Major Depressive Disorder: Pathogenesis and Medications

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Outline

- Diagnostic Criteria

- Pathogenesis hypothesis

    - The monoamine-deficiency hypothesis

    - The glutamatergic dysfunction hypothesis

    - Brain-derived neurotrophic factor

    - The hypothalamic–pituitary–cortisol hypothesis

- Antidepressant Treatments

    - Electroconvulsive therapy & Cognitive behavioral therapy

    - Monoamine oxidase inhibitors (MAOIs)

    - TCAs, SSRIs, SNRIs, NDRIs and SARIs

    - Other medications

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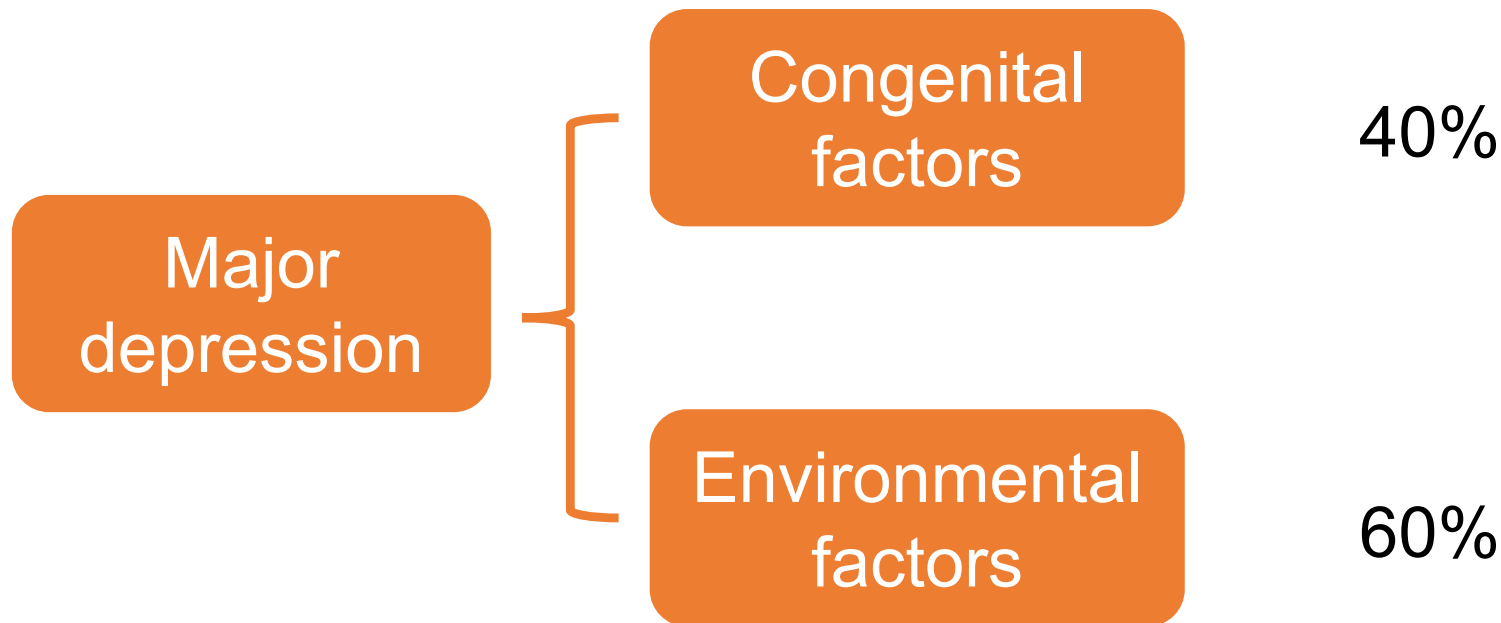 - TCAs, SSRIs, SNRIs, NDRIs and SARIs

  - Other medications

Introduction

Brain diseases

Neurodegenerative disorder

Affective disorder

Bipolar disorder
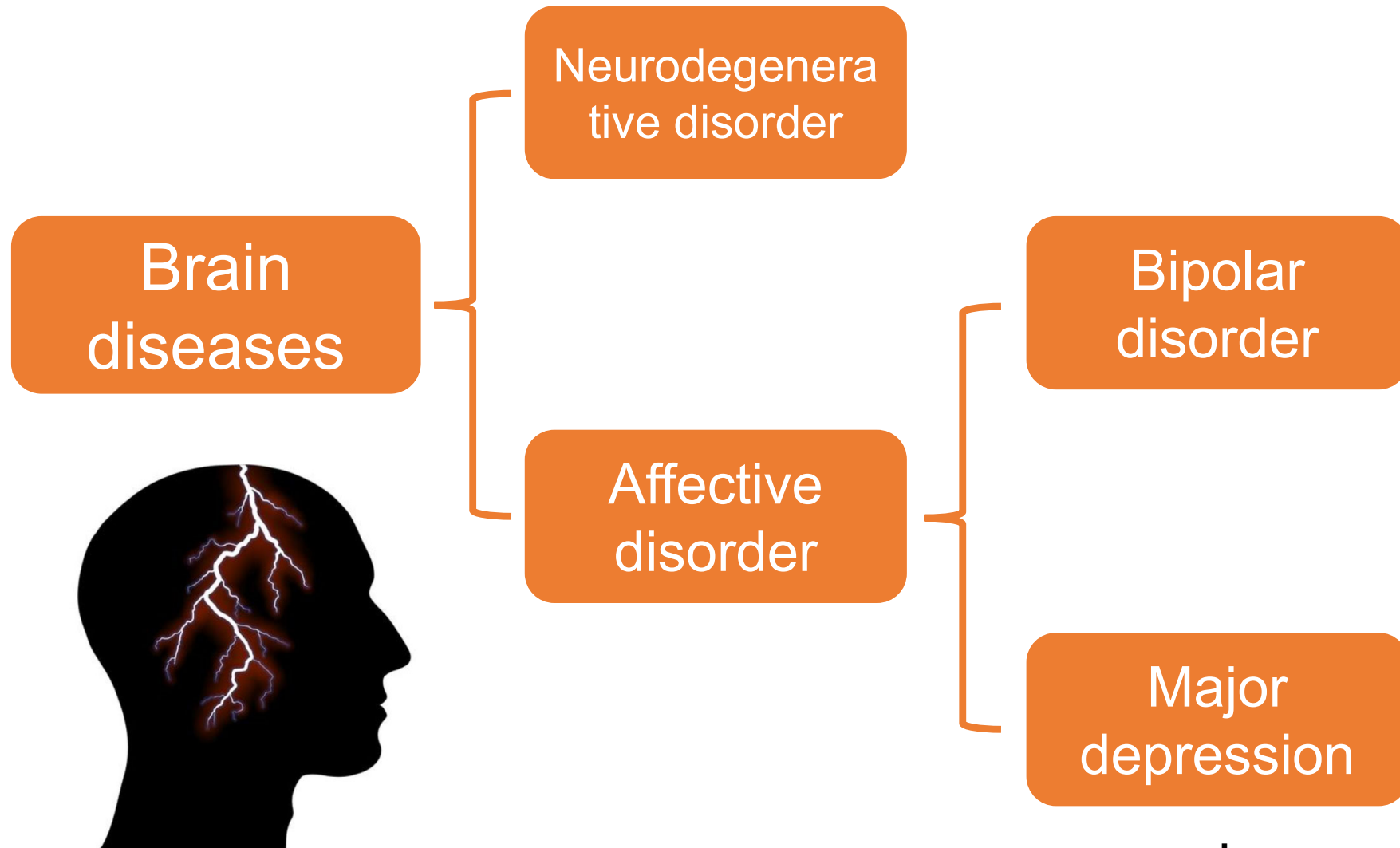
Major depression

Major Depressive Disorder

"郁极乃发，待时而作也。"

——《黄帝内经·素问 六元正纪大论篇》

Major depression

Congenital factors — 40%

Environmental factors — 60%

Major Depressive Disorder

- 350 million in the world, less cured

- 1 million death per year, or complications

- 90 million in China (1/14)

- young/old people, pregnant women…

因郁而病

Major depression

Syndrome rather than a single disease

因病而郁

——明 张介宾《景岳全书》
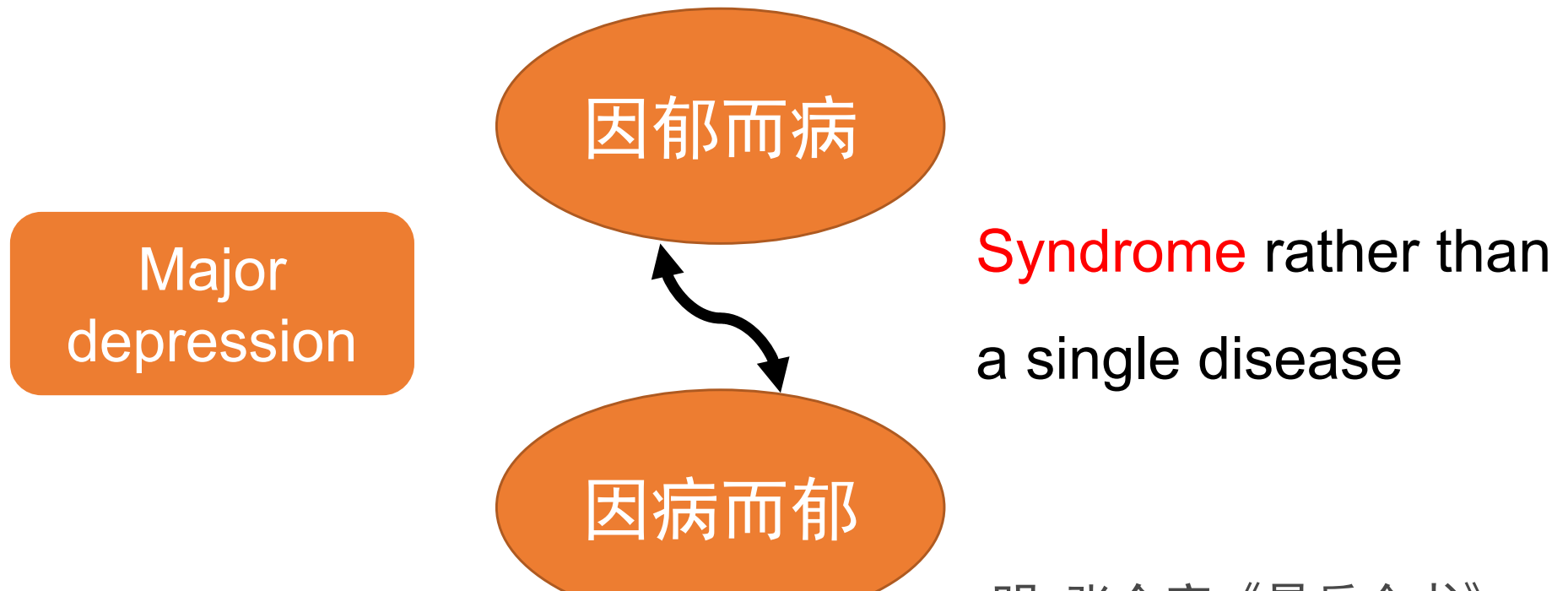
Diagnostic Criteria

- Having a depressed mood
- Loss of interest or pleasure in activities once enjoyed
- Changes in appetite
- Trouble sleeping or sleeping too much
- Loss of energy or increased fatigue
- Increase in purposeless physical activity or slowed movements
- Feeling worthless or guilty
- Difficulty thinking, concentrating, or making decisions
- Thoughts of death or suicide
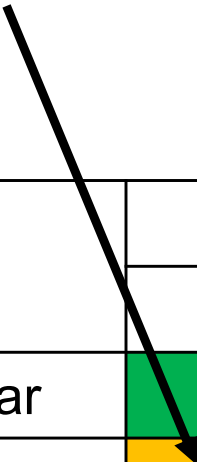
Sorrowing Old Man
**Vincent Willem van Gogh**
（1853—1890）

Clinical research

Problems :

- Helplessness (patients)

- Difficulties in diagnosis   ➤ Need to understand

- Long treatment cycle (human)   in many ways !

- Uncertaint pathogenesis

- ……

Difficulty		Drug mechanisms	
		Clear	Unknown
Pathogenesis	Clear	**Easy**	**Hard**
	Unknown	**Hard**	**Hell**

Rodent models in depression research

- Create depressed rodent

- Observing behavior
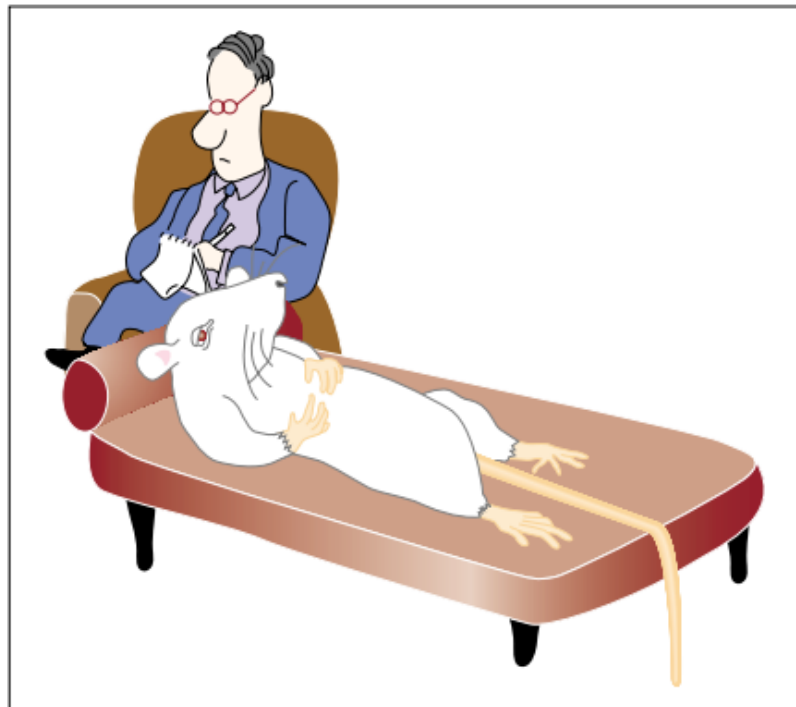
John, F. C.; Athina, M.; Irwin, L.
Trends Pharmacol. Sci. **2002**, *23*, 238.

a Early life stressors
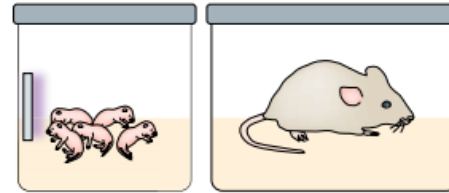
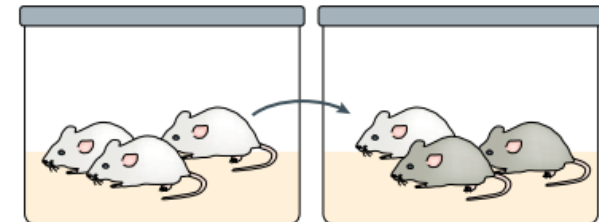b Learned helplessness

c Drug withdrawal
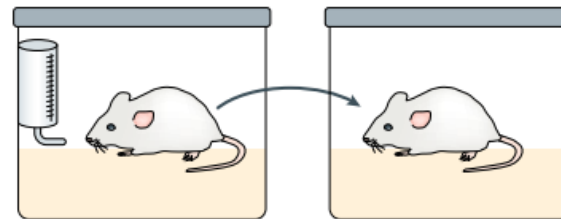
d Corticosterone manipulation or immune activation

e Genetic modification
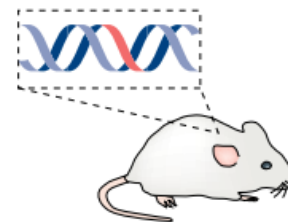
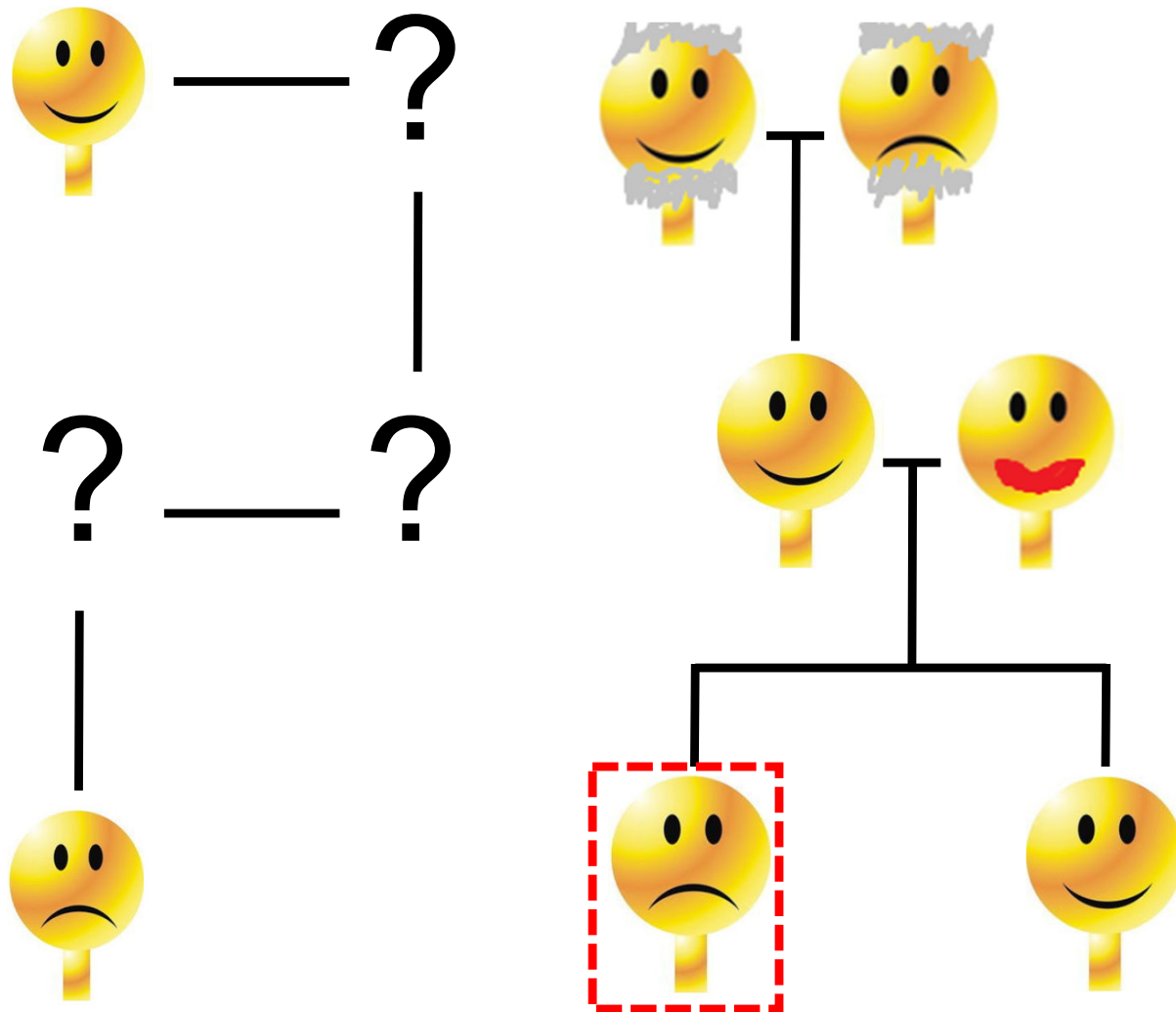f Social instability

g Social transmission of stress

h Social defeat stress

Anand, G.; Andreas, R.; John, F. C.; David, A. S. *Nat. Rev. Neurosci.* **2020**, *20*, 687.

Summary

Major Depressive Disorder (MDD):

◆ Syndrome ?

◆ Genetics ?

◆ Difficulties…

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  - Other medications

Pathogenesis hypothesis

Congenital factors
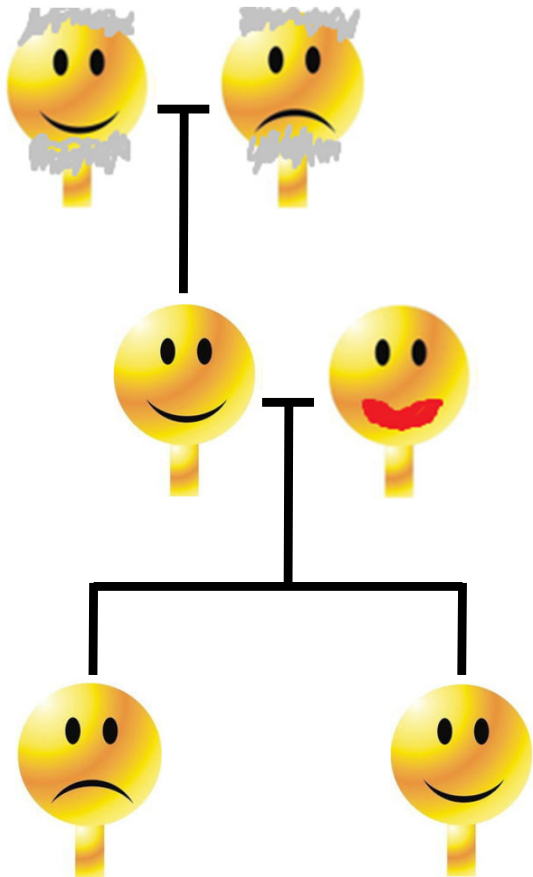
Environmental factors
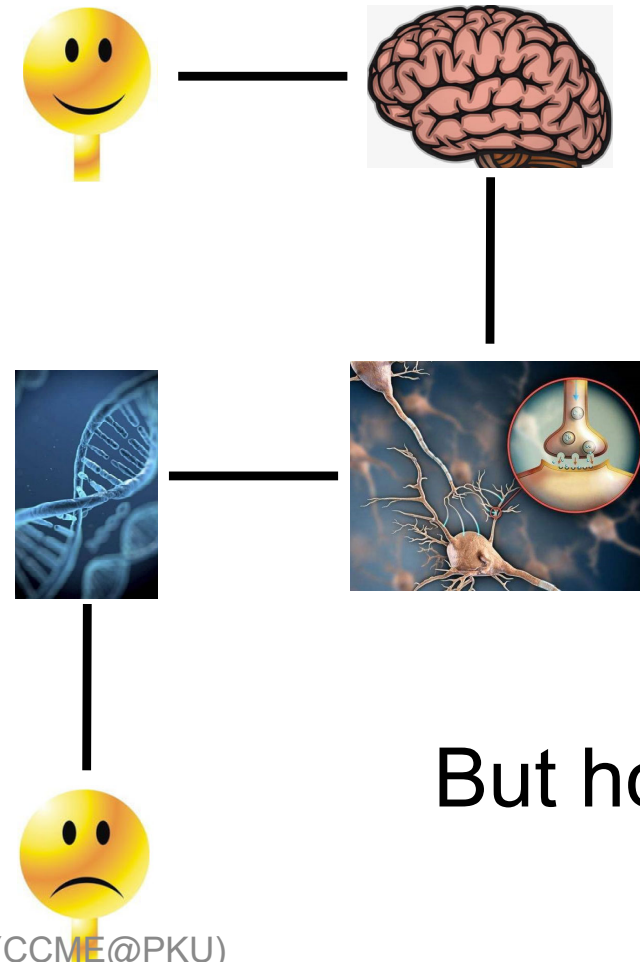
But how ?

Pathogenesis hypothesis

Elena, D.; Benny, B. A.; Connie, S. *Biochem. Pharmacol.* **2015**, *95*, 81.
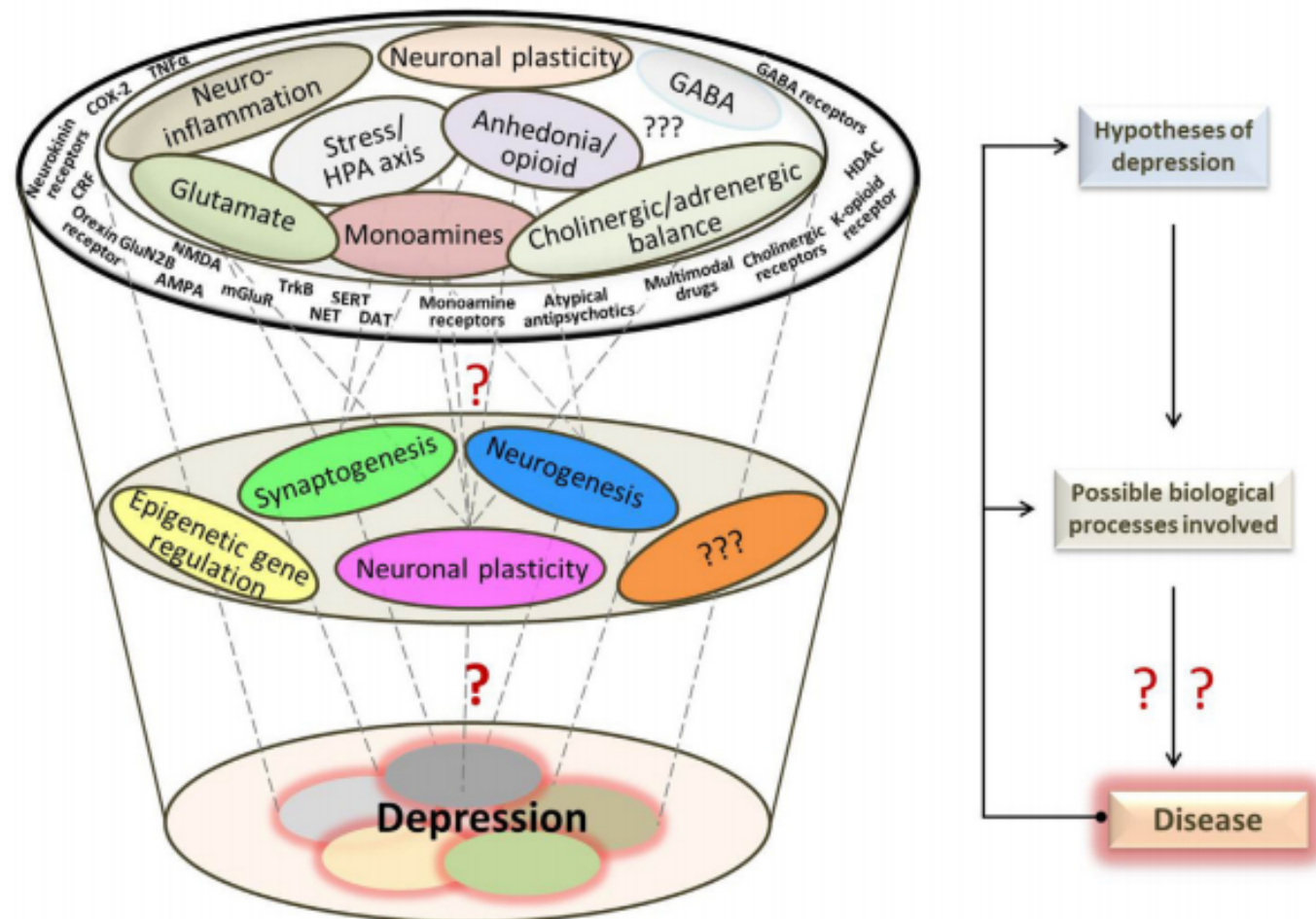
Neurotransmitters
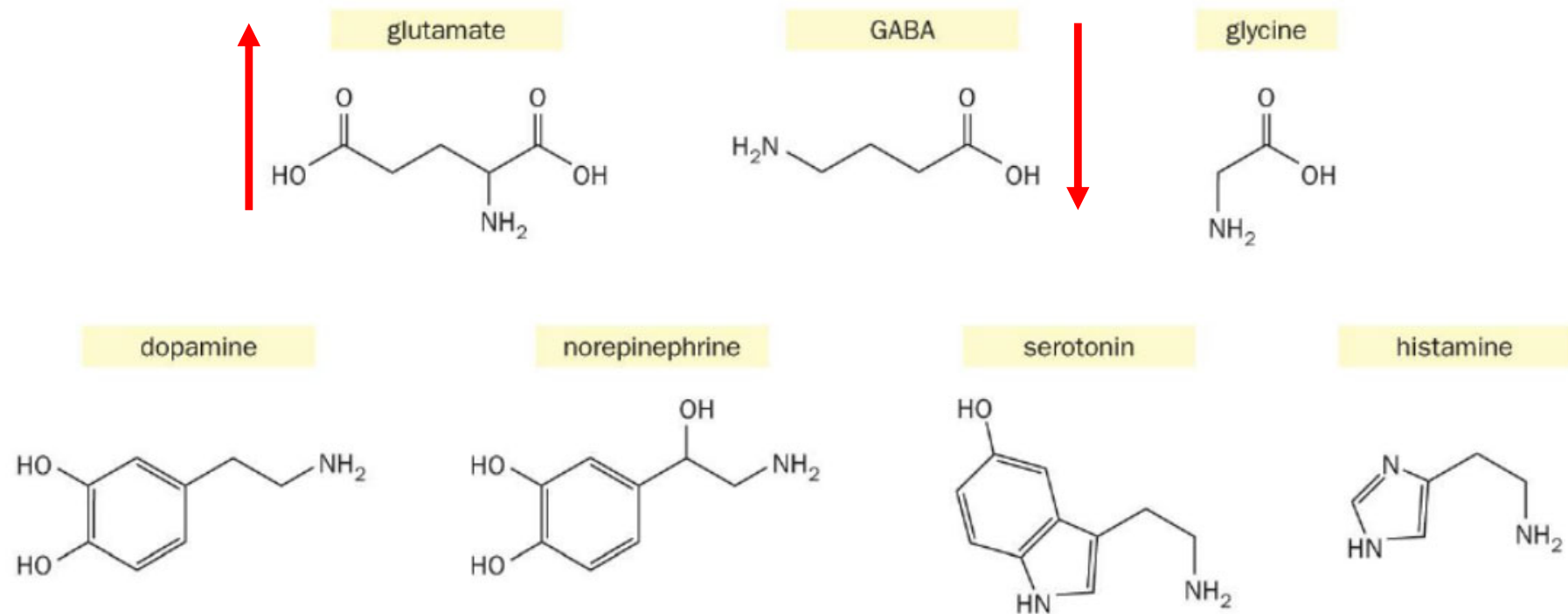
Figure 3-16 Principles of Neurobiology (© Garland Science 2016)
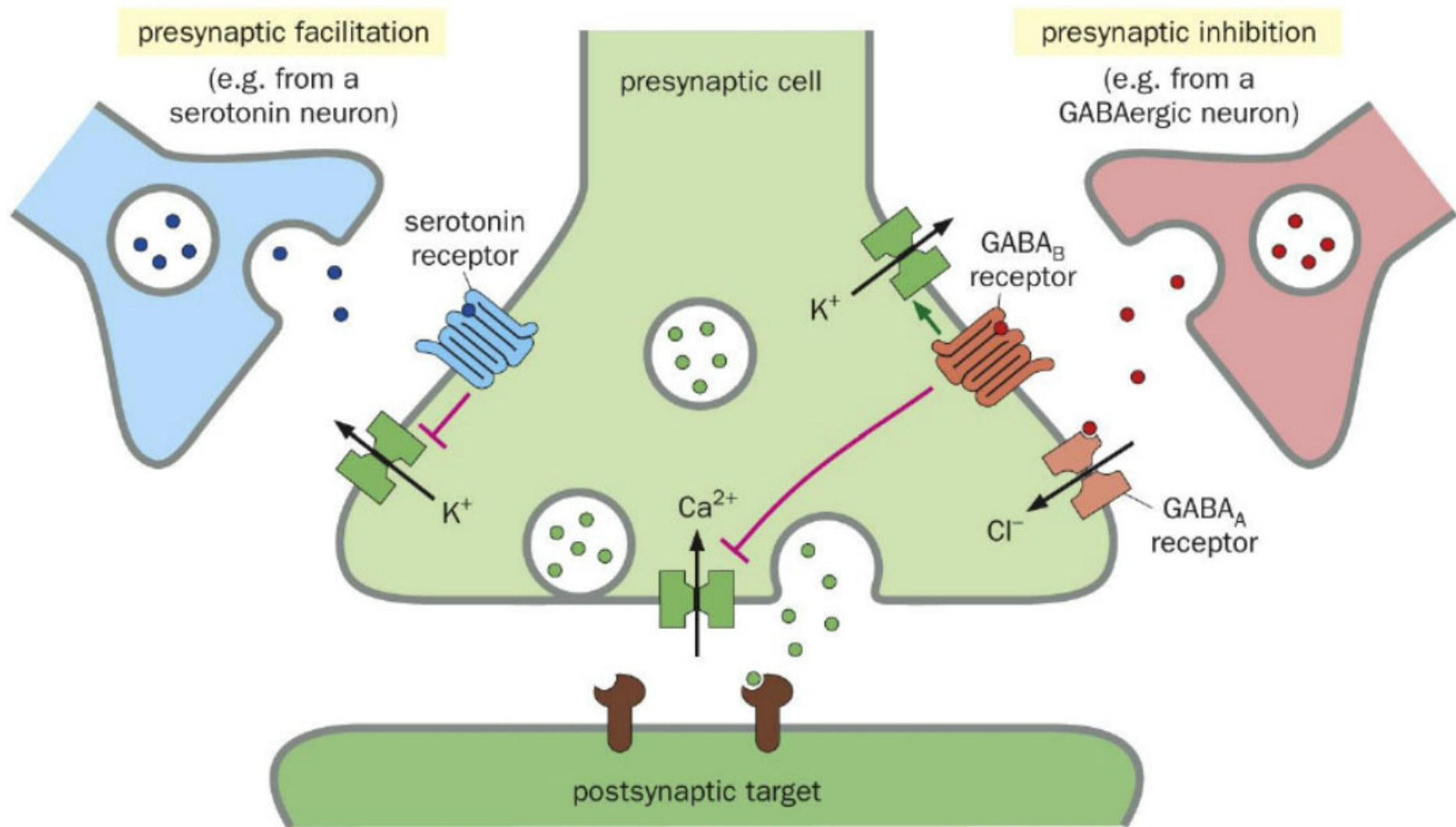
Neurotransmitters

Figure 3-37 Principles of Neurobiology (© Garland Science 2016)

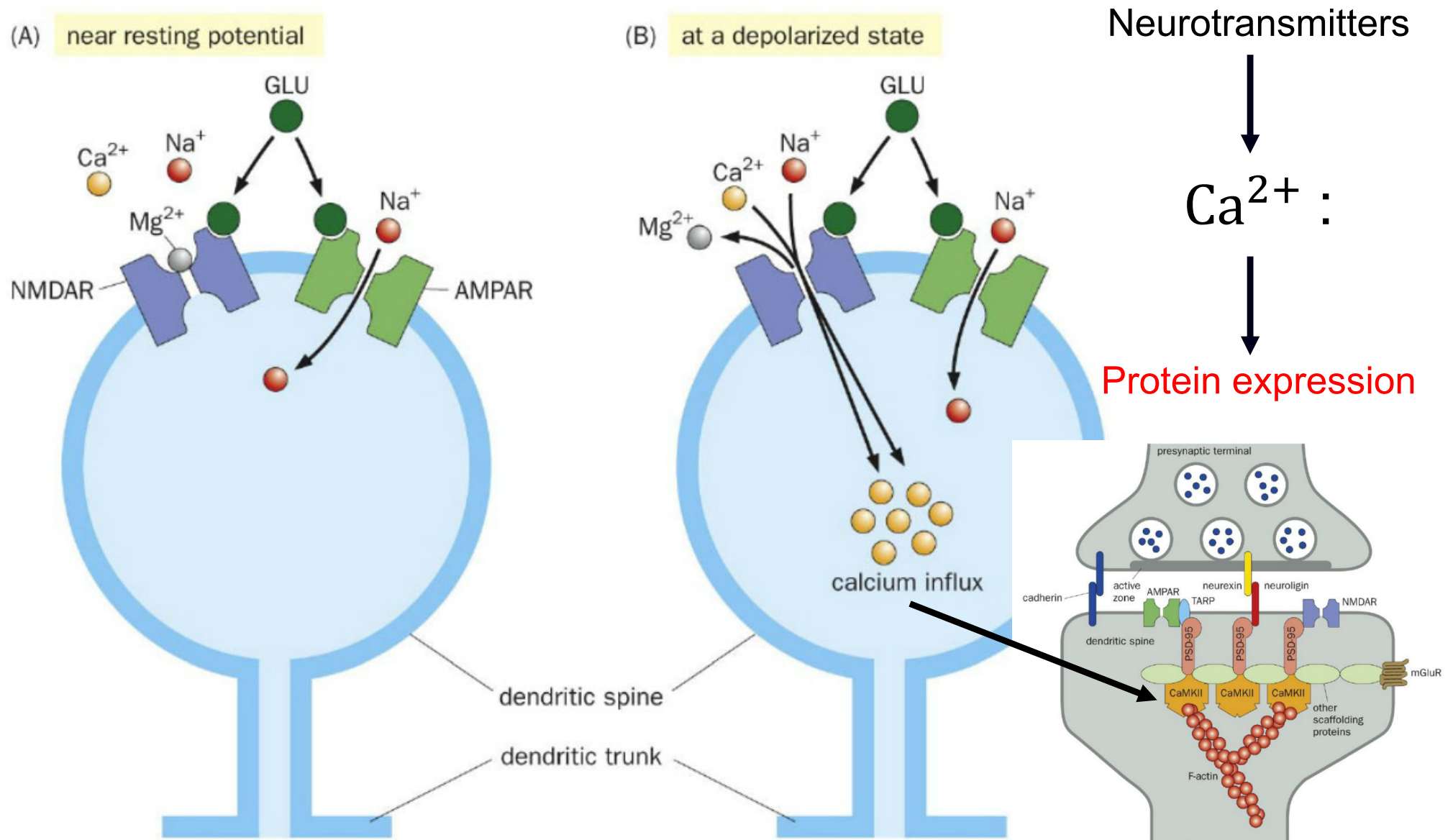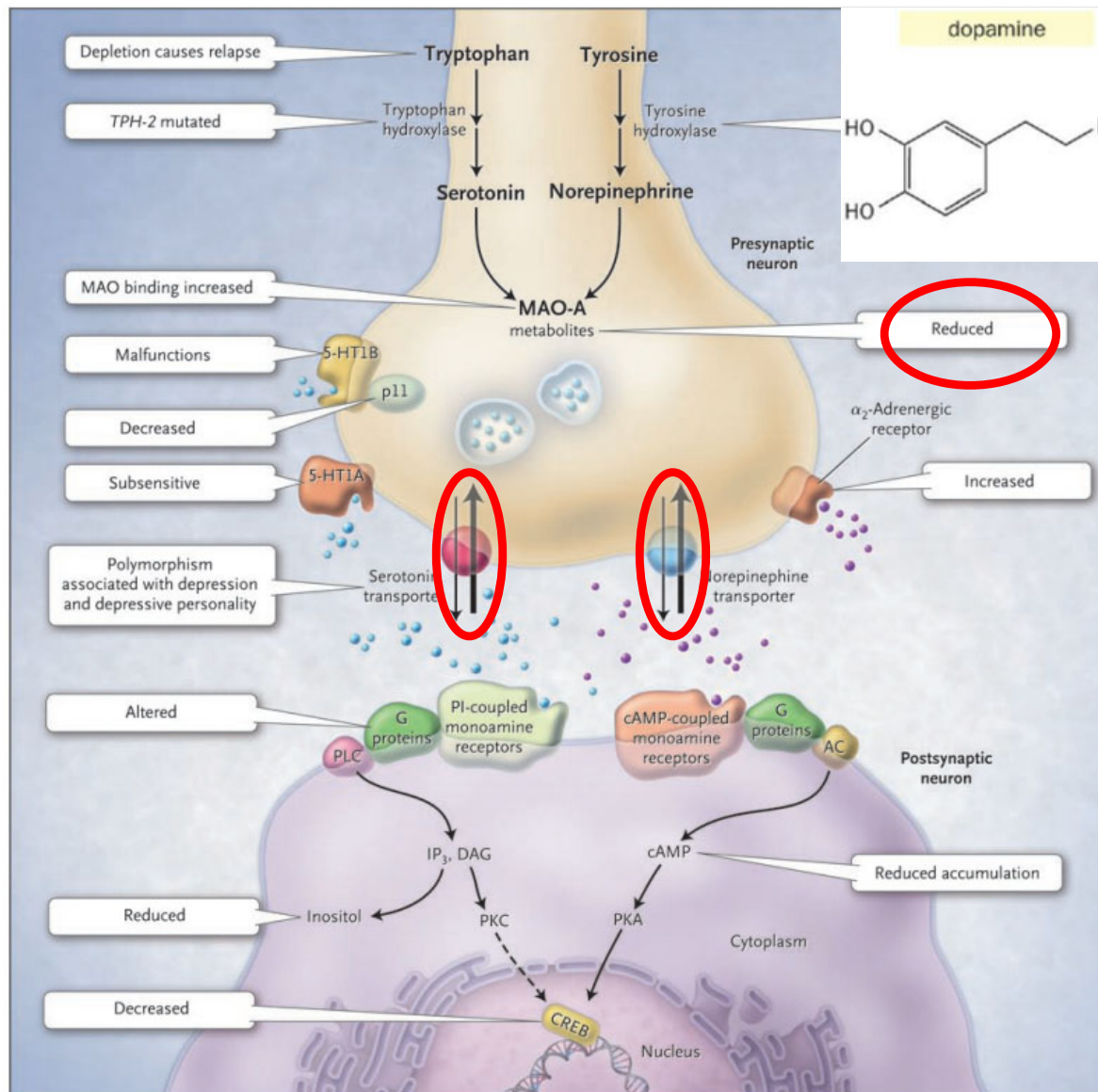$$K^+ \longrightarrow Ca^{2+} \longrightarrow Neurotransmitters$$

Neurotransmitters

Neurotransmitters

↓

Ca^{2+} :

↓

Protein expression

Figure 3-27 Principles of Neurobiology (© Garland Science 2016)

The monoamine-deficiency hypothesis
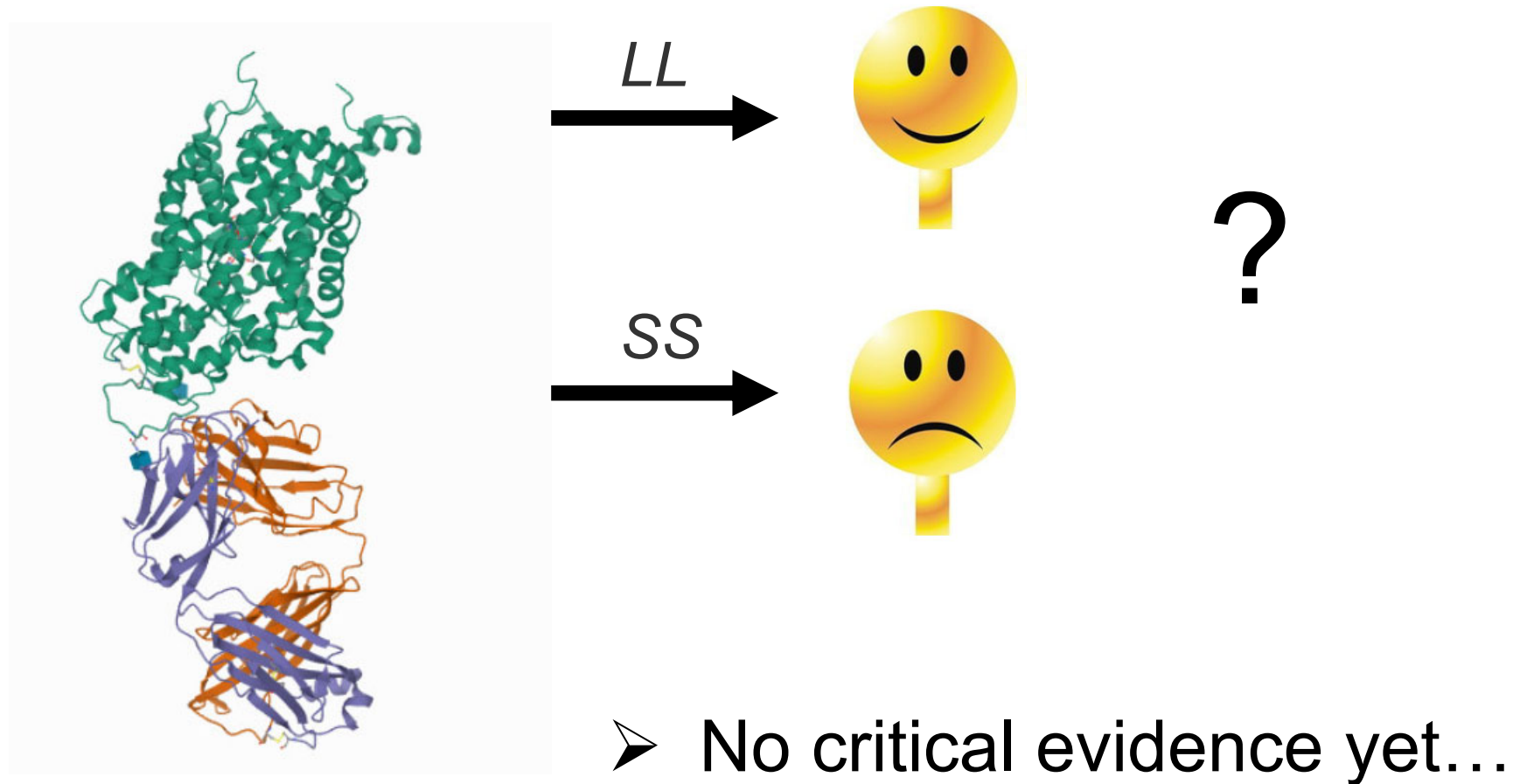

Environmental stimulation/

Genetic defects

↓

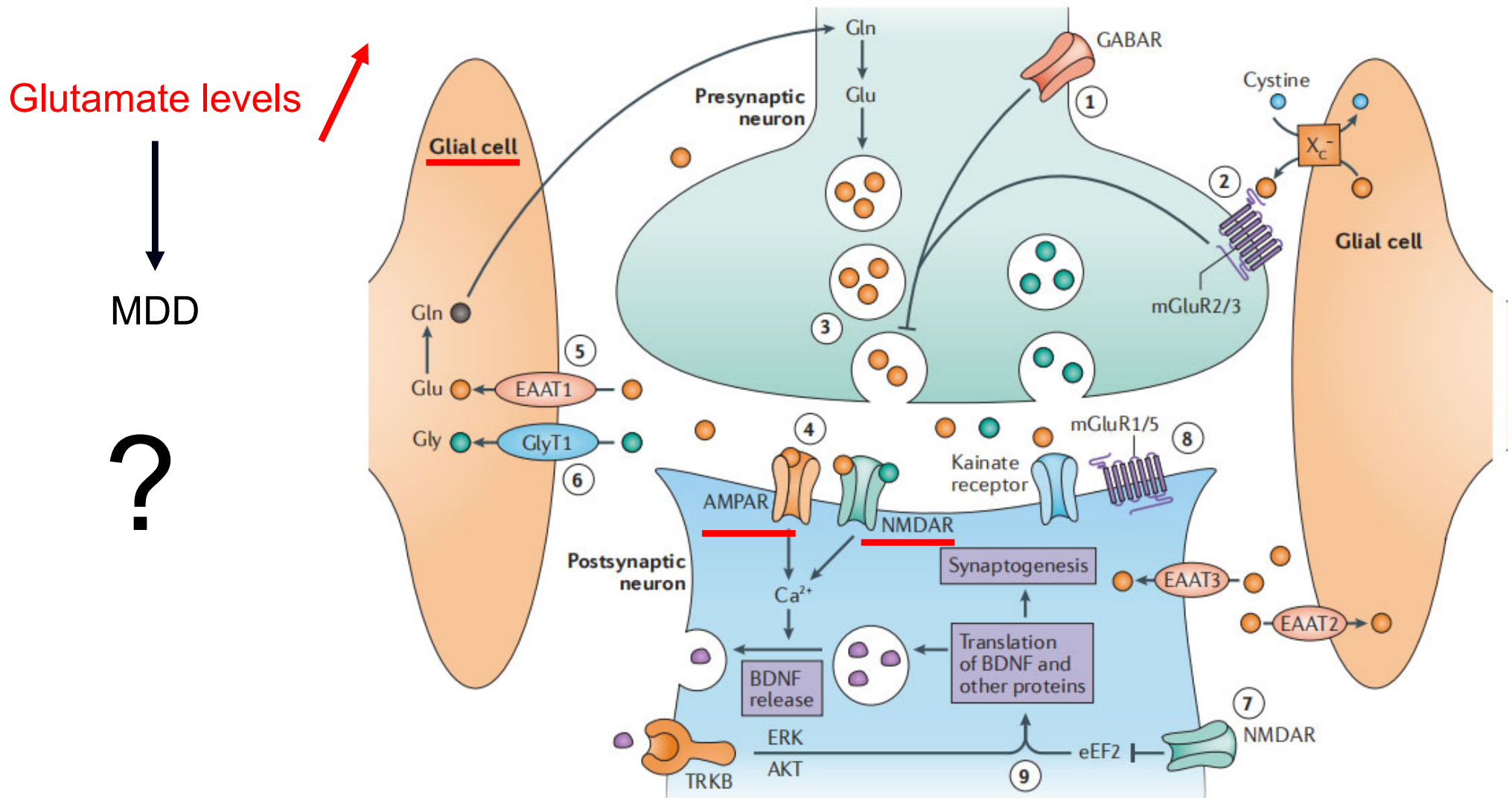Monoamine-deficiency

↓

Major Depressive Disorder (MDD)

R. H. Belmaker,; Galila, A. *N. Engl. J. Med.* **2008**, *58*, 55.

Genetics

X-ray structure of the human serotonin transporter (SERT)

➢ No critical evidence yet…

Jonathan, A. C.; Eric, G. *Nat. Struct. Mol. Biol.* **2018**, *25*, 170.
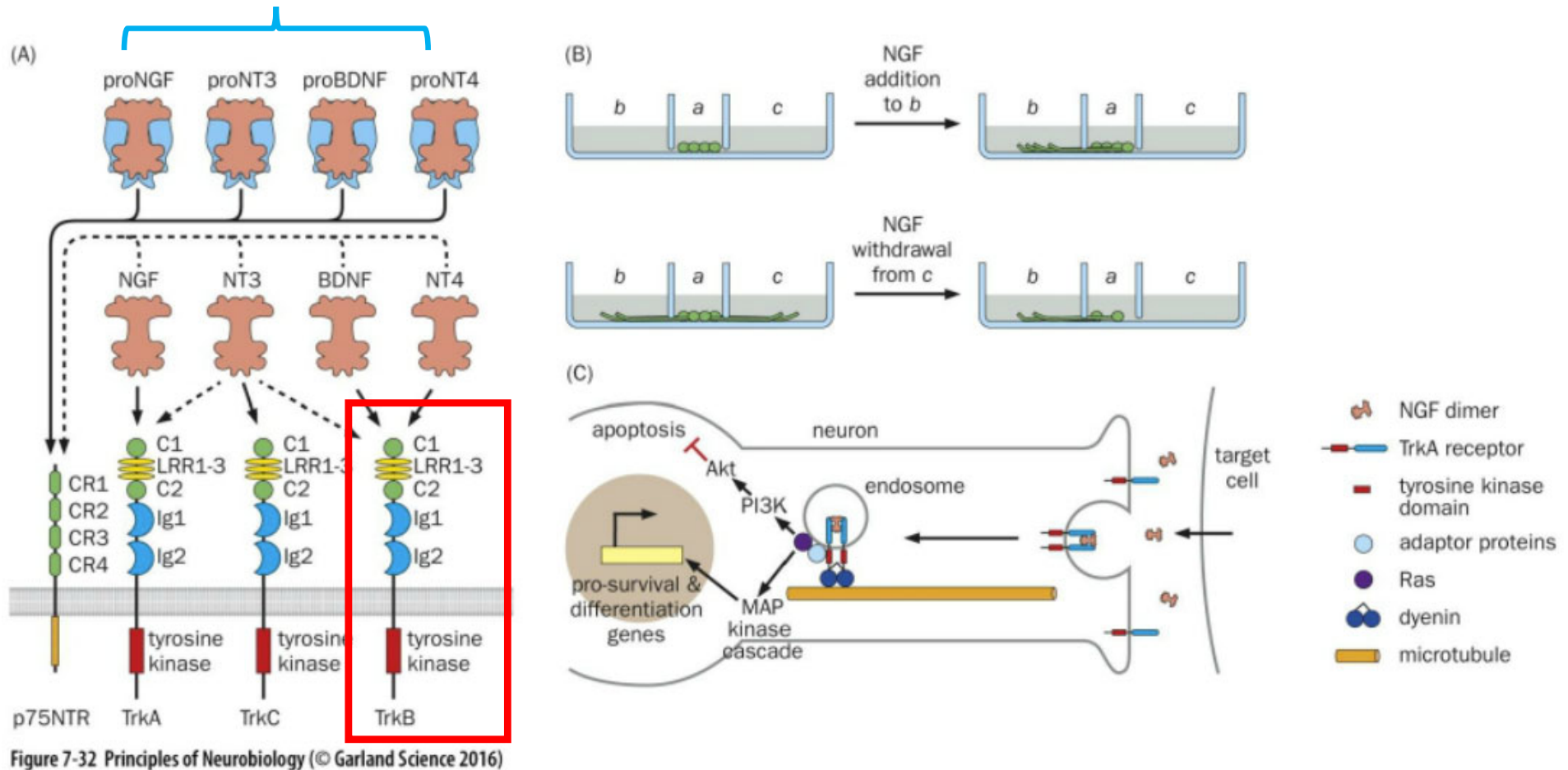
NMDA Recepter

Glutamate levels

MDD

?

James, W. M.; Chadi, G. A.; Sanjay J. M. *Nat. Rev. Drug Discov.* **2017**, *16*, 472.

Brain-derived neurotrophic factor

NGF :

Figure 7-32 Principles of Neurobiology (© Garland Science 2016)

➢ Low BDNF in **Hippocampus** - Depression ?

Brain-derived neurotrophic factor

> Growth/Death

Anirvan, G.; Josette, C.; John, F. C.; Michael, E. G. *Science* **1994**, *263*, 1618.
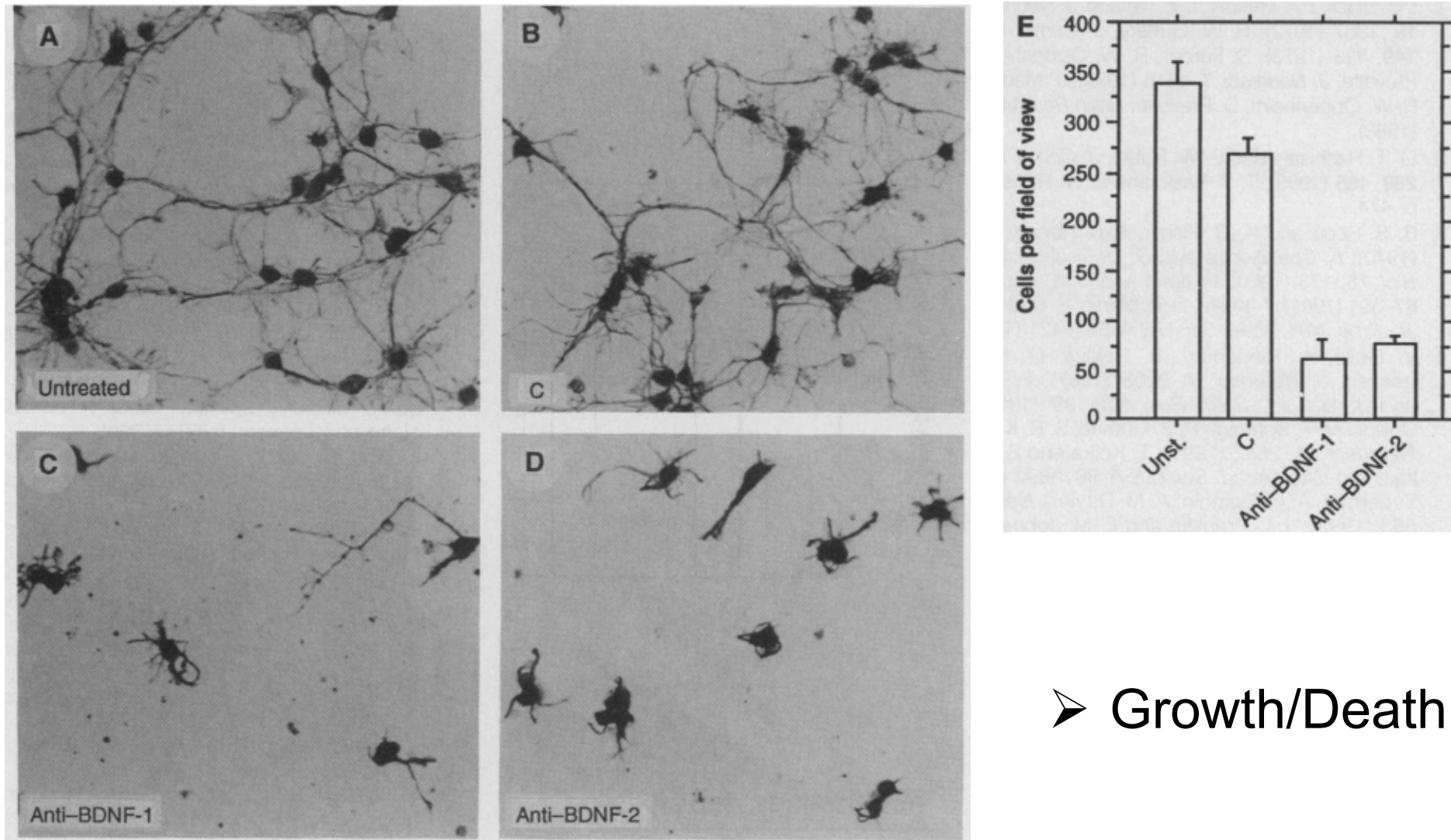
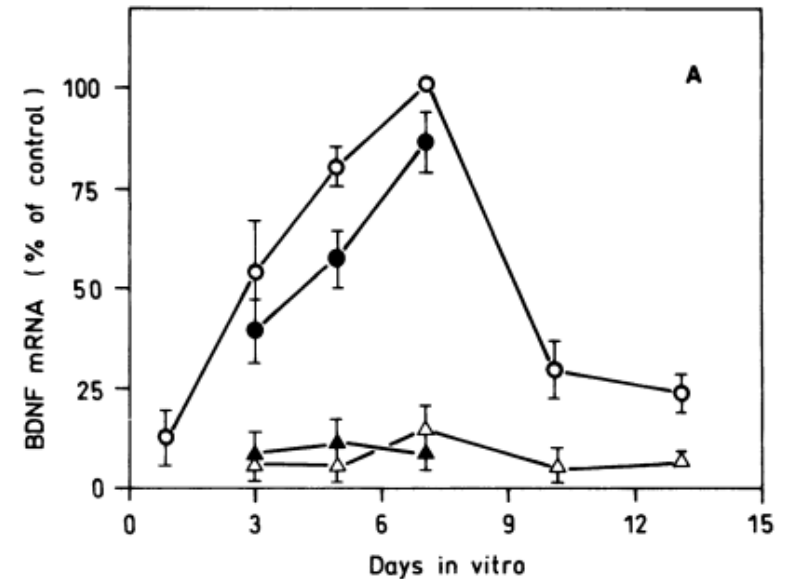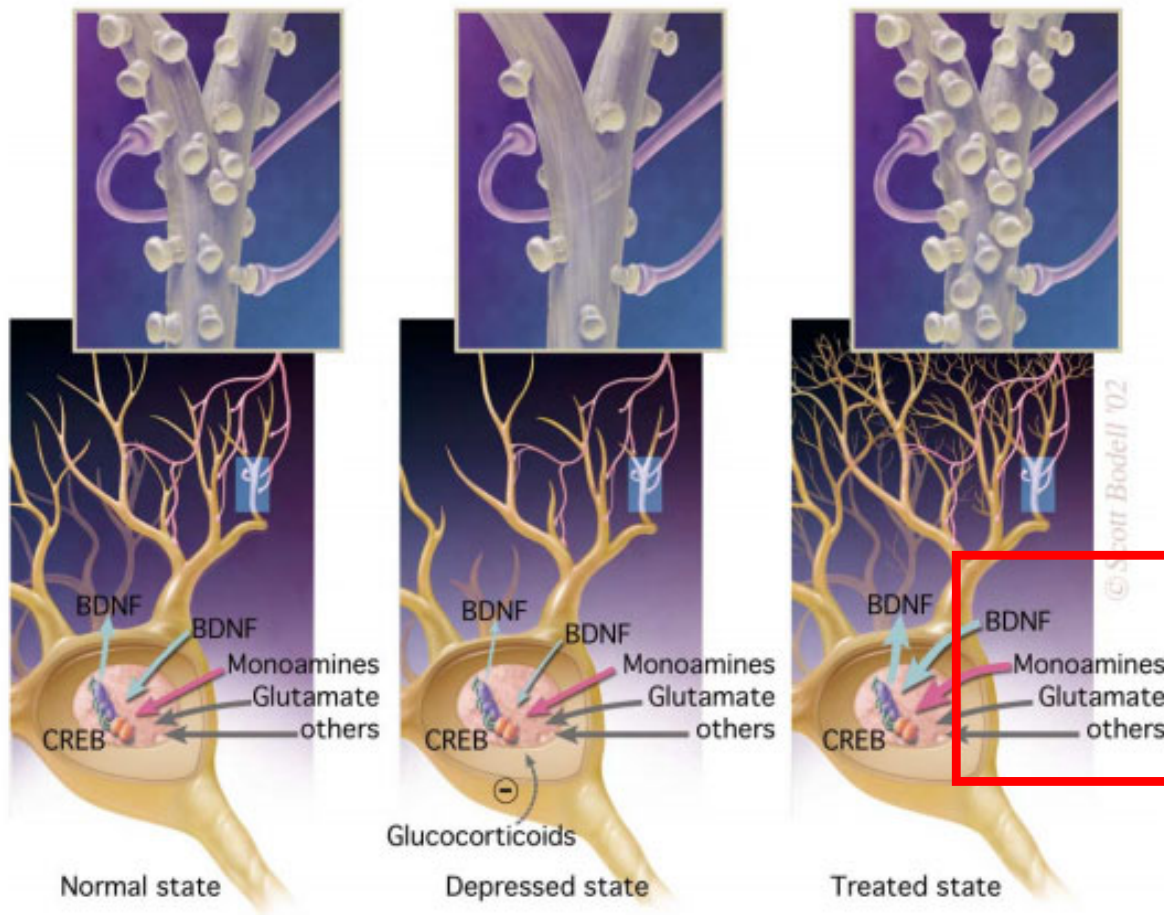# Genetics

Both pro BDNF & BDNF can affect nerve cell
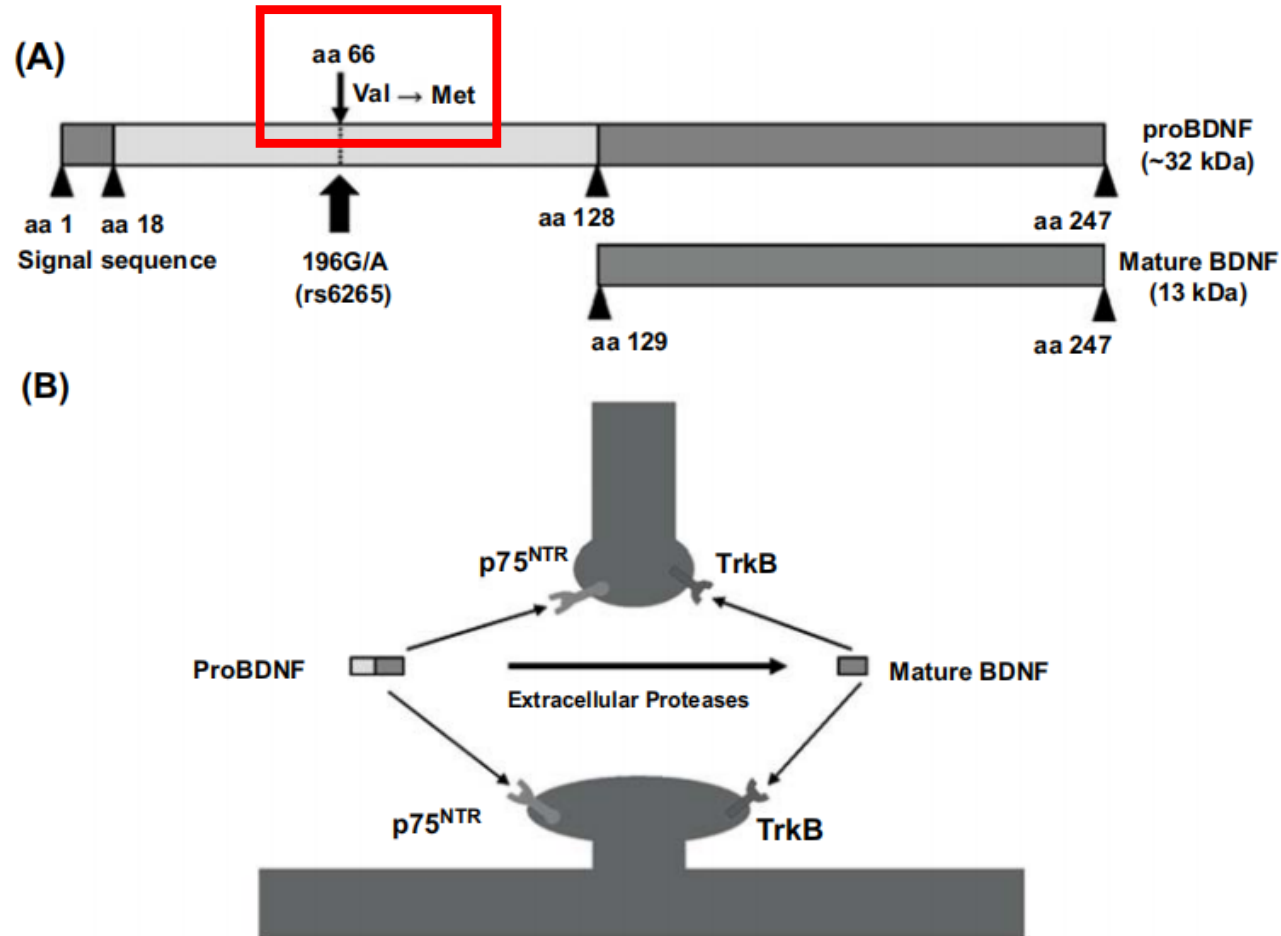
> Calcium controlled

> Upperstream ?

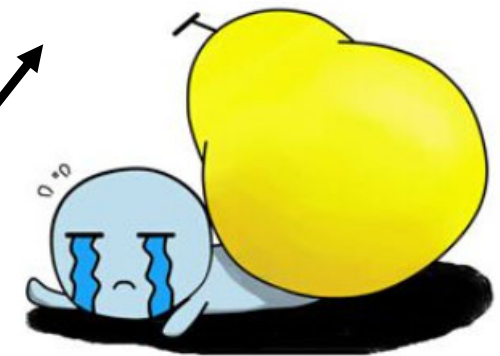Zhang, J. C.; Yao, W.; Hashimoto, K. *Curr Neuropharmacol* **2016**, *14*, 721.
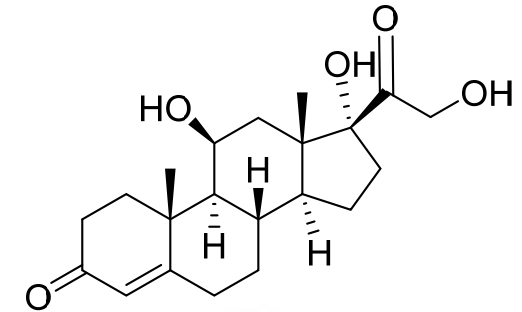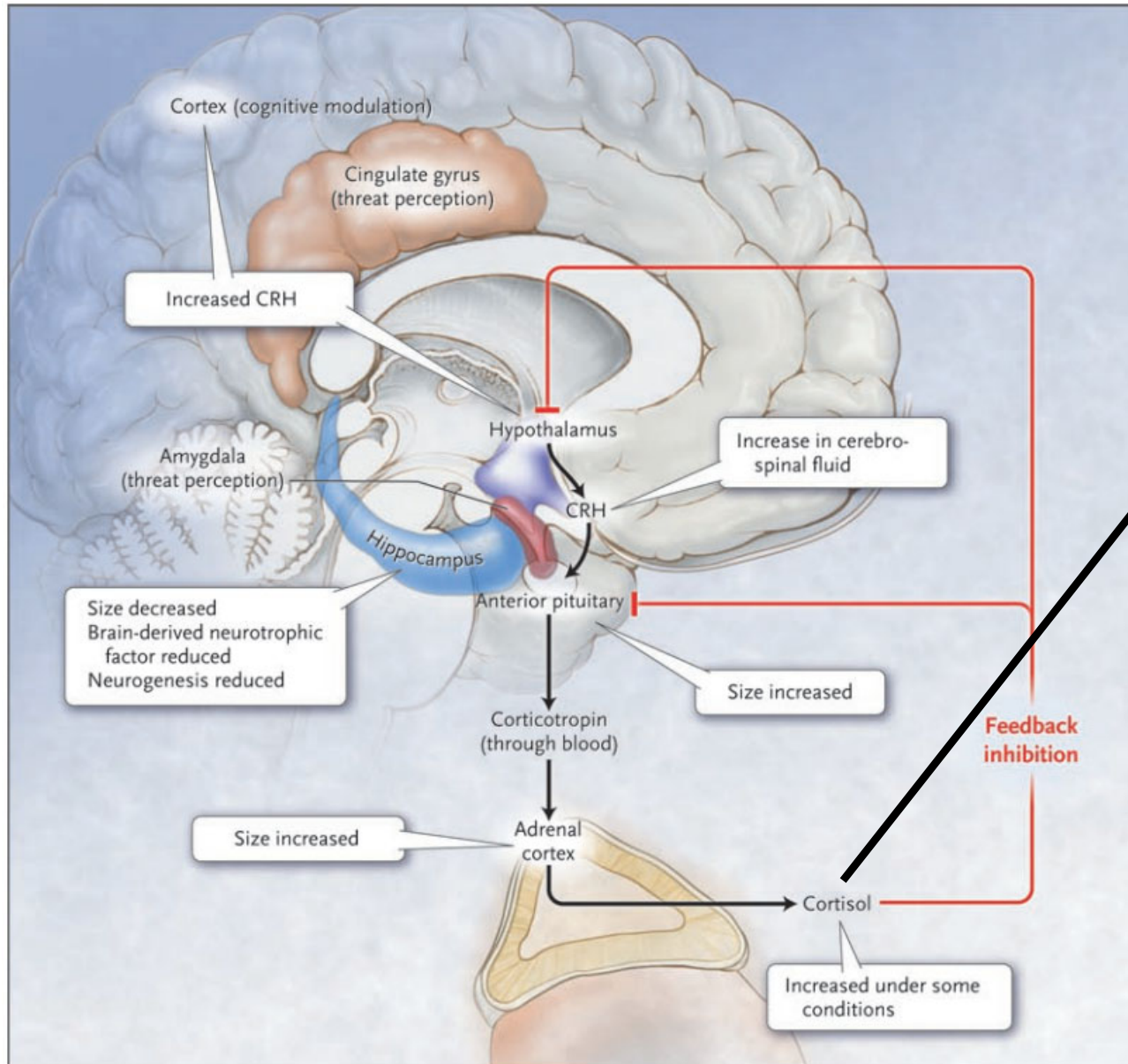
Upperstream

Complicated…
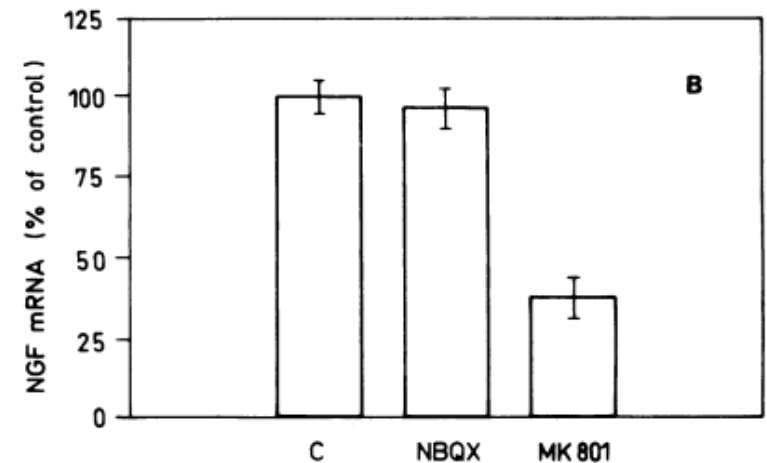
Eric, J. N.; Michel, B.; Ralph, J. D. Amelia, J. E.; Stephen, J. G.; Lisa, M. M. *Neuron* **2002**, *34*, 13.

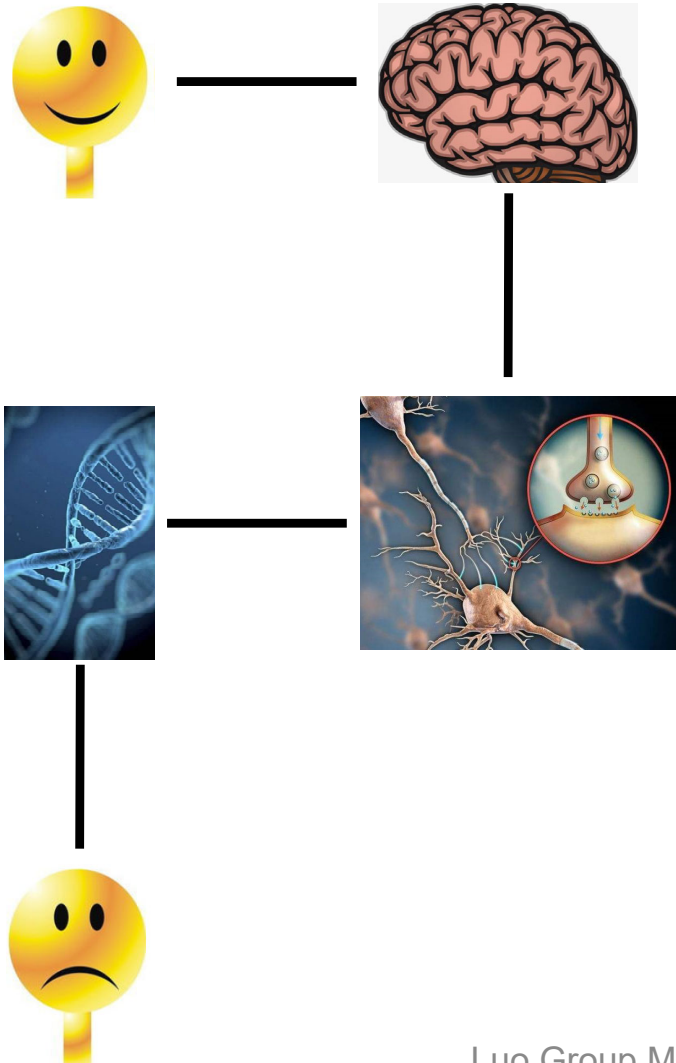Francisco, Z.; Eero. C.; Hans, T.; Dan, L. *Proc. Natl. Acad. Sci.* **1991**, *88*, 10037.
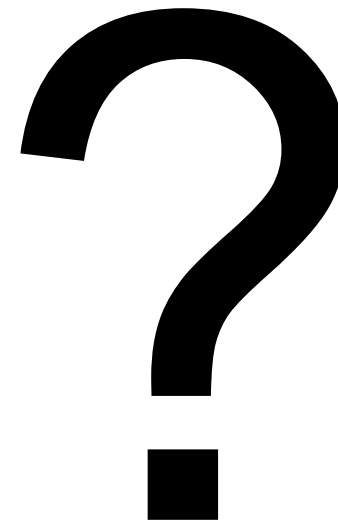
The HPC hypothesis

➤ Also cause
other problems

Summary

Remain a mystery

- ➢ Nervous system
- ➢ Neurotransmitters
- ➢ Genetics
- ➢ Epigenetics
- ➢ …

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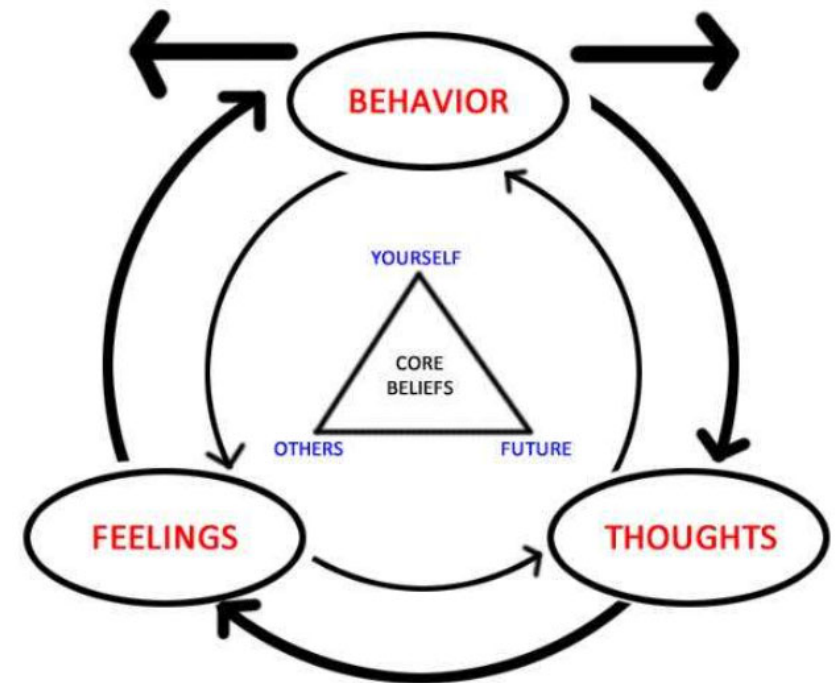
  - Other medications

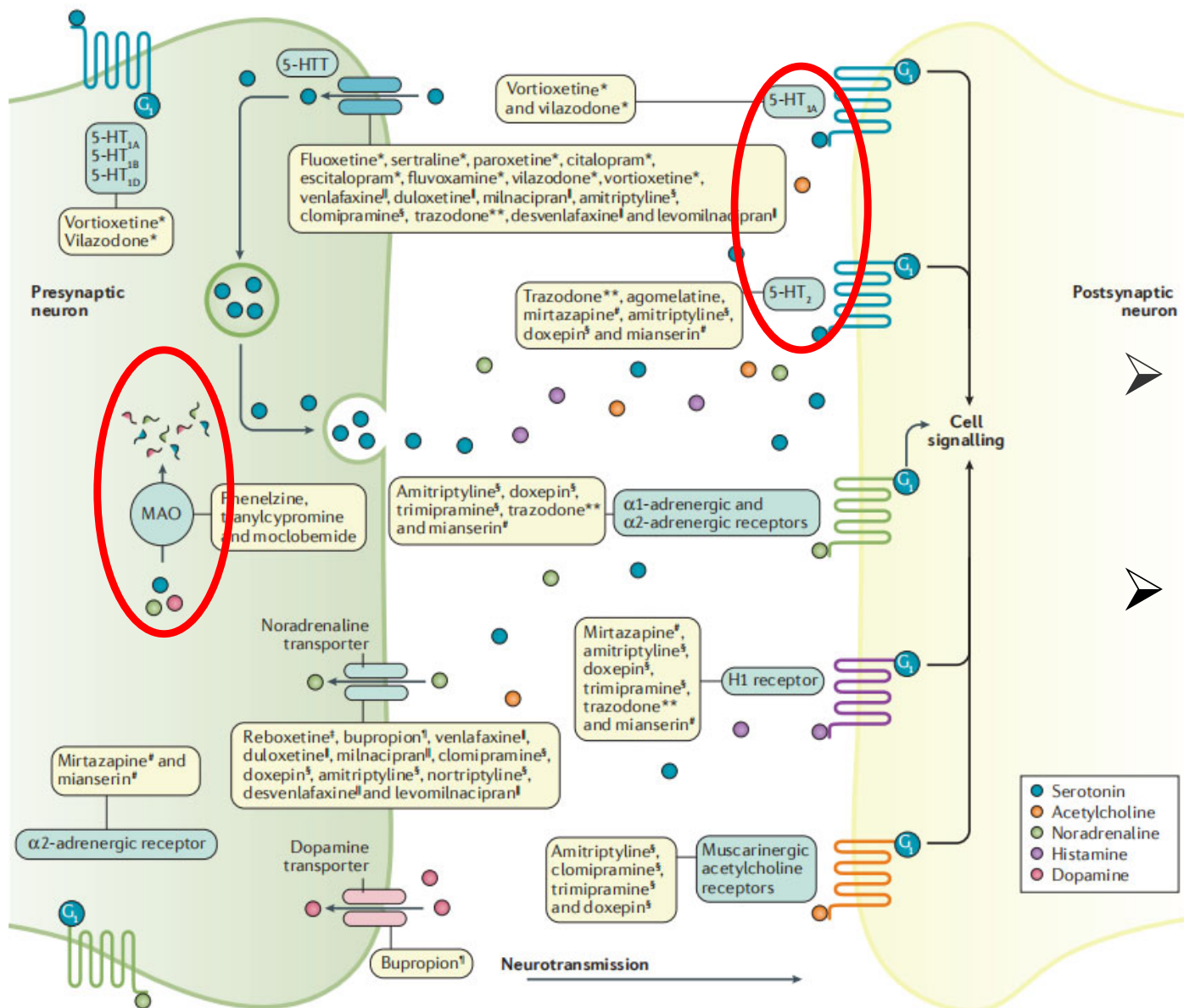# Physical & Behavioral

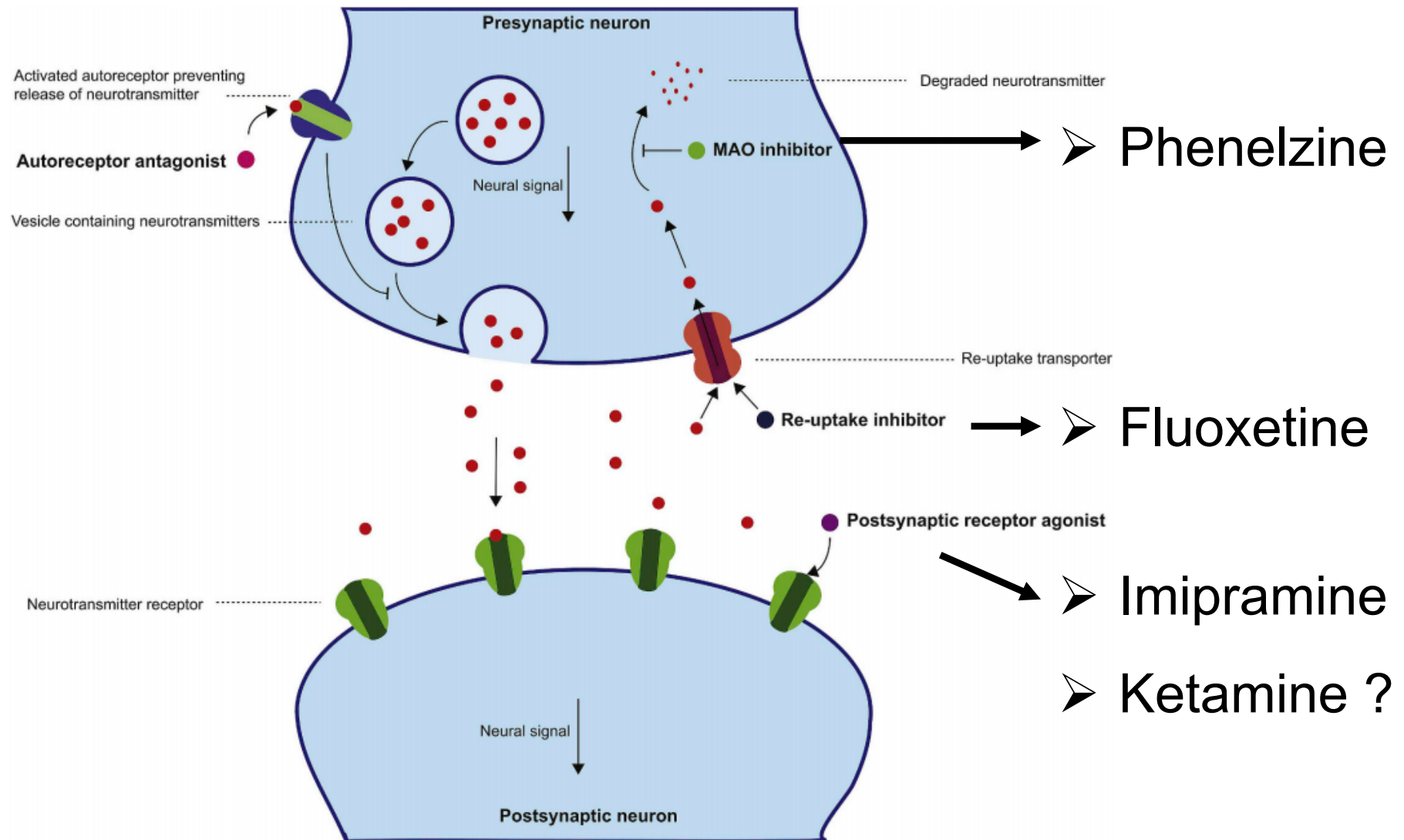Electroconvulsive therapy

Ugo Cerletti

1938

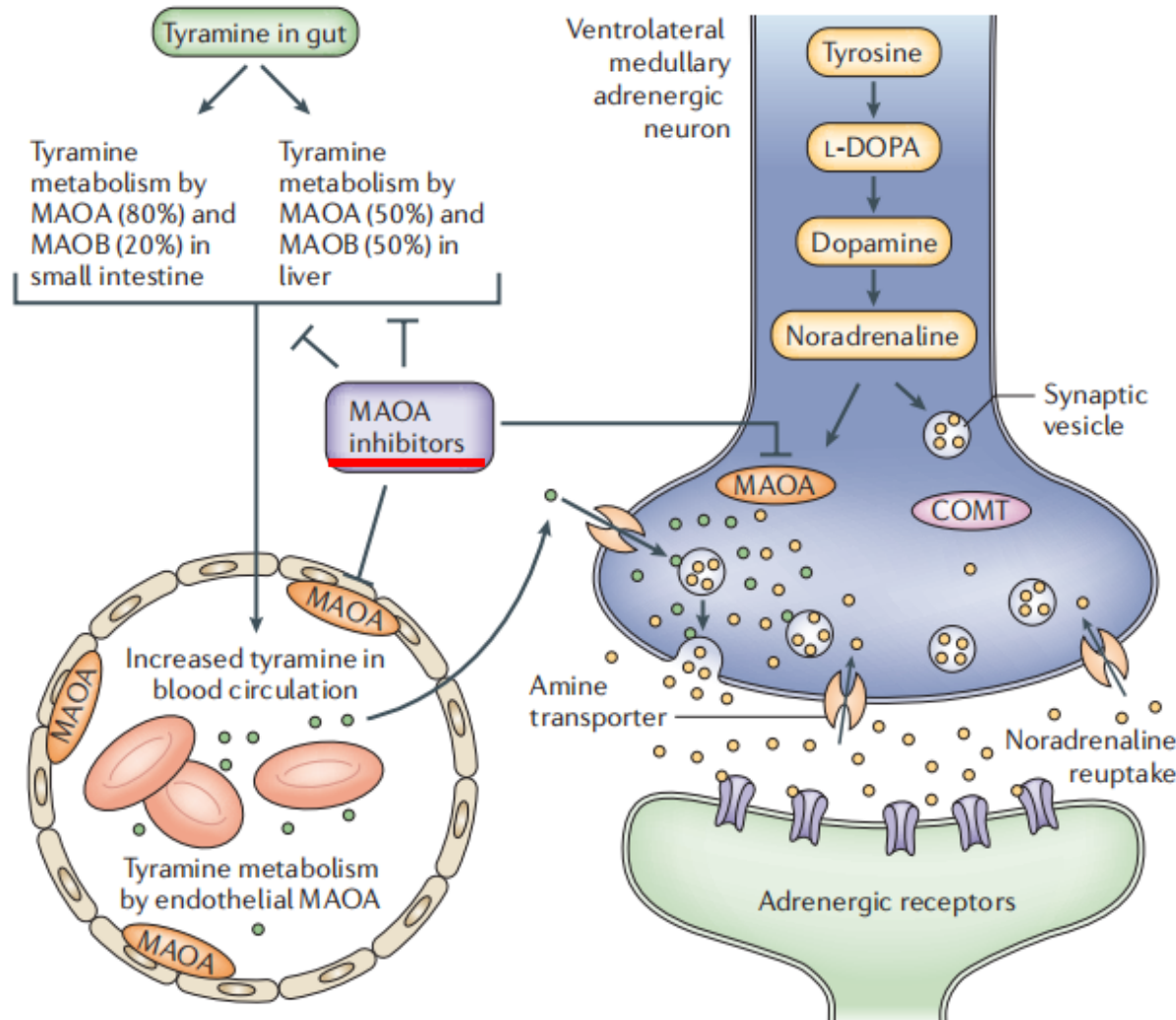Behavioral therapy

1950s

Antidepressant drugs

> More than 20 different medicant

> Over 10 billion $

Christian, O.; Stefan, M. G.; Brenda, W. P.; Carmine, M. P.; Amit, E.; Maurizio, F.; David, C. M.; Alan, F. S. *Nat. Rev. Dis. Primers* **2016**, 2, 1.

Active site of antidepressant drugs

> Phenelzine

> Fluoxetine

> Imipramine

> Ketamine ?

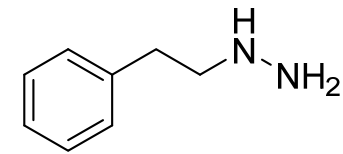Sigrid, S. S.; Artur, C. P. *Eur. J. Clin. Pharmacol.* **2019**, *865*, 172732.

Monoamine oxidase inhibitors

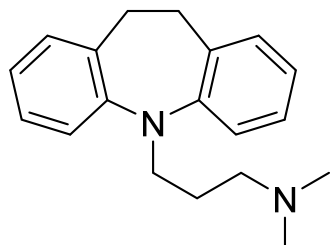From antituberculosis to antidepressant

1950s

Phenelzine

Side effect
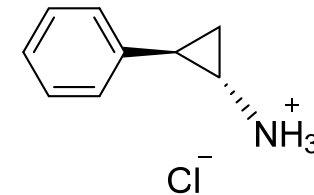
Tranylcypromine

Moclobemide

Moussa, B. H. Y.; Dale, E.; Keith, F. T. *Nat. Rev. Neurosci.* **2006**, *7*, 295.

TCAs

Imipramine · HCl   1958
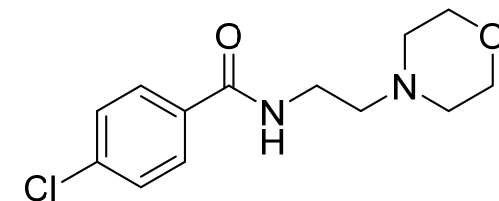
| Anesthetic | No… |
| Antidepressant | Yes ! |

Trazodone · HCl   1980s
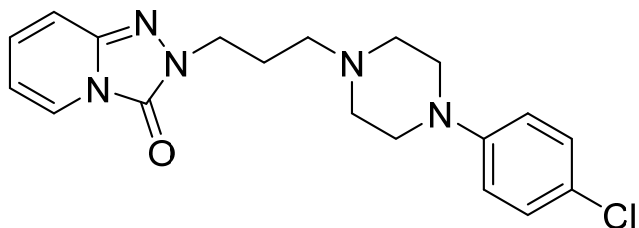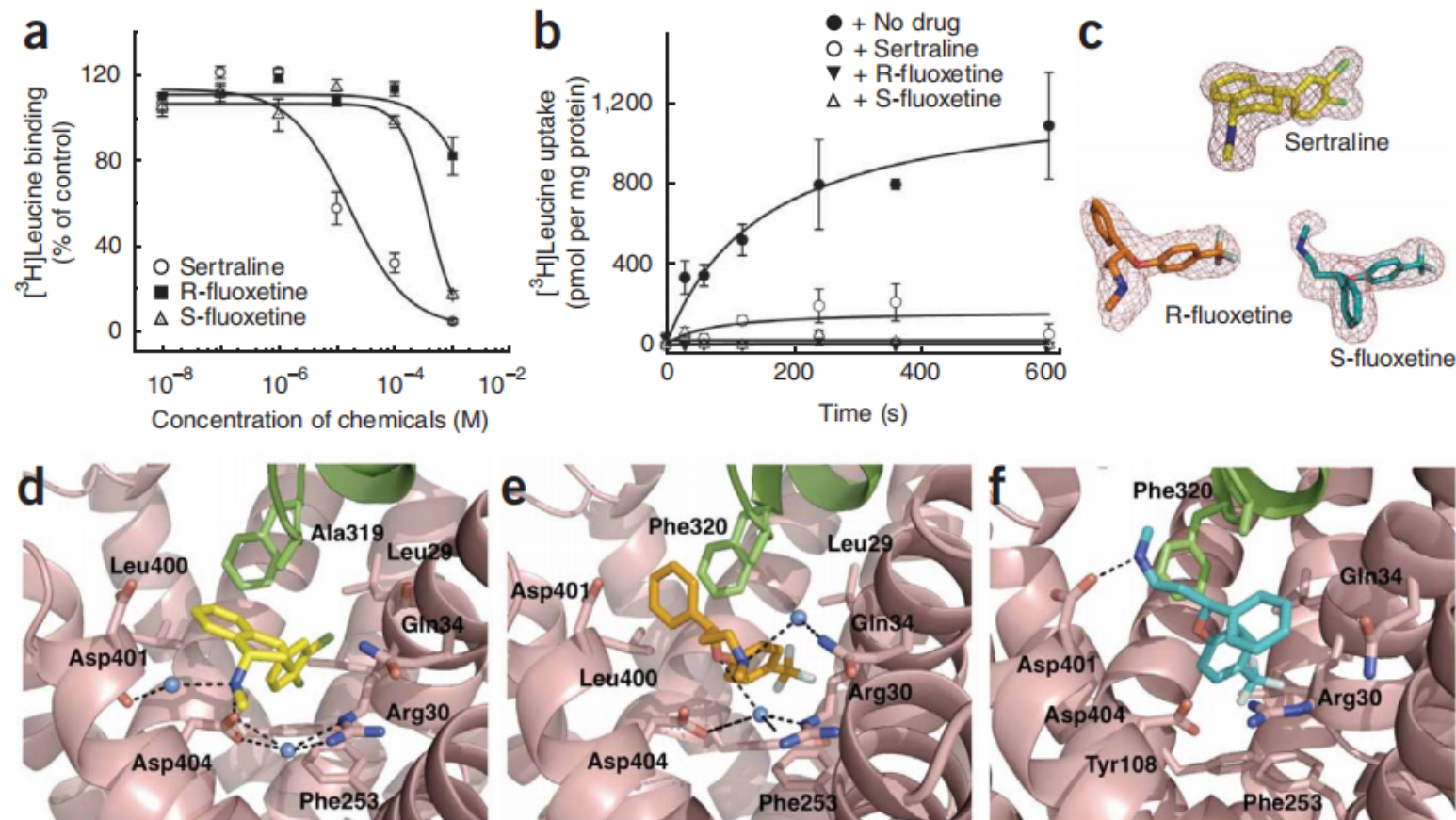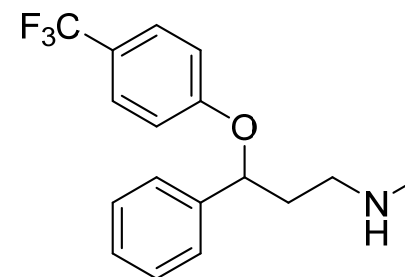
Effective: 30%

Inhibit only one channel ⟶ Not enough !

Fluoxetine

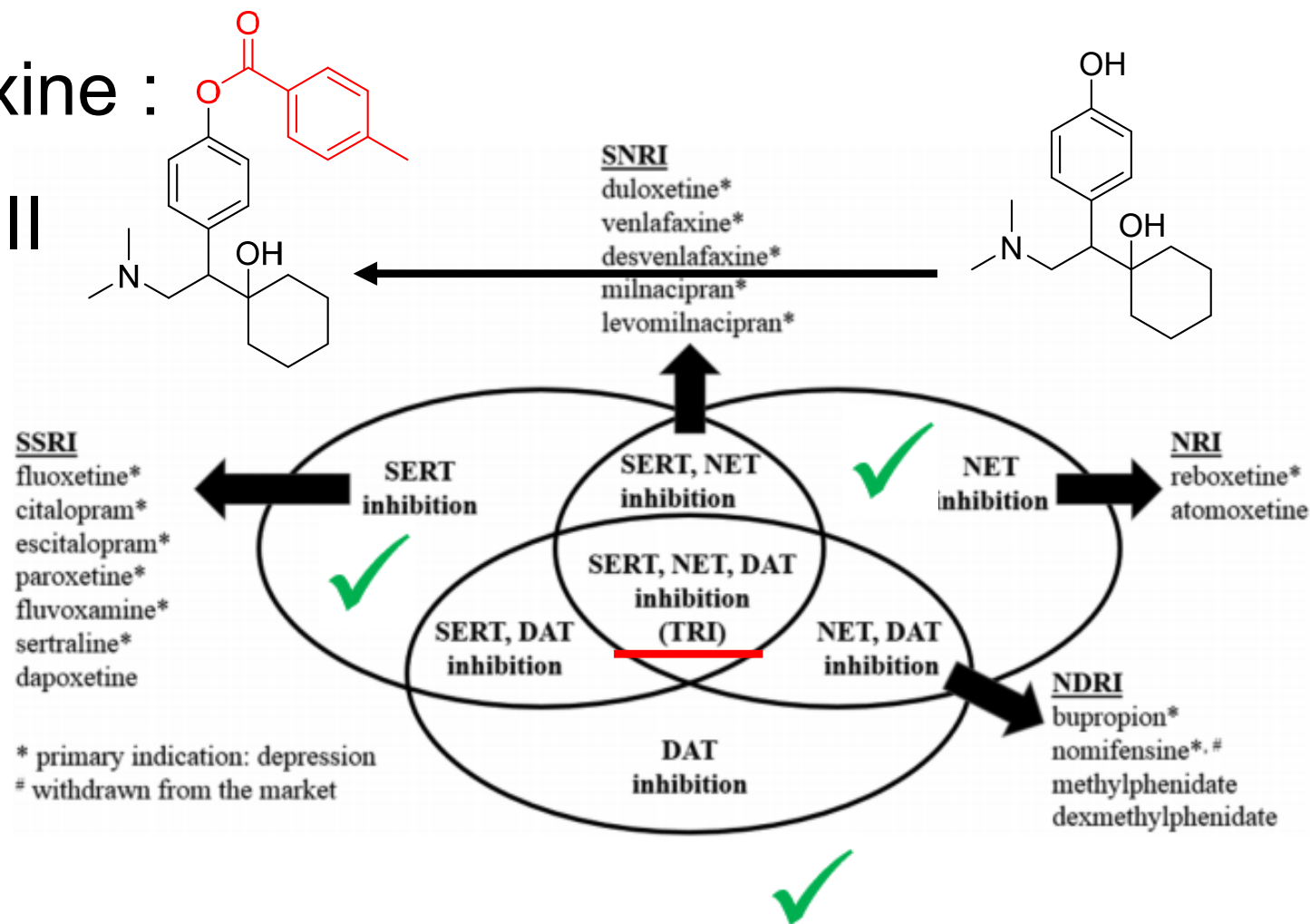Best-selling antidepressant drugs

Zheng, Z.; Juan, Z.; Nathan, K. K.; Christopher, J. L.; Maarten, E. A. R.; Da, N. W. *Nat. Struct. Mol. Biol.* **2009**, *16*, 652.
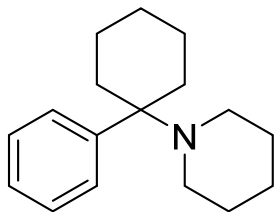
Triple Reuptake Inhibitors
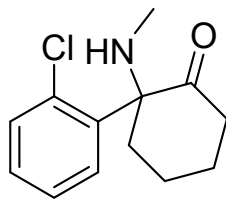
Ansofaxine :

Phase III

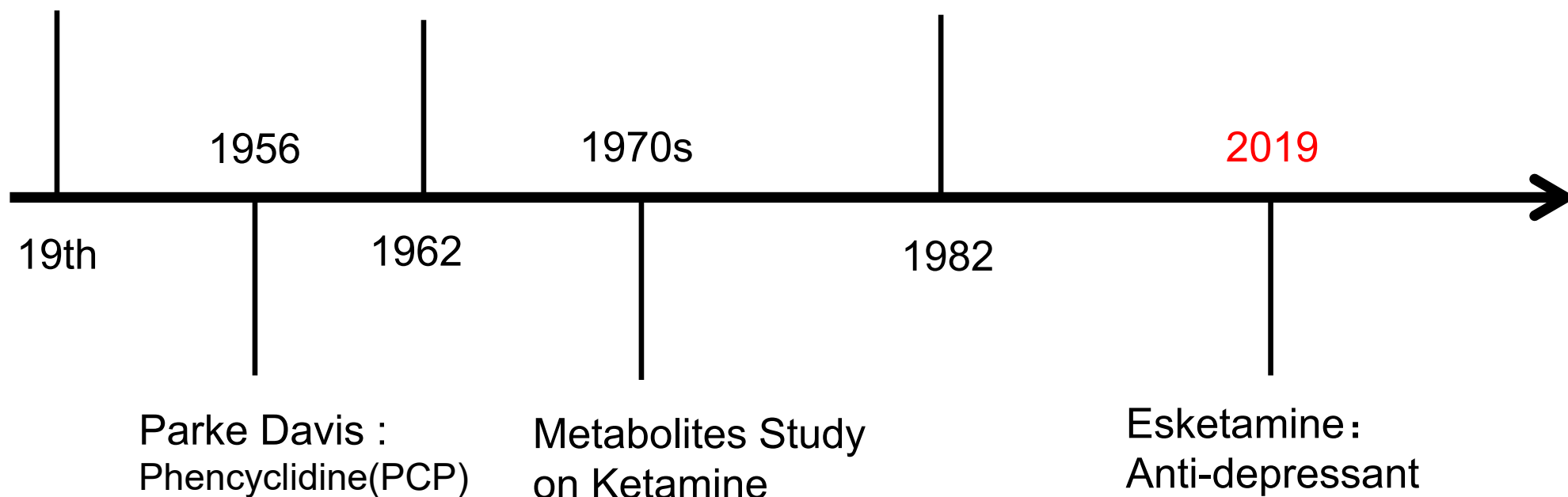Murugaiah, A. M. S. *J. Med. Chem.* **2018**, *61*, 2133.

Ketamine
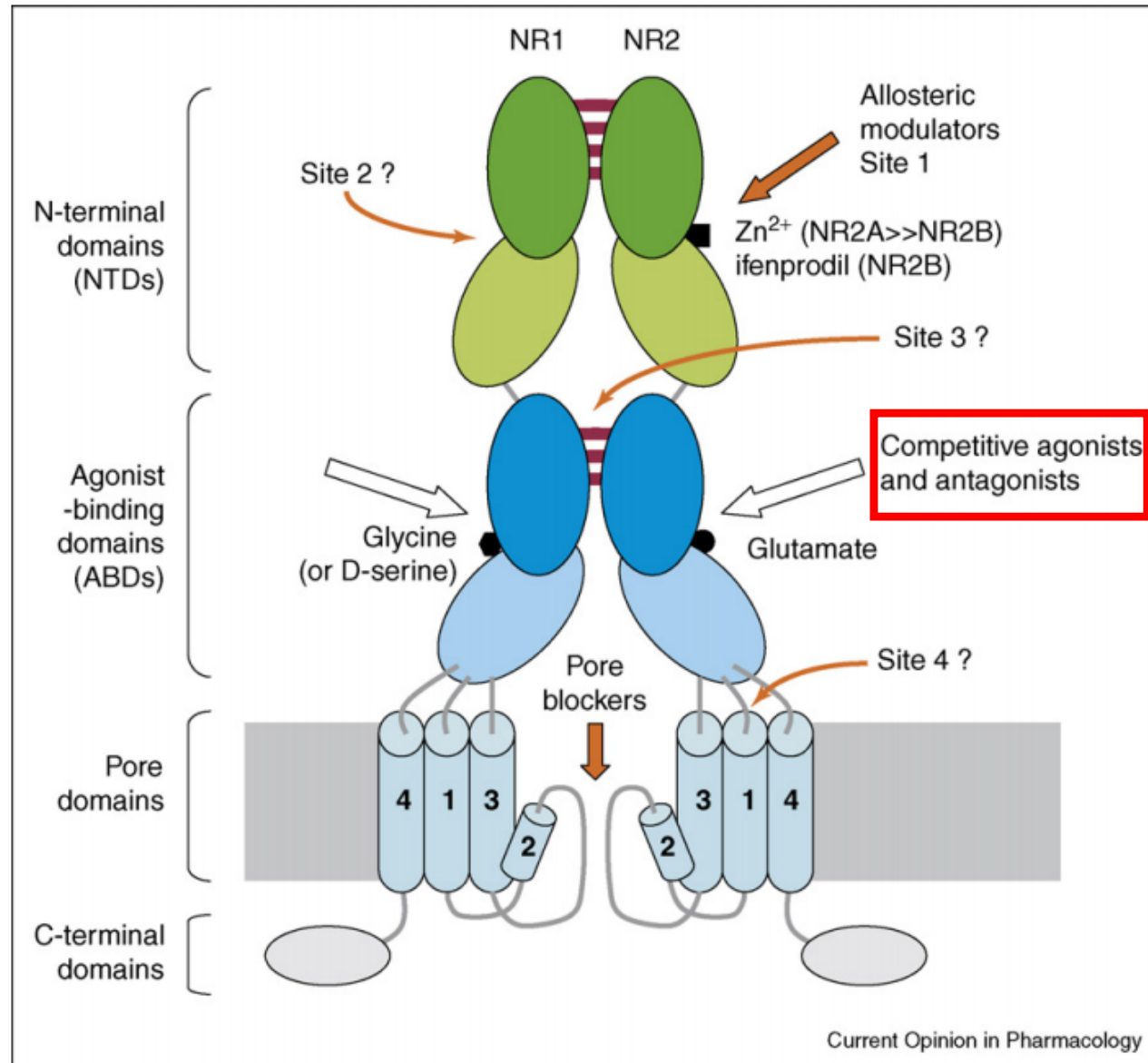

PCP

Ketamine

Dawn of Anesthetic (Anesthetic in red)

Calvin Lee Stevens : CI-581(ketamine)

David Lodge : glutamate N-Methyl-D-aspartate calcium channel receptor(NMDA receptor)

1956

1970s

2019

19th

1962

1982

Parke Davis : Phencyclidine(PCP)

Metabolites Study on Ketamine

Esketamine： Anti-depressant

Ketamine

Current Opinion in Pharmacology

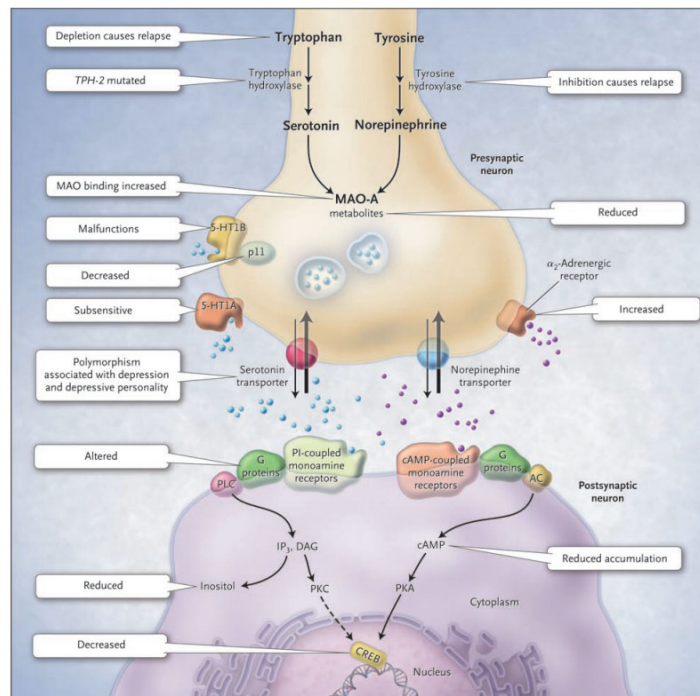Pierre, P.; Jacques, N. *Curr Opin Pharmacol* **2007**, 7, 39–47

Ketamine
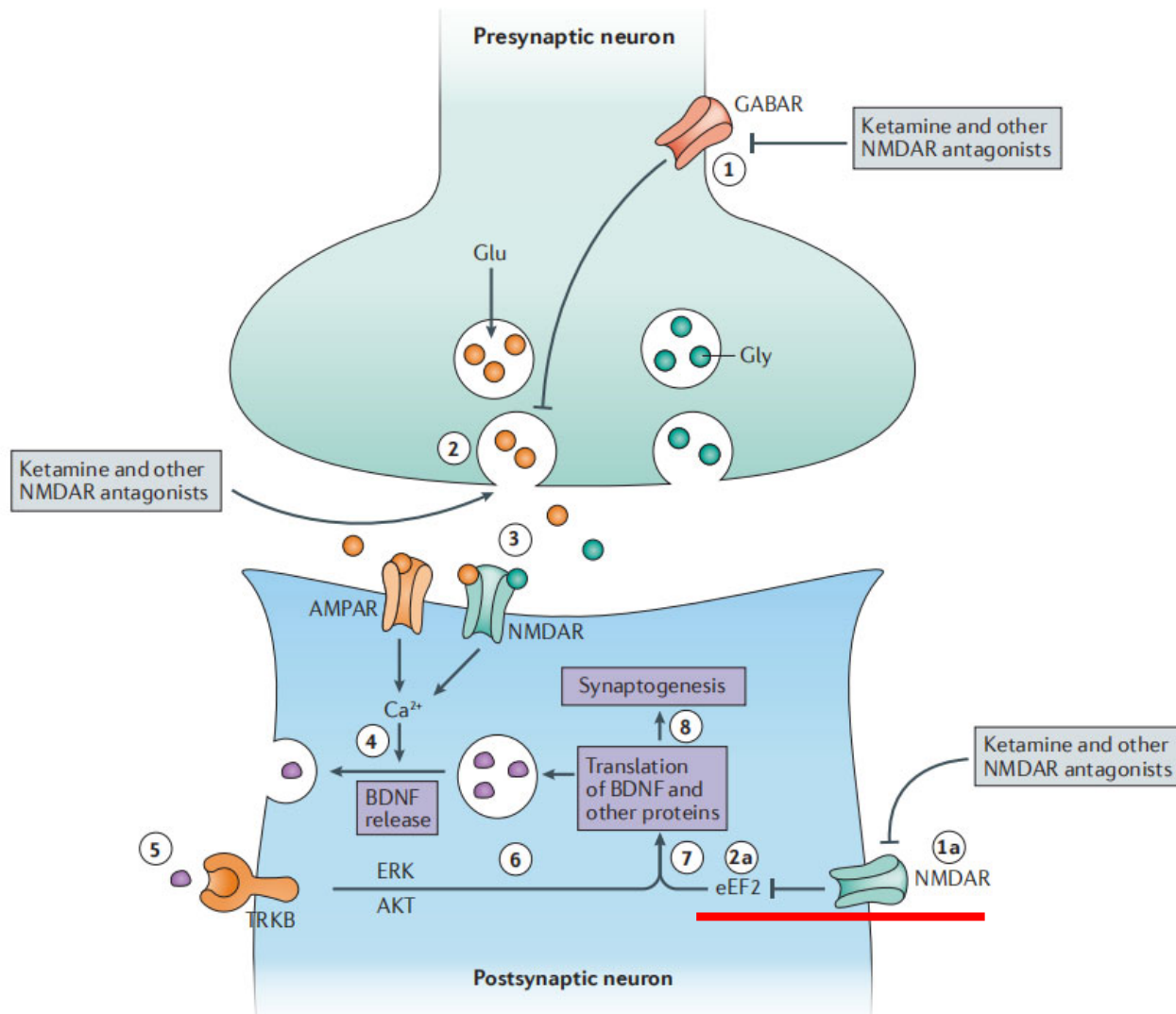
➤ Rapid-onset

➤ Low-dose

James, W. M.; Chadi, G. A.; Sanjay J. M. *Nat. Rev. Drug Discov.* **2017**, *16*, 472.

Summary

Diffculty		Drug mechanisms	
		Clear	Unknown
Pathogenesis	Clear	**Easy**	**Hard**
	Unknown	**Hard**	**Hell**

➢ Mechanism - May be right

➢ Efficacy - Multiple therapy

➢ Limitation - Side effect …

R. H. Belmaker,; M.D.; Galila, A. *N. Engl. J. Med.* **2008**, *58*, 55.

Expectation

Antidepressant drugs :

- ➢ Rapid onset
- ➢ Higher Efficacy
- ➢ Lower Side effect
- ➢ Broader spectrum
- ➢ Reveal the mechanism

Normal life

Prevention

Treatments

MDD
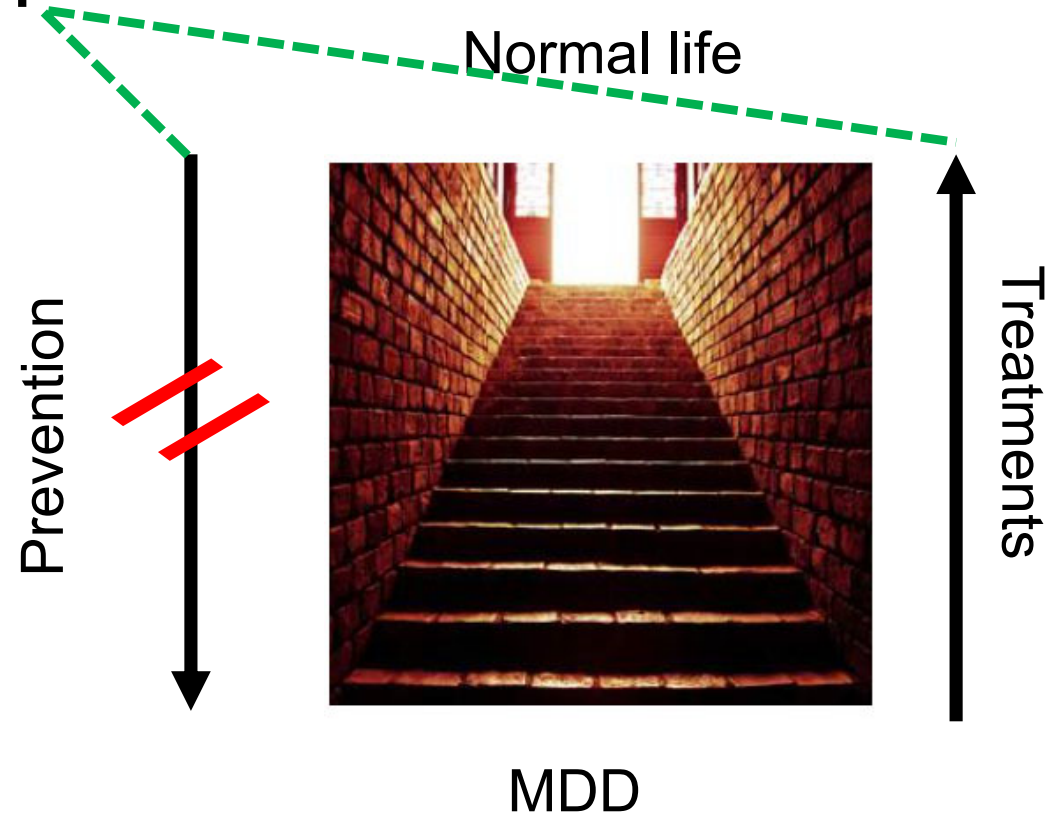
Take care of yourself, and be well !