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Basics in Psychopharmacology

May 2020 MRC2.PSY.D.00078

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Organization of the Nervous System

The central nervous system (CNS; brain, spinal cord) and peripheral nervous system (PNS) are composed of two main types of neural cells[1]:

- Neurons[1]
- Glial cells[1,2]

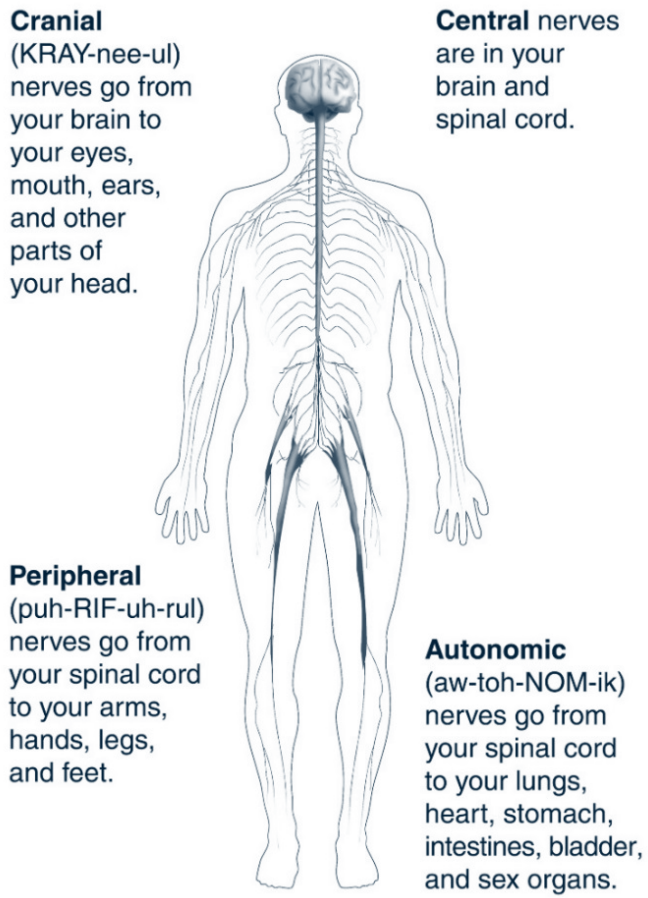
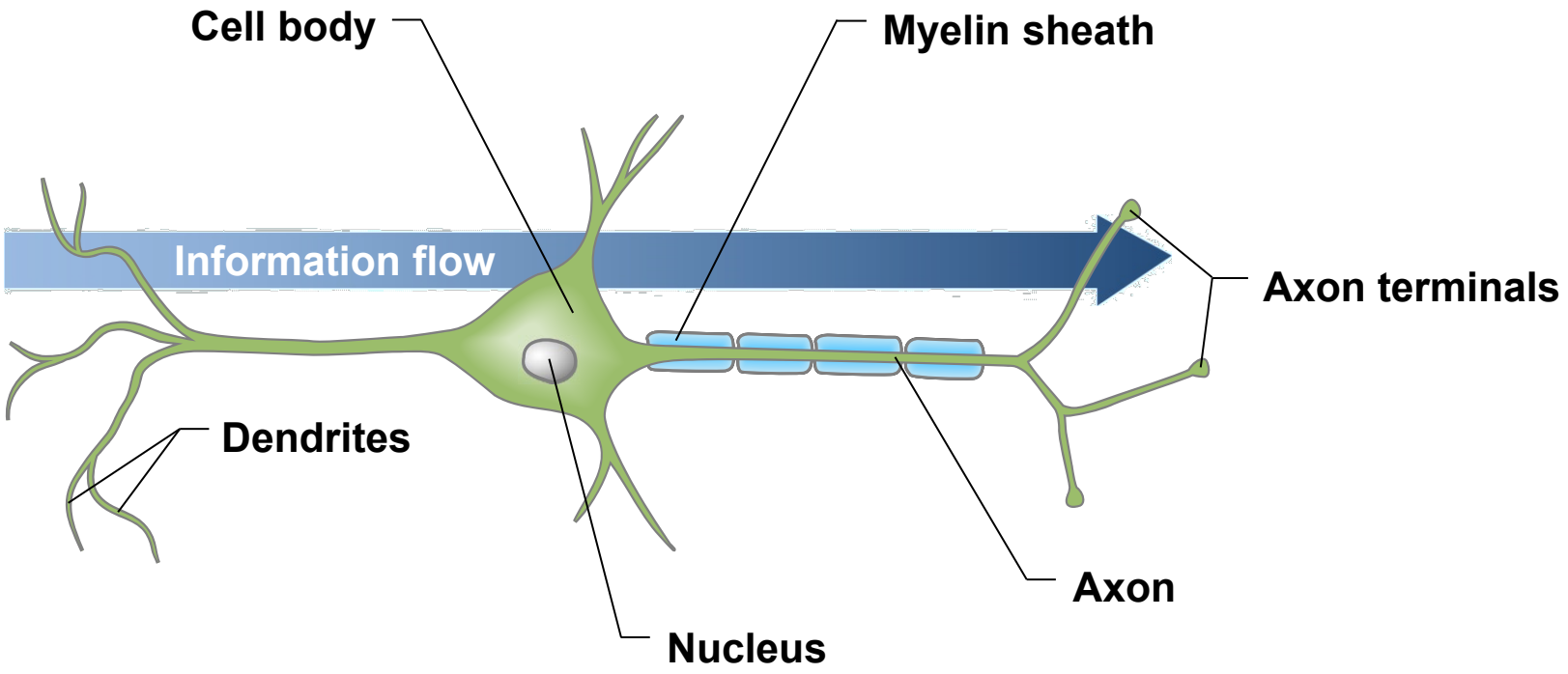


Image from: NIDDK Image Library[3]

1. Tortora GJ, Derrickson B. *Principles of Anatomy and Physiology*. 12th edition. John Wiley & Sons; 2009.
2. Kandel ER, Schwartz JH, Jessell TM (eds). *Principles of Neural Science*. 4th edition. McGraw-Hill; 2000.
3. Drawing of the nervous system showing the four types of nerves with descriptions labeled for each type (Image number N00165). In: Prevent diabetes problem: Keep your nervous system healthy (DM-208). National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Website. Available at: https://www.niddk.nih.gov/health-information/diabetes/preventing-diabetes-problems/nerve-damage-diabetic-neuropathies. Accessed 28 July 2016.

Anatomy of a Neuron[1–3]

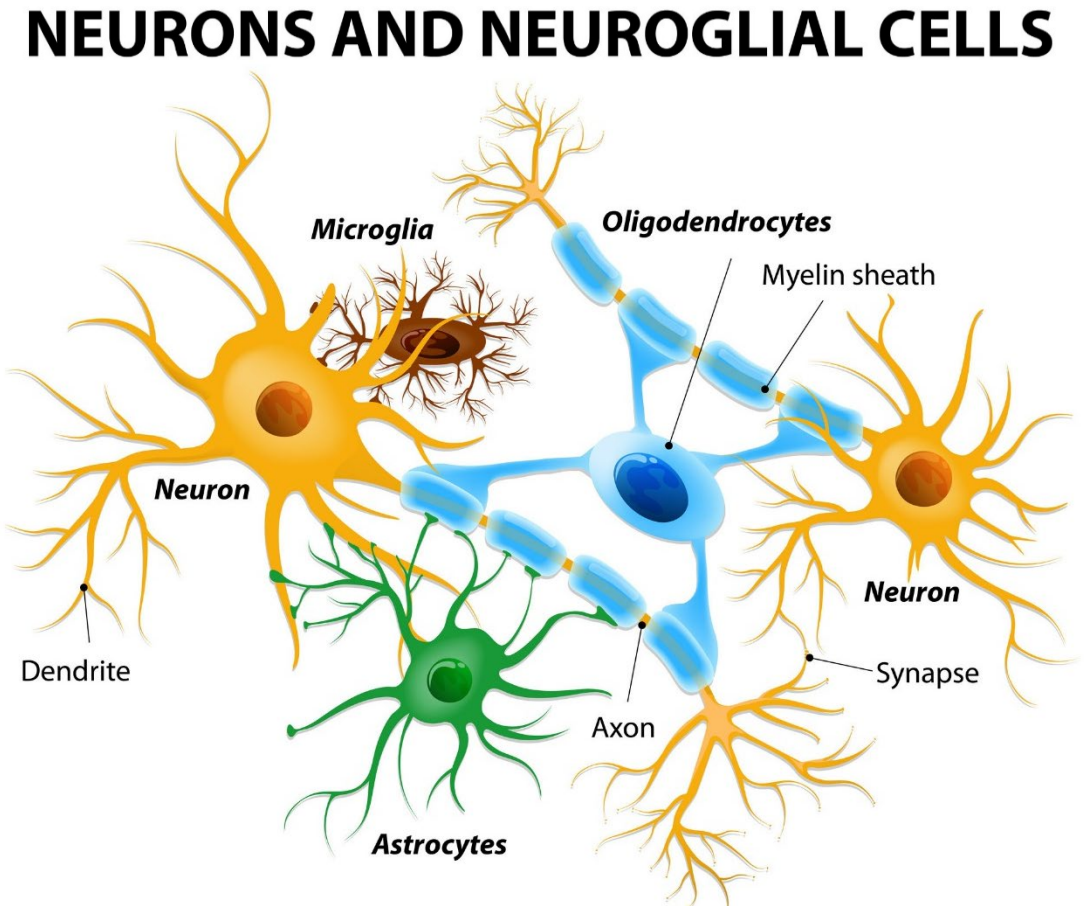


Neurotransmitters: chemicals in the nervous system that transmit nerve impulses between neurons[3]

Action potential: in neurophysiology, an electrical charge that moves through an axon[3]

1. Kandel ER, Schwartz JH, Jessell TM (eds). *Principles of Neural Science*. 4th edition. McGraw-Hill; 2000.
2. Tortora GJ, Derrickson B. *Principles of Anatomy and Physiology*. 12th edition. John Wiley & Sons; 2009.
3. *Oxford Concise Medical Dictionary*. 9th edition. Oxford University Press; 2015.

Various Types of Glia Cells in the Brain[1,2]

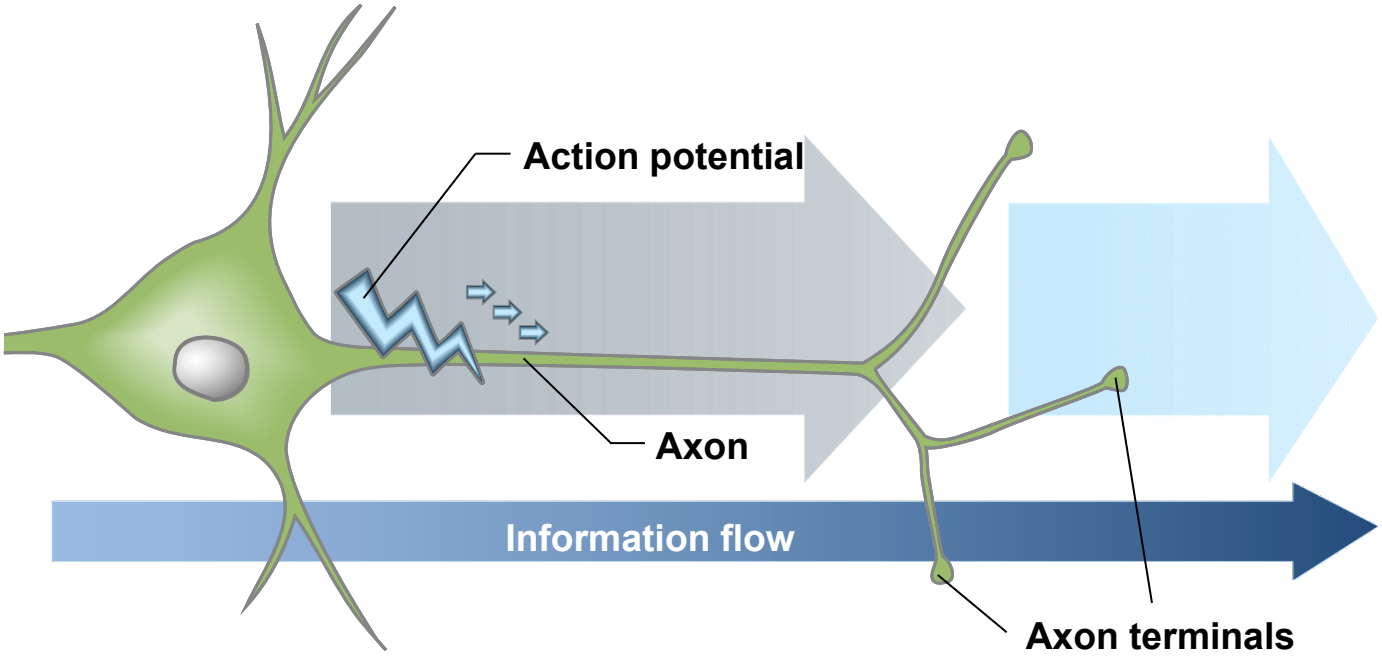


1. Purves D, Augustine GJ, Fitzpatrick D, et al (eds). *Neuroscience*. 3rd edition. Sinauer Associates; 2004.
2. Tortora GJ, Derrickson B. *Principles of Anatomy and Physiology*. 12th edition. John Wiley & Sons; 2009.

Process of Electrical Neurotransmission[1–3]

Information moves through the nervous system via two integrated forms of communication

- Electrical neurotransmission through action potentials (shown here)
- Chemical neurotransmission (detailed next)



1. Tortora GJ, Derrickson B. *Principles of Anatomy and Physiology*. 12th edition. John Wiley & Sons; 2009.
2. Purves D, Augustine GJ, Fitzpatrick D, et al (eds). *Neuroscience*. 3rd edition. Sinauer Associates; 2004.
3. Kandel ER, Schwartz JH, Jessell TM (eds). *Principles of Neural Science*. 4th edition. McGraw-Hill; 2000.

Process of Chemical Neurotransmission[1,2]

1. **Action potential**
2. **Neurotransmitters released**
3. **Neurotransmitters bind**
4. **Signal transduction**
5. **Neurotransmitters cleared**

Receptor: a protein molecule on a cell membrane that binds to a specific chemical, such as a neurotransmitter or drug, and produces a specific physiological effect.[3]

Reuptake: a mechanism by which a neurotransmitter is taken back into the axon terminal that released it; the most common mechanism for removal and inactivation of neurotransmitters.[2]

Diffusion: in regard to neurotransmission, a mechanism by which neurotransmitters drift out of the synaptic cleft.[2]

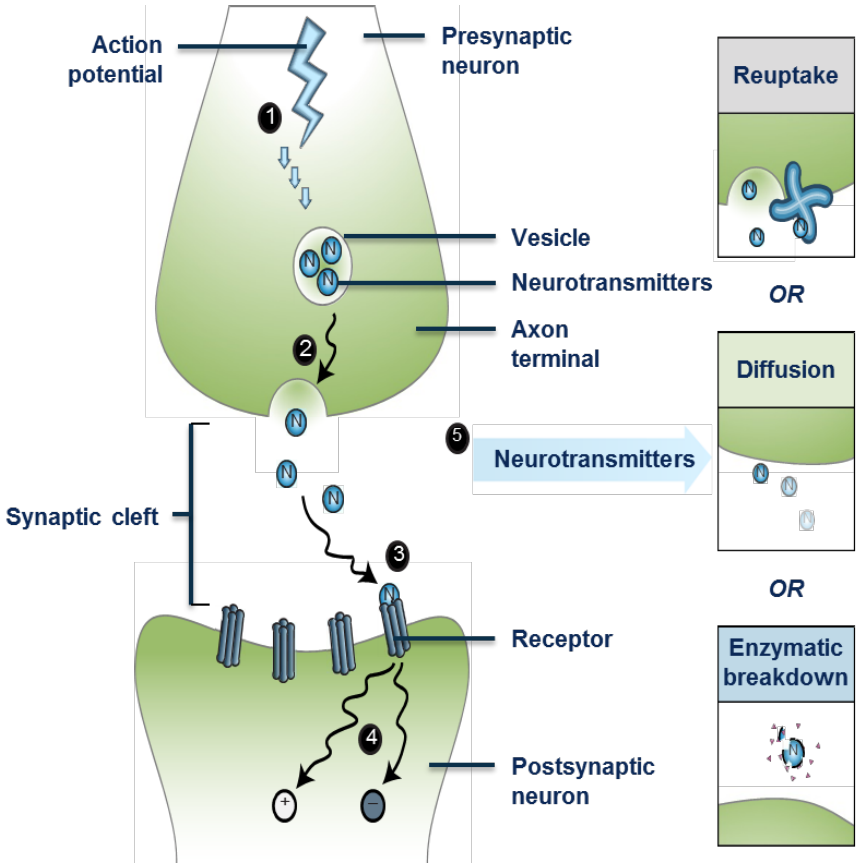


Image adapted from: Purves D, et al. 2004[1]

1. Purves D, Augustine GJ, Fitzpatrick D, et al (eds). *Neuroscience*. 3rd edition. Sinauer Associates; 2004.
2. Tortora GJ, Derrickson B. *Principles of Anatomy and Physiology*. 12th edition. John Wiley & Sons; 2009.
3. *Oxford Concise Medical Dictionary*. 9th edition. Oxford University Press; 2015.

Neurotransmitters and Receptors*

Neurotransmitter receptor subtypes	
Neurotransmitter	**Receptor subtypes**
Dopamine[1]	Dopaminergic receptors ($D_{1\text{-}5}$ subtypes)
Serotonin[2]	5-HT receptors ($5\text{-}HT_{1A\text{-}B}$, $5\text{-}HT_{1D\text{–}F}$, $5\text{-}HT_{2A\text{-}C}$, $5\text{-}HT_{3\text{-}7}$ subtypes)
Noradrenaline[1,3]	α-adrenergic receptors ($\alpha_{1A,\ B,\ D}$, $\alpha_{2A\text{-}C}$ subtypes) β-adrenergic receptors ($\beta_{1\text{-}3}$ subtypes)
Glutamate[1,4]	Ionotropic receptors: non-NMDA (AMPA, kainate), NMDA receptors Metabotropic receptors (mGluRs)
GABA[1]	$GABA_A$, $GABA_B$, and $GABA_C$ receptors
Acetylcholine[1]	Cholinergic receptors: muscarinic receptors ($M_{1\text{-}5}$ subtypes), nicotinic receptors
Histamine[1]	Histaminic receptors ($H_{1\text{-}3}$ subtypes)

5-HT, serotonin; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; D, dopamine; GABA , gamma-aminobutyric acid; H, histamine; M, muscarinic; mGluRs, metabotropic glutamate receptors; NMDA, N-methyl-D-aspartate.
*Common targets for drugs; will be discussed in further detail in disease-specific modules.

1. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th edition. Cambridge University Press; 2013.
2. Polter AM, et al. *Front Mol Neurosci*. 2011;4:31.
3. Quaglia W, et al. *Expert Opin Ther Pat*. 2011;21(4):455-81.
4. Purves D, Augustine GJ, Fitzpatrick D, et al (eds). *Neuroscience*. 3rd edition. Sinauer Associates; 2004.

Principles of Receptor Pharmacology

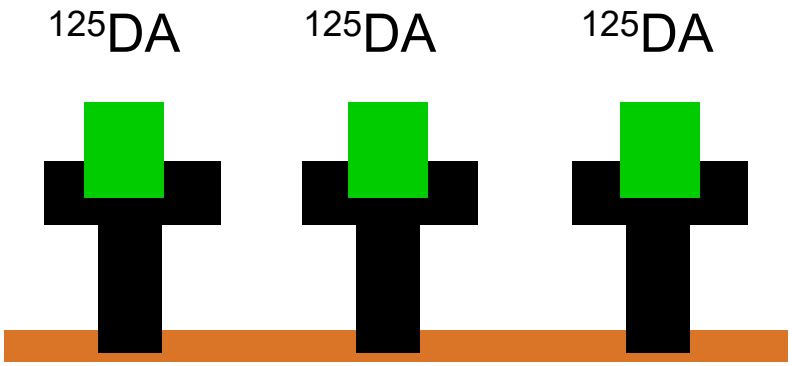
- Affinity:
  - How strongly does a molecule or drug bind to a specific receptor?[1,2]
  - Typically discussed as high, moderate, or low based on Ki values (nM)[3]
- Intrinsic activity[1,2]:
  - Once bound, what is the effect of the drug at the specific receptor?
  - Determined by ability of molecule/drug to either stimulate a specific receptor (ie, an agonist) or inhibit an agonist from stimulating that receptor (ie, an antagonist)
- Receptor occupancy[1]:
  - How many receptors are bound to by a molecule or drug at a particular dosage (% of receptors bound)?*

*More detail in section 201
Ki, inhibitory constant; nM, nanomolar.

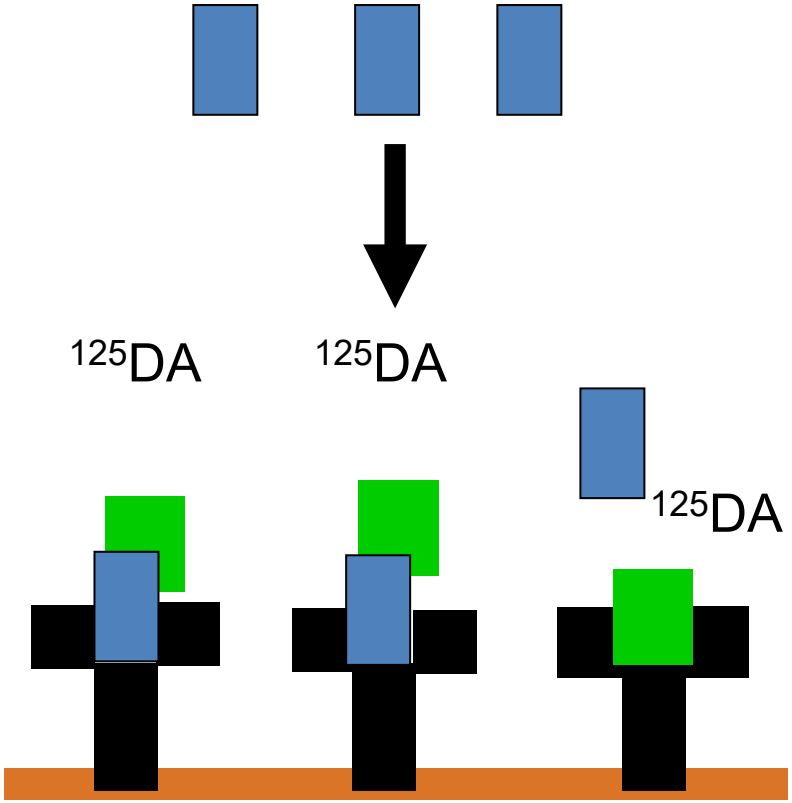
1. Hardman JG, Limbird LE (eds). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 10th edition. McGraw-Hill; 2001;36-40.
2. Tamminga CA. *J Neural Transm*. 2002;109:411-420.
3. Inoue A, Nakata Y. *Jpn J Pharmacol.* 2001;86:376-380.

Inhibition Constant, K_i — How is it determined?[1,2]

A set concentration of labeled drug



+ varying concentrations unlabeled competitor (eg, molecule of interest)



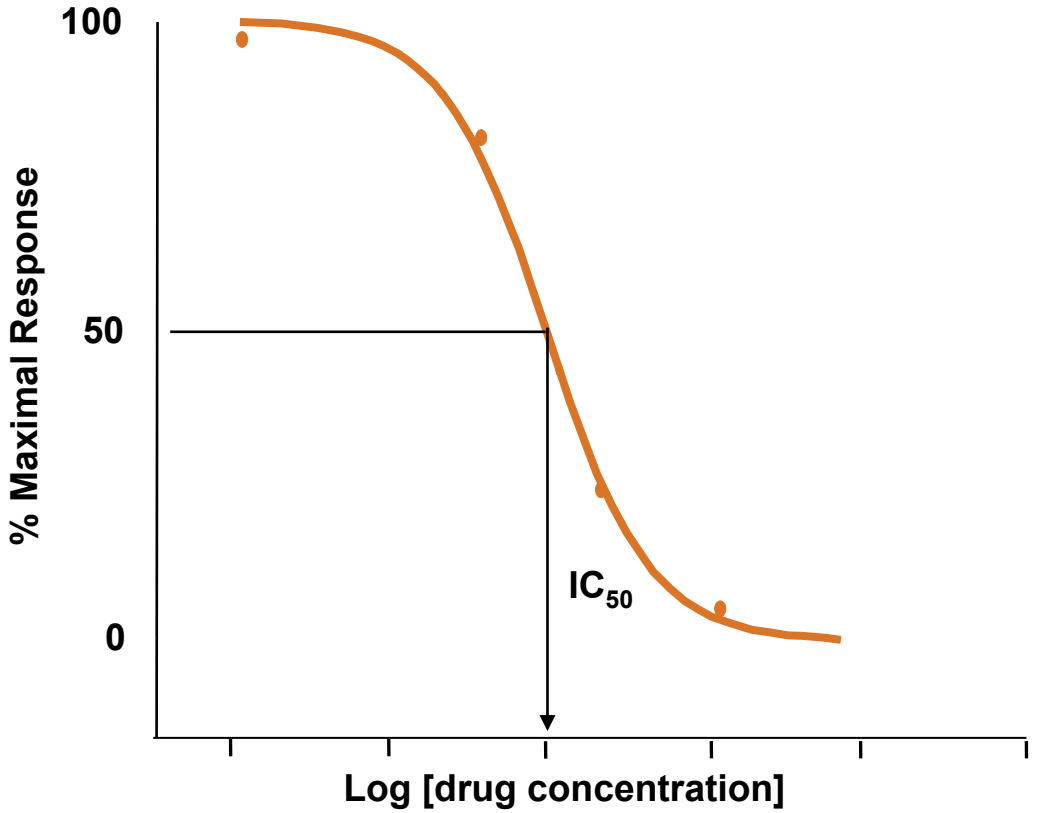
K_i is the concentration of competing ligand in a competition assay which would occupy 50% of the receptors if no radioligand were present.

1. Blass BE, et al (eds). *Basic Principles in Drug Discovery and Development*. 1st edition. Elsevier; 2015; 146-202.
2. Kenakin, T. *Pharmacologic Analysis of Drug-Receptor Interaction*. 2nd edition. Raven Press; 1993; 385-410.

Concepts of Receptor Pharmacology — Binding Affinity

Affinity of drug at a receptor

- Strength of binding between a ligand (molecule or drug) and its target receptor[1]
- Competitive binding experiments are used to investigate drug binding properties and affinities
  - Typically categorized as high, moderate, or low binding based on K_i value (nM), the lower the K_i, the higher the binding affinity



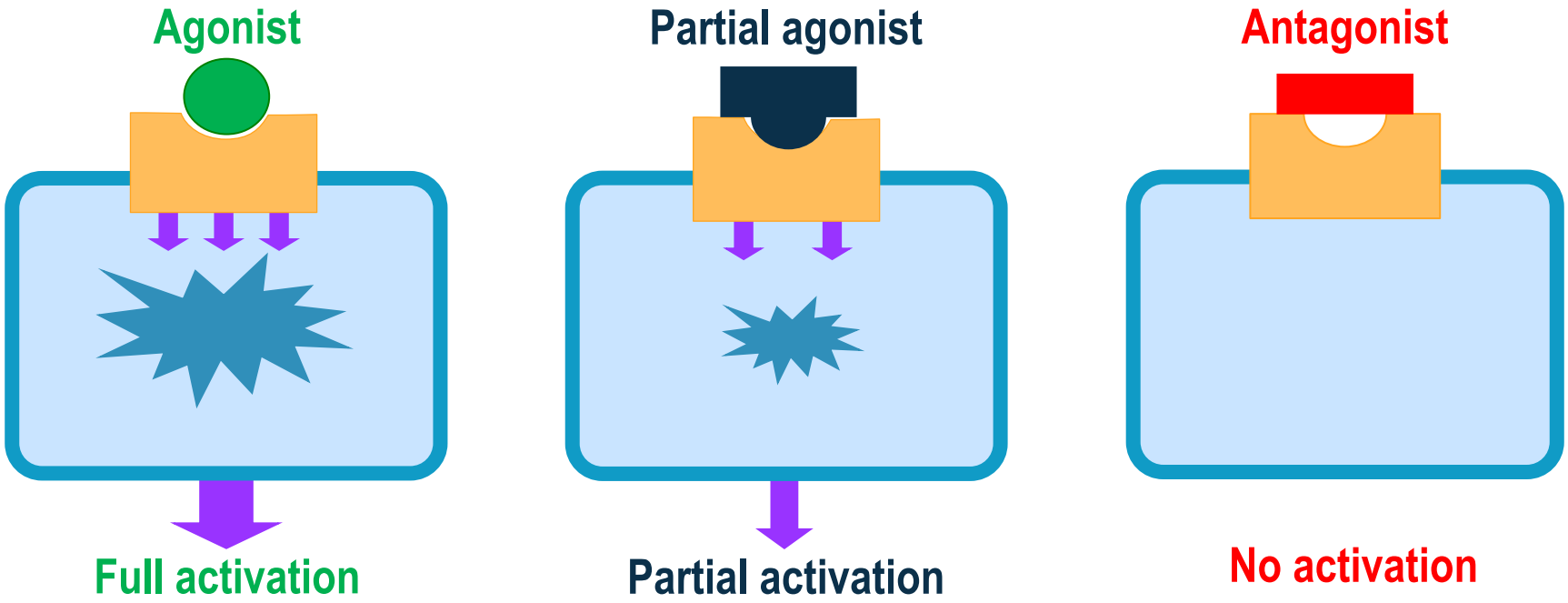
IC_{50}, the concentration of a drug that is required for 50% inhibition in vitro; nM, nanoMolars (unit of quantity/concentration of a drug/molecule).

1. Motulsky HJ, Neubig RR. *Curr Protoc Neurosci*. 2010;Chapter 7:Unit 7.5.

Concepts of Receptor Pharmacology — Intrinsic Activity

Intrinsic activity of drug at a receptor

- The physiologic effect a ligand elicits once bound to its receptor
- Ligand can partially or fully stimulate (agonism) or inhibit (antagonism) receptor activity



Hardman JG, Limbird LE (eds). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 10th edition. McGraw-Hill; 2001 pp36-40.

Summary

- The nervous system is organized into two main anatomical divisions: the CNS and the PNS[1]
- Neurons are the basic nerve cells, which transmit messages throughout the nervous system[1]
- Glia cells help support and protect neurons (see section 201)[2]
- Neurons communicate with each other via transmission (electrical and chemical)[2,3]
- Neurotransmitters are hypothesized to directly regulate human physiology and behaviour through neuronal communication[1]
- These neurotransmitter signals are the pharmacologic targets of medications (see section 201)[3]
- The pharmacological profile of a neurotransmitter (or receptor drug targets) can be described by binding affinity and intrinsic activity[4]

1. Tortora GJ, Derrickson B. *Principles of Anatomy and Physiology*. 12th edition. John Wiley & Sons; 2009.
2. Kandel ER, Schwartz JH, Jessell TM (eds). *Principles of Neural Science*. 4th edition. McGraw-Hill; 2000.
3. Purves D, Augustine GJ, Fitzpatrick D, et al (eds). *Neuroscience*. 3rd edition. Sinauer Associates; 2004.
4. Brunton LL (ed). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th edition. McGraw-Hill; 2011; 41–72.

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