Pathophysiology

NERVOUS SYSTEM

2024-2025

Alzheimer Disease

- Dementia of the Alzheimer type occurs in middle or late life and accounts for 60% to 80% of all cases of dementia. The disorder affects more than 4.5 million Americans and is the fourth leading cause of death in the United States.72,74 The risk for development of Alzheimer disease increases with age, starting at a level of 1% for the 60- to 64-year-old population and increasing to 40% or more for the 85- to 89-year-old

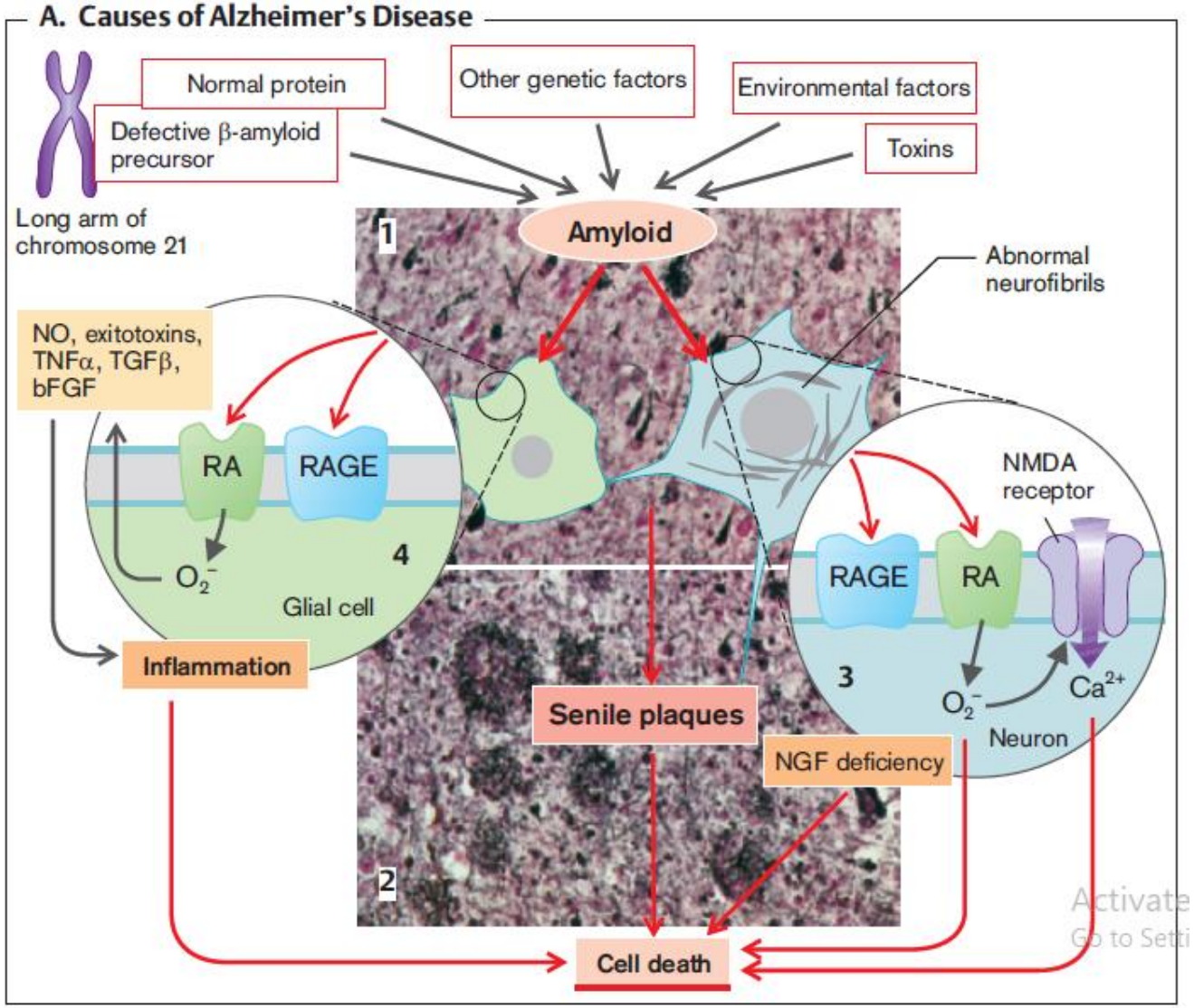
Alzheimer Disease

- Alzheimer disease most often presents with a subtle onset of memory loss followed by slowly progressive dementia that has a course of several years. Pathologically, there is diffuse atrophy of the cerebral cortex with enlargement of the ventricles. The major microscopic features of Alzheimer disease are the presence of neuritic (senile) plaques, neurofibrillary tangles, and amyloid angiopathy

Alzheimer Disease

1- on chromosome 21 a genetic defect of the protein β-amyloid precursor is found that can be broken down to amyloid peptides of 42 amino acids. These can bunch themselves together into protein fibrils 7–10nm long.

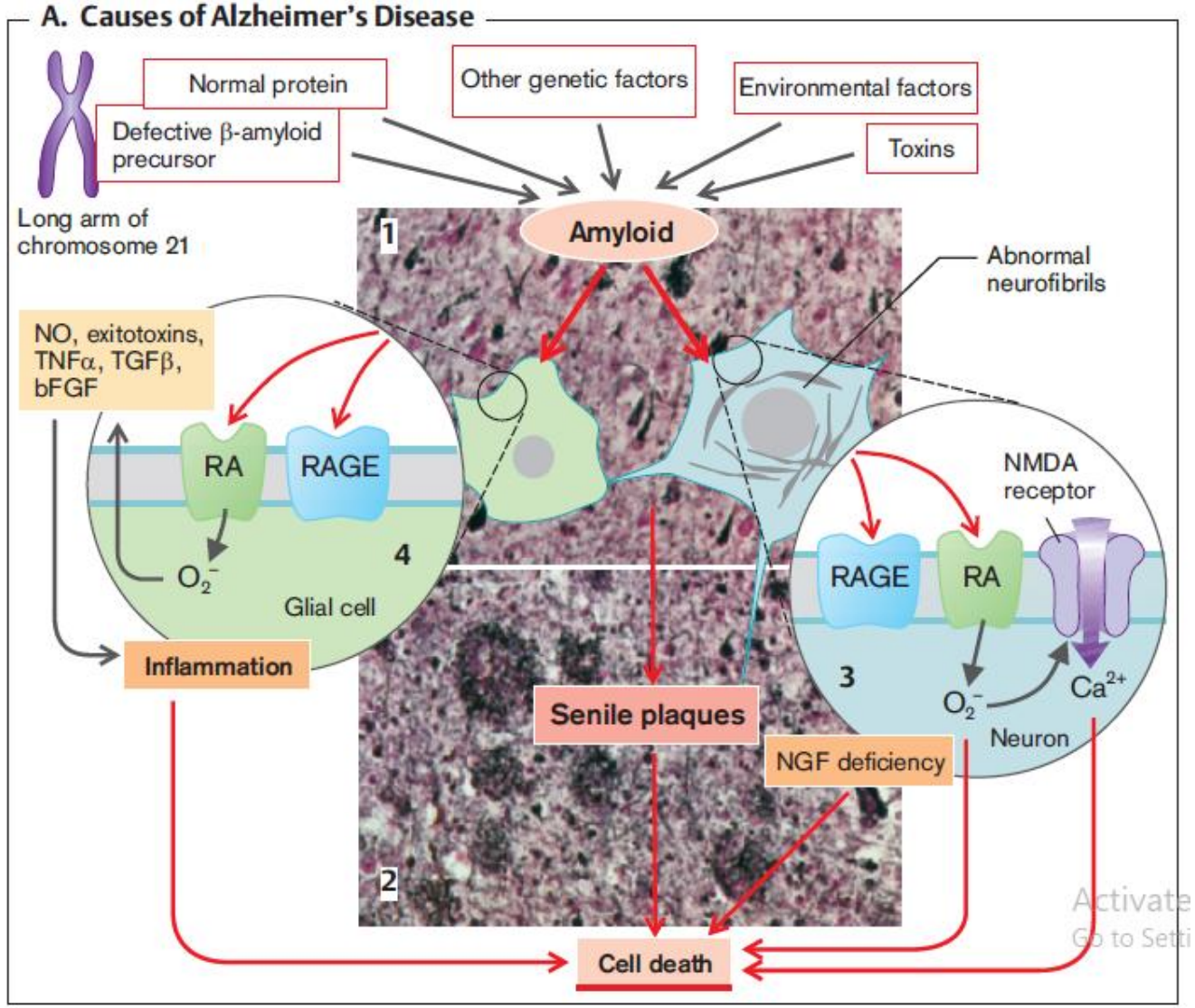
2- Together with ApoE4, proteoglycans and a1-antichymotrypsin these amyloid fibrils can then form aggregates, 10 μm to several hundred μm in diameter (senile plaques), which are frequently found in the brain of patients with Alzheimer's disease



Alzheimer Disease

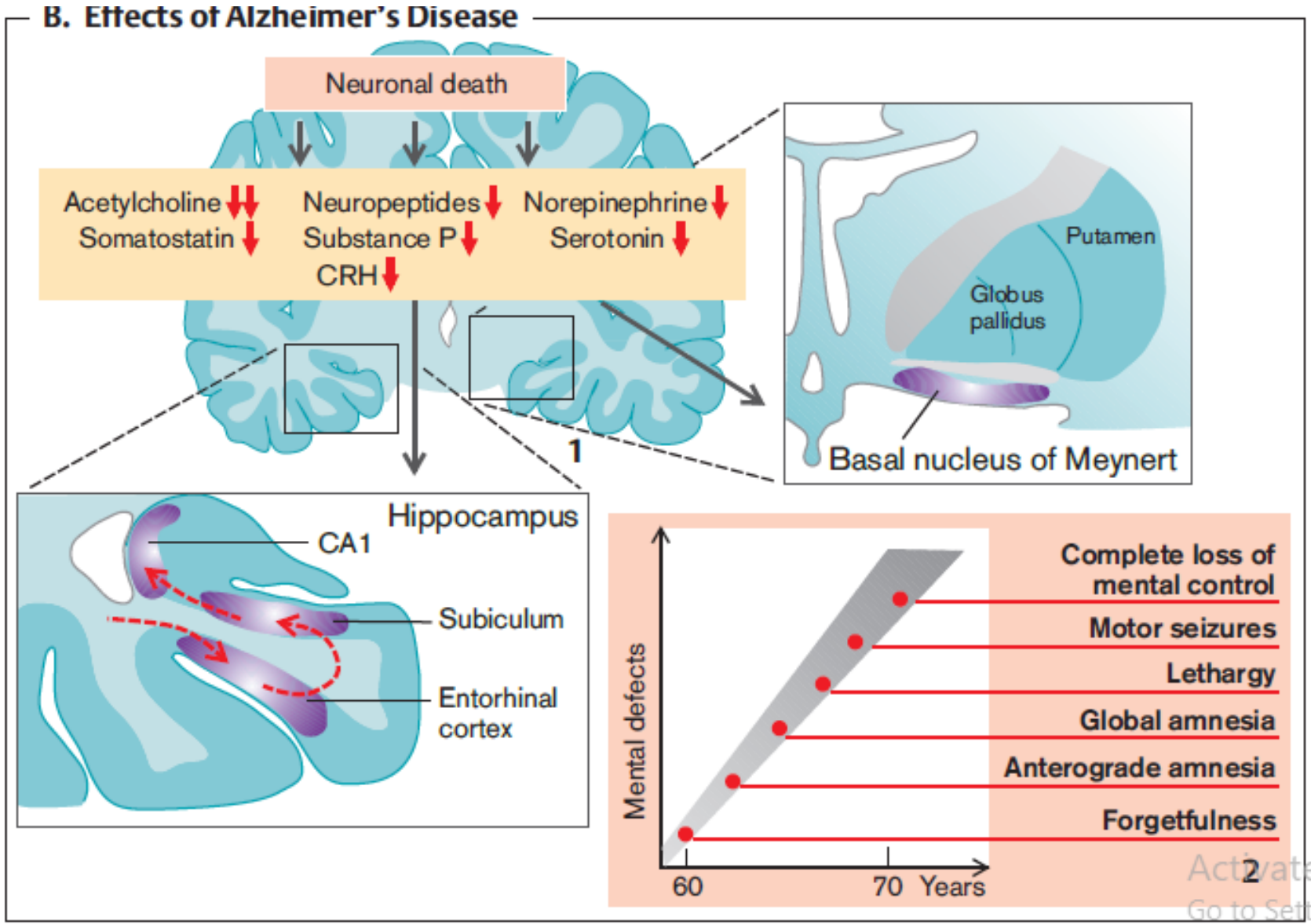
3- β-amyloid peptides can react with receptors at the cell surface, such as the receptor for advanced glycation end products (RAGE), and a scavenger receptor (RA). In the following oxygen radicals are formed, which may increase the neuronal intracellular concentration of Ca2+

4- In microglial cells the activation of RAGE and RA stimulates the formation or release, respectively, of NO, prostaglandins, excitotoxins, cytokines, tumor necrosis factor (TNF- a), tumor growth factor (TGF-β1), and fibroblast growth factor (b-FGF). This results in inflammation that also impairs neurons



Alzheimer Disease

Neuronal death is accompanied by decreased formation and concentration of neurotransmitters in the brain. Acetylcholine is markedly affected: in the cerebral cortex and the hippocampus there is an up to 90% decrease in the concentration of choline-acetyl transferase, the enzyme that is necessary for the formation of acetylcholine. The concentration of other neurotransmitters is also reduced, for example, norepinephrine, serotonin, somatotropin, neuropeptide Y, substance P, and corticotropin-releasing hormone ([CRH] corticoliberin).



Alzheimer disease take home message?

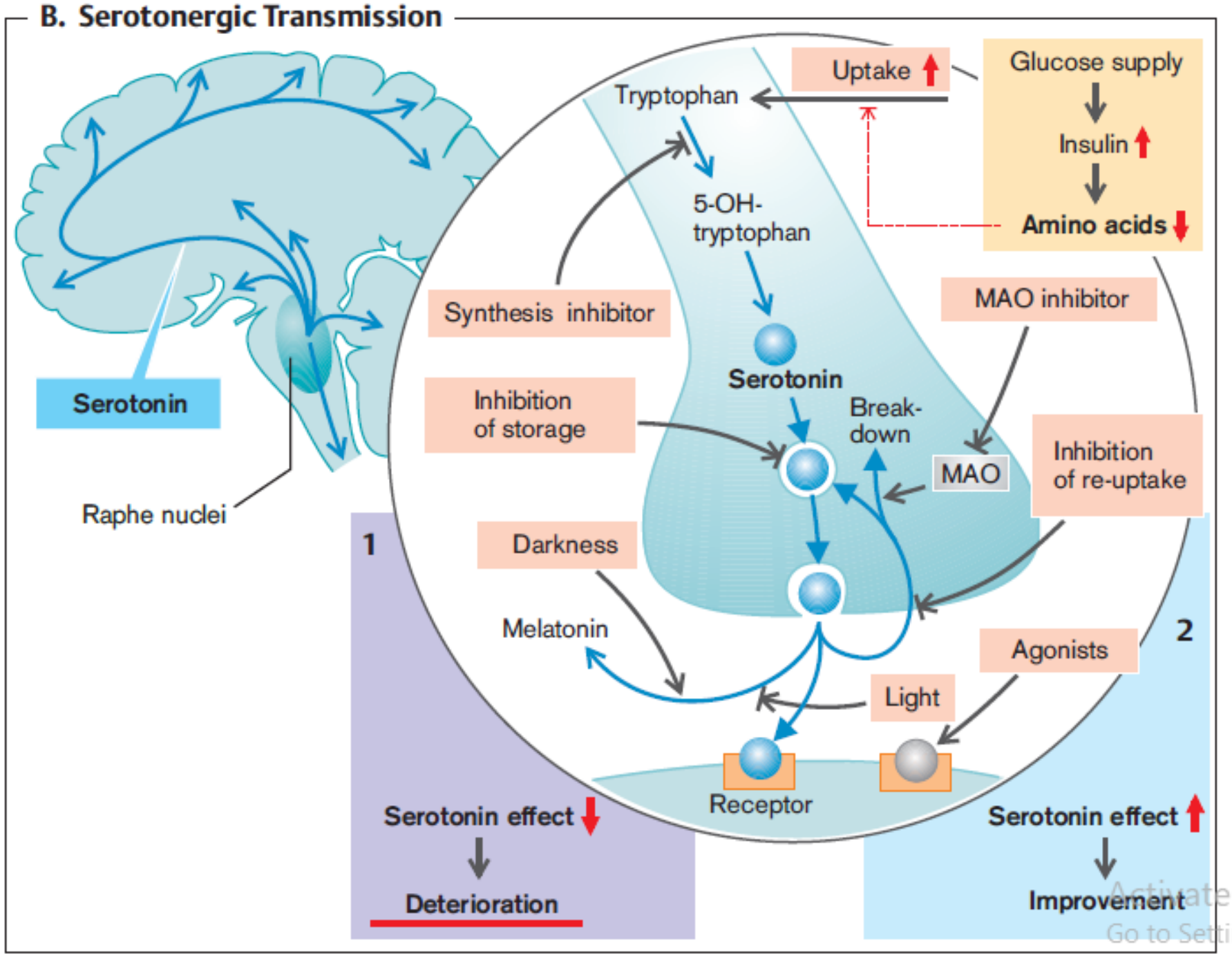
- Amyloid beta?
- Tangles?
- Neurofibrils?
- Acetylcholine?

Depression

- Depression is a disease with an increased familial incidence. It can alternate with manic phases (bipolar disorder) or can occur in isolation (unipolar disorder).
- depression is thought to be connected with decreased (relative or absolute) availability of serotonin and/or norepinephrine in the brain.

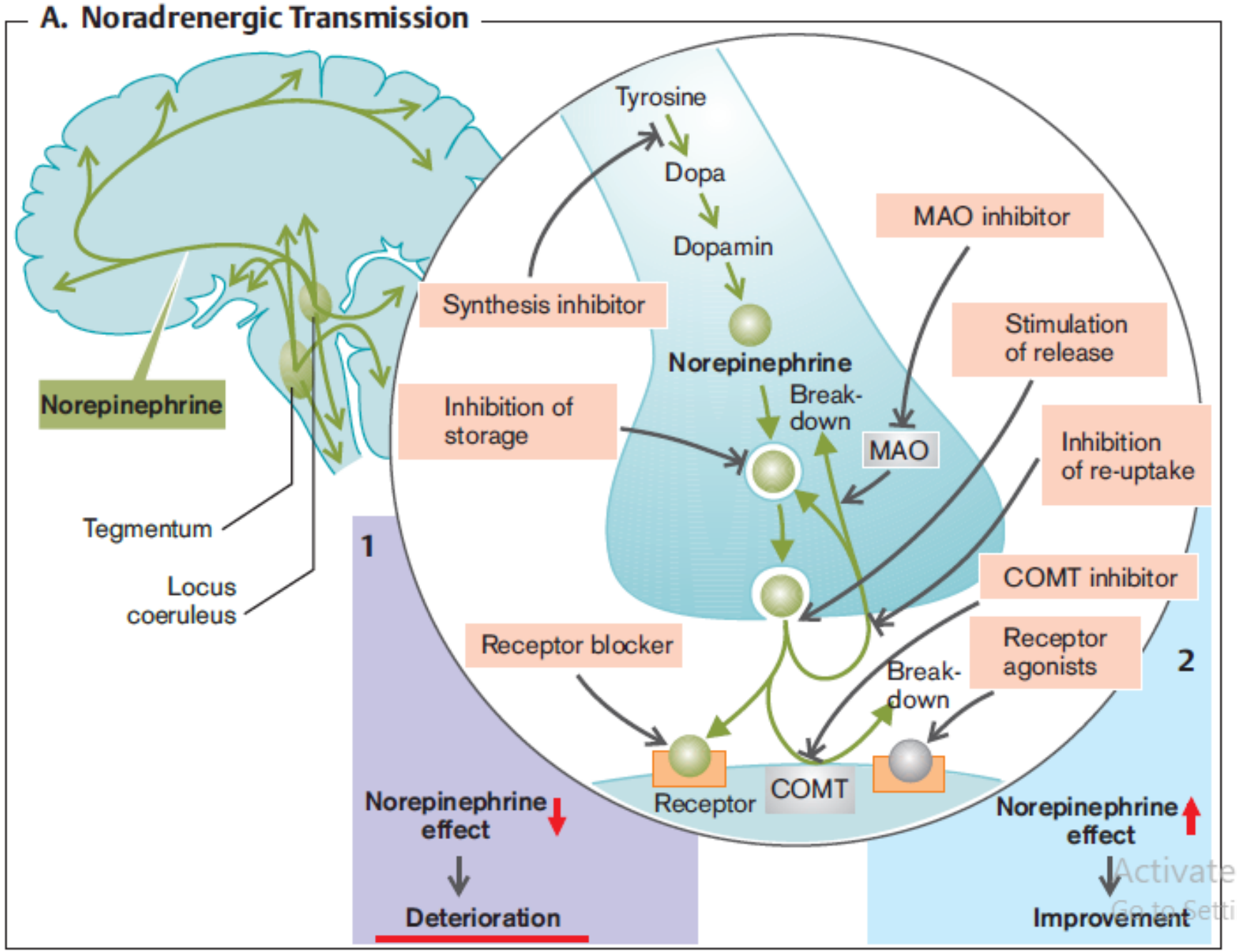
Depression

- A reduced availability or action of serotonin favors development of depression:
- (1) in genetic gene variants of the serotonin transporter (5-HTT);
- (2) by inhibiting synthesis from tryptophan (e.g., chlorophenylalanine);
- (3) by inhibiting uptake in presynaptic stores (e.g., reserpine);
- (4) due to increased consumption of serotonin through formation of inactive melatonin (when dark, in the pineal gland).


B. Serotonergic Transmission
Serotonin
Raphe nuclei
Tryptophan
Uptake
Glucose supply
Insulin
Amino acids
5-OH-tryptophan
Synthesis inhibitor
MAO inhibitor
Serotonin
Inhibition of storage
Break-down
MAO
Inhibition of re-uptake
1
Darkness
Melatonin
2
Agonists
Light
Receptor
Serotonin effect
Deterioration
Serotonin effect
Improvement

Depression

- The release and action of norepinephrine at the nerve endings may be reduced in depressive patients by a decreased number of noradrenergic neurons in the locus ceruleus. It can further be reduced by a number of substances, leading to depression:
- 1. The synthesis of norepinephrine from tyrosine via DOPA can be reduced by enzyme inhibitors (e.g., methyltyrosine).
- 2. The uptake of norepinephrine in presynaptic stores can be inhibited (e.g., by reserpine).
- 3. Norepinephrine can be displaced at the postsynaptic receptors (e.g., phenoxybenzamine, phentolamine).


A. Noradrenergic Transmission
Norepinephrine
Tegmentum
Locus coeruleus
Tyrosine
Dopa
Dopamin
Norepinephrine
Synthesis inhibitor
Inhibition of storage
Break-down
MAO
MAO inhibitor
Stimulation of release
Inhibition of re-uptake
COMT inhibitor
Receptor blocker
Receptor agonists
Break-down
Receptor
COMT
1
2
Norepinephrine effect
Deterioration
Norepinephrine effect
Improvement

Depression take home message?

- Enzyme inhibitors
- Uptake?
- Light vs dark?
- Synthesis?