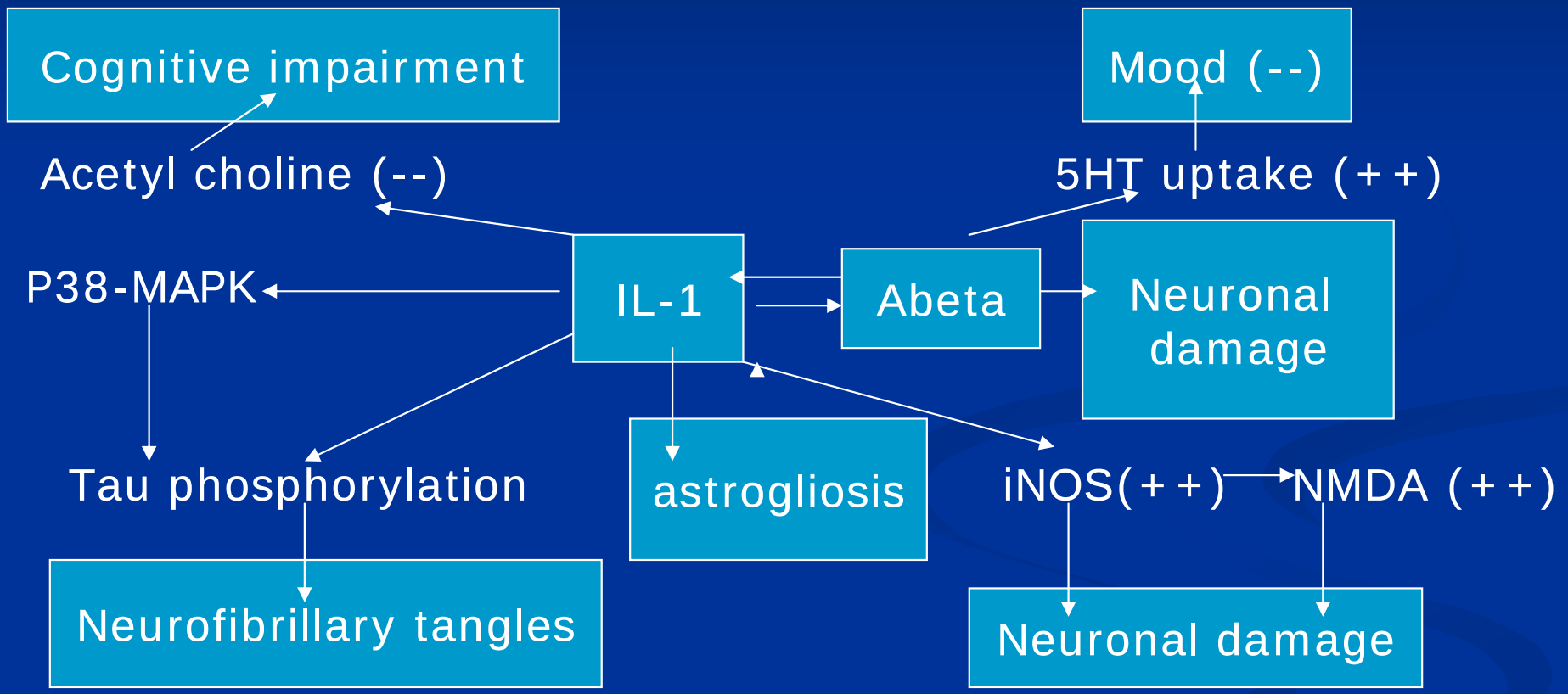
Major depression and the progression to Alzheimer's disease.

- Study by Rapp et al. Arch,Gen.Psychiat. 63,161,2006.
- Postmortem brains from AD patients with a life-time history of depression showed a markedly higher plaque density and tangle formation in the hippocampi than AD patients who had not been chronically depressed.
- Those with AD + depression showed a more rapid cognitive decline than those with depression alone. Hippocampal shrinking more pronounced in the AD+depression group.
- Possible link: in depression, reduction in serotonin prevents the conversion of amyloidogenic amyloid precursor protein to the soluble, non-amyloidgenic form

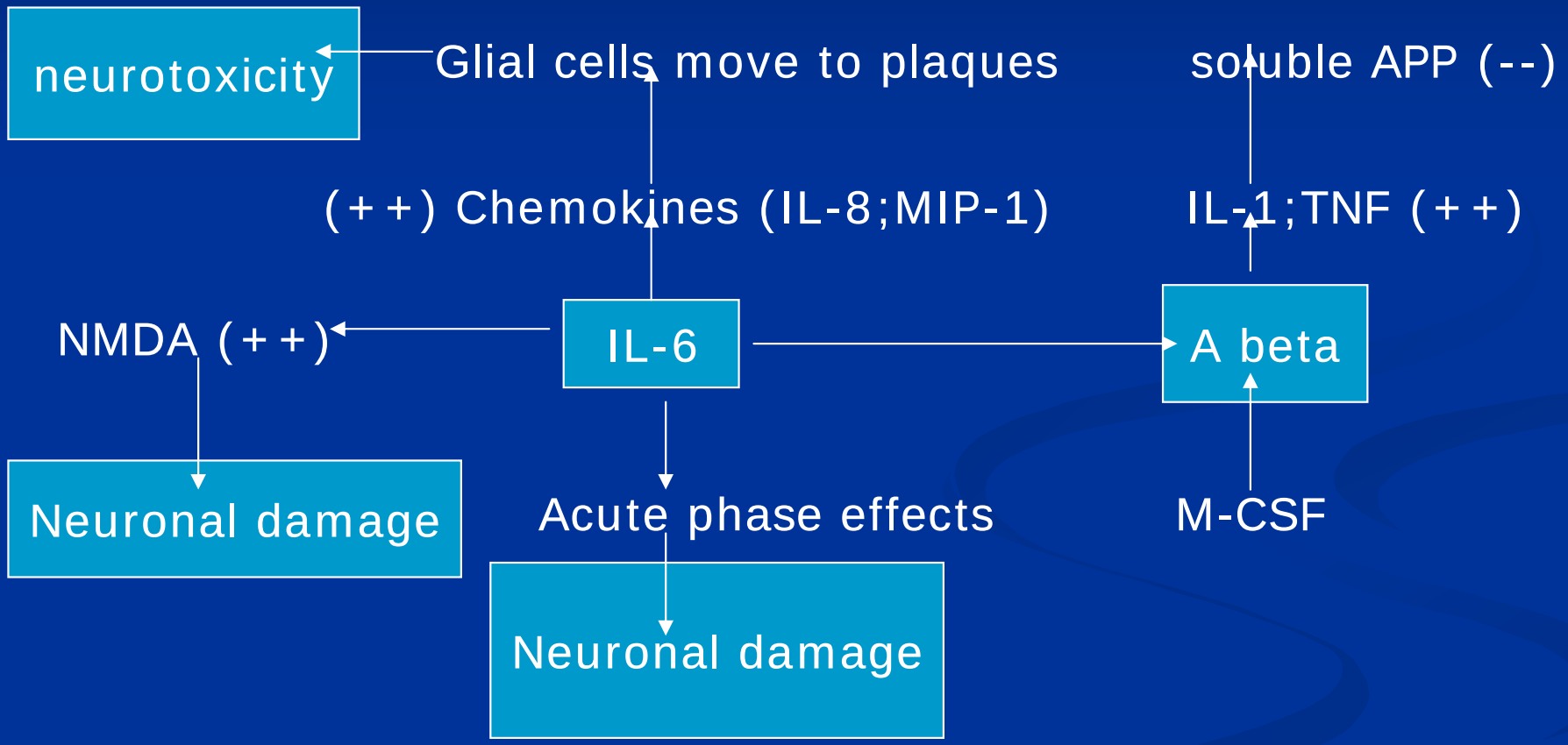
Neurodegeneration and Alzheimer's disease.

- The neuropathological changes begin before the main clinical symptoms become apparent.
- For example:
- Cognitive deficits are initially associated with minor memory loss and associated with degenerative changes in the hippocampus and the medial temporal lobe.
- Associated with hypercortisolaemia in CSF and an increase in plasma ApoE4. Older, non-demented subjects with ApoE4 also more vulnerable to trait anxiety.

IL-1 (alpha/beta): role in neurodegeneration.



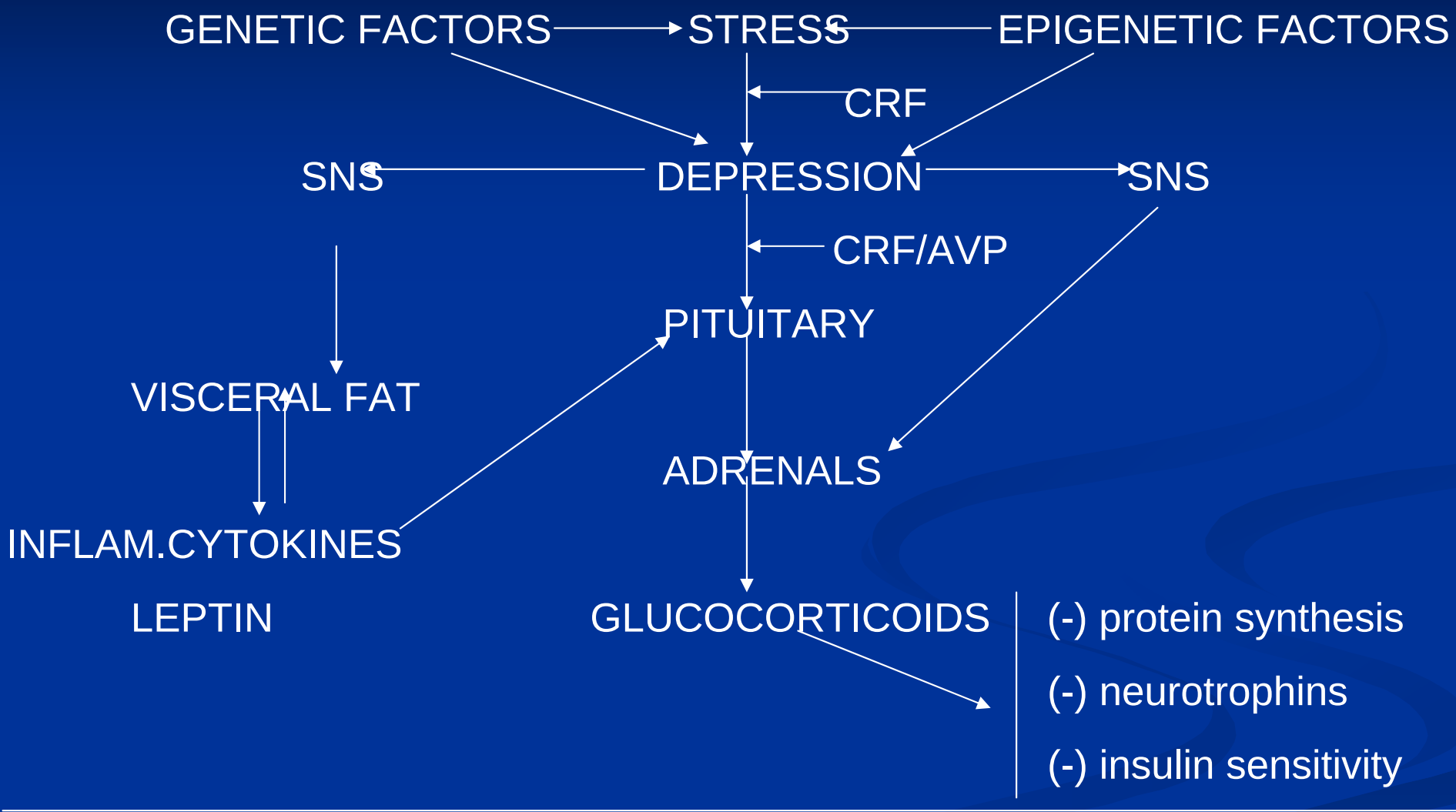
IL-6 AND TNF-ALPHA:ROLE IN NEURODEGENERATION.



Can an aspirin a day keep Alzheimer's away?

- Rotterdam epidemiological study of ageing(2001): 7000 subjects studied and showed that chronic use (> 2years) of NSAID's was associated with a significant reduction in Alzheimer's; 4 other studies have shown similar results.
- Possible mechanisms: cyclo-oxygenase (COX) and peroxisome proliferative activated receptor gamma (PPARg) control inflammatory genes.
- COX inhibition reduces synthesis of beta amyloid (Ab) by inhibiting gamma secretase (amyloidogenic), increasing alpha secretase (non amyloidogenic) and decreasing alpha-1 chymotrypsin (converts amyloid pecursor to Ab).

NEUROBIOLOGY OF DEPRESSION: METABOLIC SYNDROME.



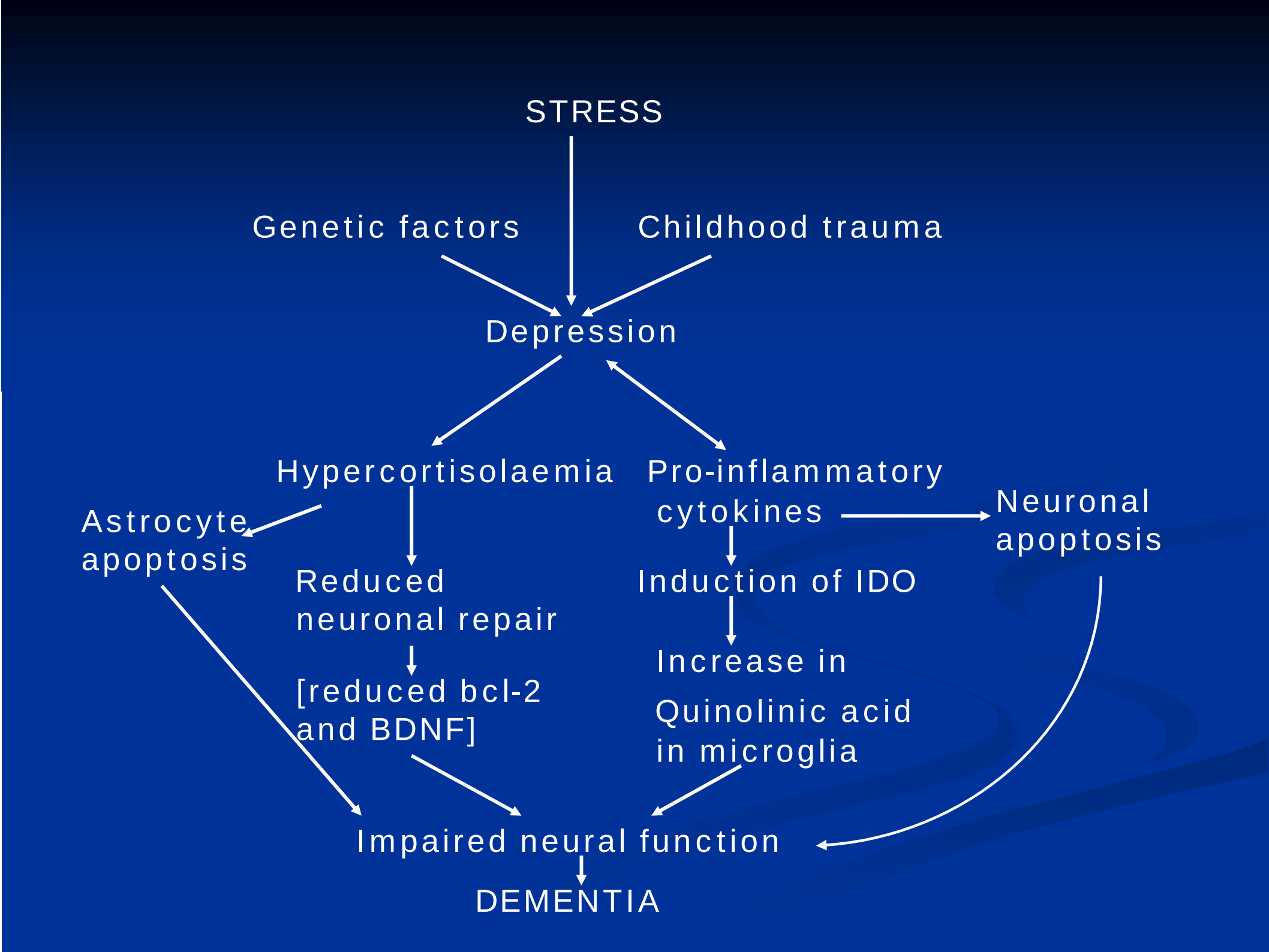
CONSEQUENCES OF METABOLIC CHANGES:

Heart disease-type 2 diabetes-cancer-psoriasis-inflammatory bowel disease etc .

Conclusion.

- Currently available antidepressants [NRI's, SSRI's, SNRI's, RIMA's etc.] may modulate the inflammatory cascade indirectly, possibly by increasing intracellular cAMP.

- A new generation of antidepressants may act more directly on the inflammatory cascade (for example, by inhibiting NF-kB).


STRESS
Genetic factors
Childhood trauma
Depression
Hypercortisolaemia
Pro-inflammatory cytokines
Astrocyte apoptosis
Neuronal apoptosis
Reduced neuronal repair
[reduced bcl-2 and BDNF]
Induction of IDO
Increase in Quinolinic acid in microglia
Impaired neural function
DEMENTIA

CONCLUSION

- The great tragedy of science: the slaying
- of a beautiful hypothesis by an ugly fact!
- Thomas Huxley (1825-1895)

Thank you !

- Ayemu Myint
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