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Book Reviews: Technical Books Section

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FEATURED BOOK: MAIN PAGE

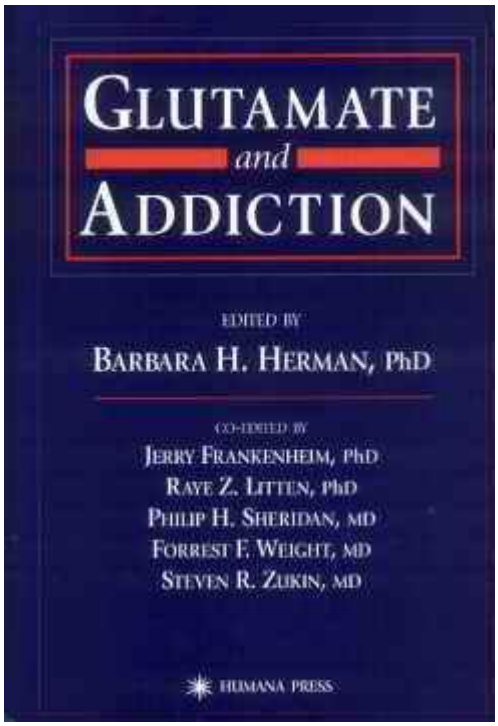
COMPREHENSIVE AND AUTHORITATIVE

[Review 1] [Main Page] [Review 2]

Glutamate and Addiction, 1st Edition, *Edited by* Barbara H. Herman, Co-edited by Jerry Frankenheim, Raye Z. Litten, Philip H. Sheridan, Forrest F. Weight and Steven R. Zukin. Hard Bound, 7" x 10".
Humana Press Inc., 999 Riverview Drive, Suite 208, Totowa, New Jersey 07512; Publication Date 26 August, 2002. xviii + 440 pages, ISBN 0-89603-879-3 (Hardcover, acid-free Paper). Price $165.50

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We keep receiving books for review from various publishers. However some books are of such paramount importance that we at the journal office thought one review may not be able to do justice to that book. One opinion may be slanted, perhaps by the individual tastes and preferences of the reviewer. Reviewers from different continents, nations, even different parts of the same nation may perceive a book differently. Why not send books to two or more different reviewers and get their opinion. We requested several publishers to do that and they obliged.

From Volume 3, Number 1, January - June 2002, we started reviews of certains books of paramount importance as "featured books". The first book to be featured on our journal was Ecotoxicology: The Study of Pollutants in Ecosystems by F. Moriarty (Published by Academic Press). Review of that book, as well as the combined index of reviews of all featured books can be accessed by clicking here.

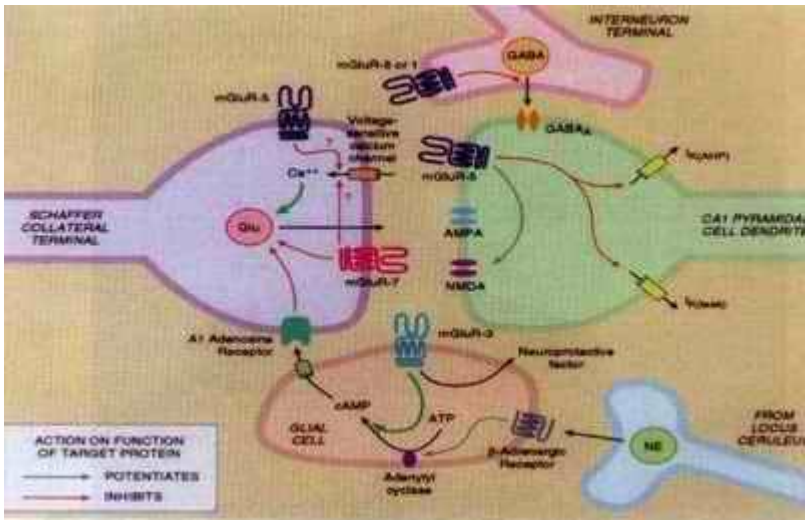
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Earlier this year we sent Endocrine Pathology- Differential Diagnosis And Molecular Advances edited by Ricardo V. Lloyd (Published by Humana Press), to two reviewers from two different continents. Their reviews appeared in this very issue on page 2.

This time we received a very fascinating book Glutamate and Addiction edited by Barbara H. Herman and co-edited by Jerry Frankenheim, Raye Z. Litten, Philip H. Sheridan, Forrest F. Weight and Steven R. Zukin (Published by Humana Press). Glutamate receptors have been very hotly discussed during recent times, particularly because they have been thought to be involved not only in learning and memory but also in neurodegenerative disorders and in addiction.

Backgrounder

Color plate 1: Example of physiological roles of mGluRs at the Schaffer collateral synapse in CA1 in the hippocampus (Color plate 1 from this book)



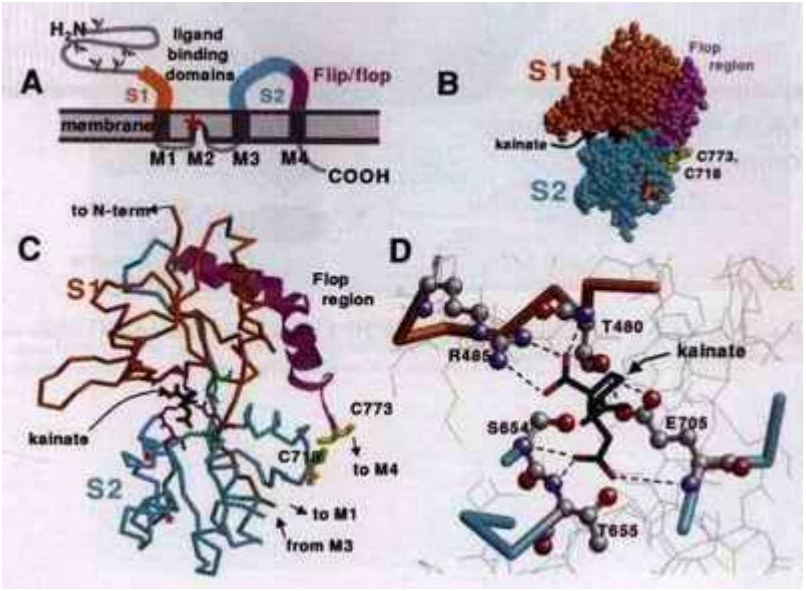
A brief recapitulation of receptors and their mechanisms may be in order here. Drugs act mainly through four types of receptors, which are classified from Type 1 through Type 4. Type 1 receptors - also known as *ionotropic receptors* - are ligand-gated ion channels (gating is a mechanism by which the flow of ions in and out of cells is regulated). These are membrane proteins with a structure similar to other ion channels (such as voltage-gated channels, calcium release channels and store-operated calcium channels). Ligand gated ion channels however incorporate a ligand-binding (receptor) site, usually in the extracellular domain. Typically these are the receptors on which fast neurotransmitters act. The action mediated through them is the fastest among all four receptor types and is effected within milliseconds. The best examples of Type 1 receptors are nicotinic acetylcholine receptors, $GABA_A$ receptor and glutamate receptors of the NMDA (N-methyl-D-aspartate), AMPA (Alpha-amino-3-hydroxy-5-methyl-4-isooxazolepropionate) and kainate types (iGluRs).

Type 2 receptors are G-protein coupled receptors (GPCRs). These are also known as metabotropic receptors or seven-transmembrane-spanning (heptahelical) receptors. They are called so, because they pass back and forth through the cell membrane seven times, their C-end dangling loose within the cytosol (remember c for cytosol as a mnemonic), and the N-end lying outside the cell. They are coupled to intracellular effector systems via a G-protein.

G-proteins

A word about G-proteins may be in order here. These may be construed as middle level managers in the cellular systems, lying between the so-called "upper level managers" - the receptors - which have the ability to "sense" the right agonist and the "lower level managers" - the effector enzymes or ion channels. These "lower level managers" need not know if the right agonist did confront the cell or not. All they need is a "command" from their immediate superiors - the G proteins - to go into action. In a way G-proteins are the "go-between" proteins between the receptors and the effector enzymes and ion channels. It is tempting to think that they are called G-proteins for this reason ("Go-between" proteins), but the actual reason is less mundane; they interact with the guanine nucleotides GTP and GDP.

Color plate 2: Glutamate receptor topology and crystal structure of the agonist-binding pocket (Color plate 2 from this book)



G-proteins consist of three subunits alpha, beta and gamma. They act in a clock work fashion to bring about the desired action. The whole process is exceedingly complex, but decidedly fascinating.

G-Protein Coupled Receptors or GPCRs

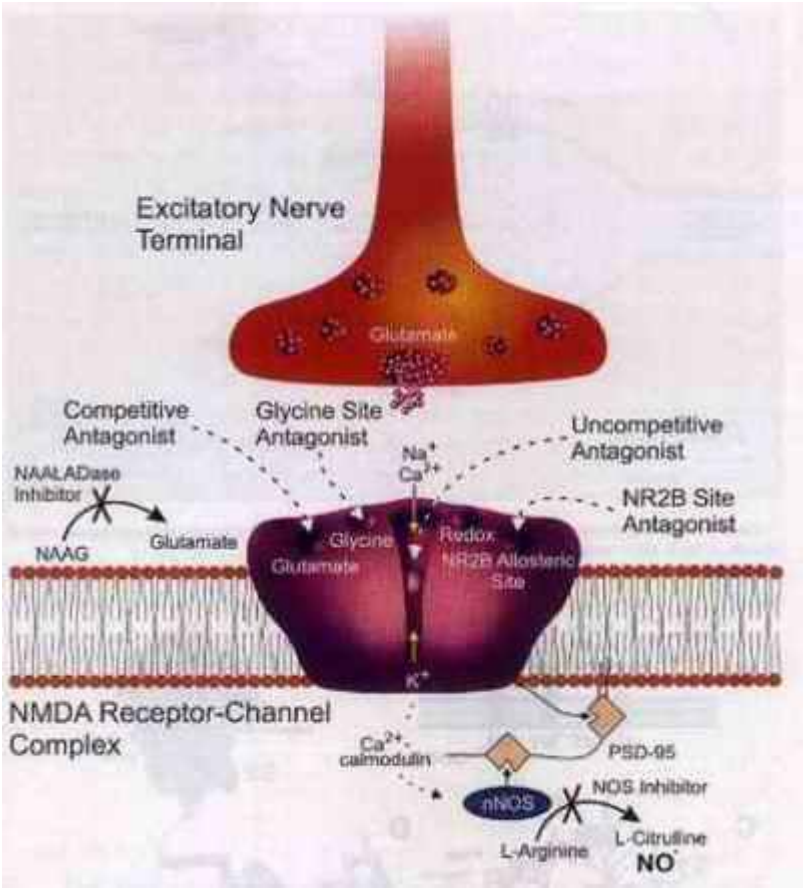
GPCRs constitute the largest family of receptors; there are more than 1000 GPCRs in the human genome. Interestingly as many as 5% of the 19,000 odd genes of the nematode *Caenorhabditis elegans* encode for GPCRs. Still more fascinating is the fact that 90% of these (nematode) GPCRs are "orphan receptors", i.e. no functional ligand is known for them (their "orphanhood" however reflects just our ignorance, not their true status).

The action of GPCRs is effected within seconds. The typical examples are muscarinic acetylcholine receptors, adrenoceptors, chemokine receptors and Glutamate receptors of the fourth (remaining) class (mGluRs).

Type 3 receptors are kinase-linked and related receptors and Type 4 are nuclear receptors. Their actions are effected in hours. Type 3 receptors include those for insulin and various cytokines and growth factors. Type 4 receptors include receptors for steroid hormones, thyroid hormone and other agents such as retinoic acid and Vitamin D. Both type 3 and 4 receptors are not of much interest to us here, because Glutamate receptors do not fall in these classes at all.

Amino Acid Transmitters

Color plate 3: A representation of the NMDA receptor with associated binding and regulatory domains (Color plate 3 from this book)

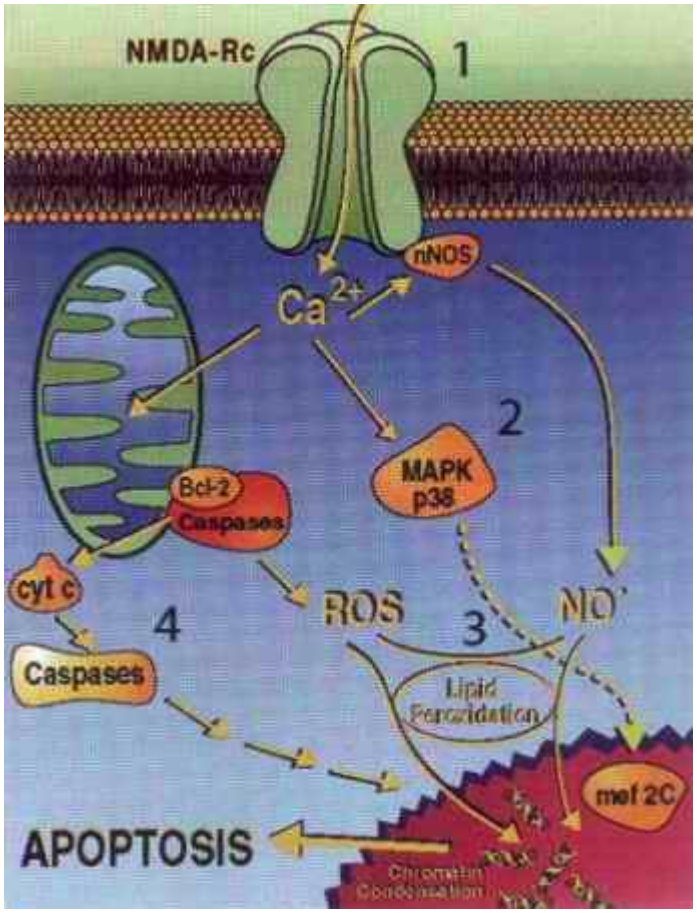


Glutamate is an amino acid transmitter. A word about Amino acid transmitters. Initially when transmitters such as acetylcholine were discovered, pharmacologists began to believe that a transmitter had to be a unique molecule (such as acetylcholine) having no other well-defined physiological function. By 1950s, work on the peripheral nervous system had highlighted the transmitter roles of acetylcholine and catecholamines. The Central nervous system (brain and spinal cord) too contained these substances and there seemed little reason not to believe that these very substances were acting as neurotransmitters in the CNS too. The presence of gamma-aminobutyric acid (GABA) in the brain and its powerful inhibitory effect on neurons were discovered in the 1950s, and its transmitter role was postulated. Around the same time, in Canberra, an elite group of scientists led by Curtis discovered that glutamate and various other acidic amino acids (aspartate and homocysteate) produced a strong excitatory effect. Were these common, not-so-exotic molecules (GABA, glutamate and the like) real neurotransmitters functioning within the brain or were they mere pharmacological curiosities? Even their discoverers opted for the latter! It was in the 1970s, that one of the simplest and perhaps the least possible exotic molecule - glycine - was proved to be an inhibitory neurotransmitter in the spinal cord. Gradually scientists came to terms with the fact that while the major transmitters in the Peripheral nervous system were acetylcholine and catecholamines, within the CNS they were GABA and glycine (inhibitory transmitters) and glutamate (Excitatory transmitters). Paradoxically GABA - an inhibitory transmitter - is synthesized from Glutamate - an excitatory transmitter! Remove one -COOH group from Glutamate and you get GABA. This is done by Glutamic Acid Decarboxylase (GAD) within the brain.

Glutamate Receptors

Chapter 1 and 2 of this book explain in some detail the basic molecular pharmacology and physiology of glutamate receptors. The three ionotropic receptors are stimulated by NMDA, AMPA and kainate respectively (kainate incidentally is a molecule isolated from seaweed). The fourth - metabotropic - receptors are of eight subtypes (termed mGluR1 through mGluR8). These are divided into three groups - Group I containing mGluR1 and mGluR5; Group II, mGluR2 and mGluR3; and Group III, mGluR4, mGluR6, mGluR7, mGluR8. All of these are widely expressed in brain, except mGluR6, which is expressed only in the retina. These are quite unusual proteins. For one, they show no sequence homology with other G-protein coupled receptors, and for another they have a very large extracellular N-terminal tail (that contains the glutamate-binding site), in contrast to most amine receptors in which the agonist binding site is buried amongst the transmembrane helices.

Color plate 4: Current model of NMDA receptor-associated neuronal injury. Schematic illustration of NMAR-related signaling pathways that lead to neuronal apoptosis and may contribute to neurodegenerative disease, including HIV-associated dementia (Color plate 4 from this book)



Another interesting fact is that certain well-known anaesthetic and psychotomimetic agents such as ketamine and phencyclidine (chemically phencyclohexylpiperidine; and hence often called PCP) seem to act by blocking NMDA-operated channels. Ketamine closely resembles PCP - both chemically and pharmacologically. Both drugs produce a similar anaesthesia like state and profound analgesia, but ketamine produces considerably less euphoria and sensory distortion than PCP. Thus ketamine is more useful as an anaesthetic, while PCP is mainly used as a "street drug" (of

course drug addicts have been more adventurous in recent times and have been using ketamine for achieving euphoria too).

Ketamine produces a "different" kind of anaesthesia than most other anaesthetics. It is known as "dissociative anaesthesia" in which there is a marked sensory loss, analgesia, amnesia and paralysis of movement without actual loss of consciousness. Its cardiovascular and respiratory effects are also different from most other anaethetics; blood pressure and heart rates are usually increased and respiration is unaffected (by effective anaesthetic doses). Ketamine's main drawback as an effective anaesthetic agent is the hallucinations that are often produced during recovery period. Delirium and irrational behavior are also common. Interestingly these effects are less marked in children (perhaps because they can not verbalise their experiences!), and for this reason ketamine - often with a benzodiazepine - is used for minor procedures in paediatrics.

It appears that two glutamate receptors - namely NMDA and metabotropic receptors - play a role in long-term adaptive and pathological changes in the brain. These are also of particular interest as potential drug targets.

The book frequently talks of - and explains lucidly - two very important concepts connected with glutamate receptors, namely *synaptic plasticity* and *excitotoxicity*. Let us briefly recapitulate these two important concepts.

Synaptic Plasticity

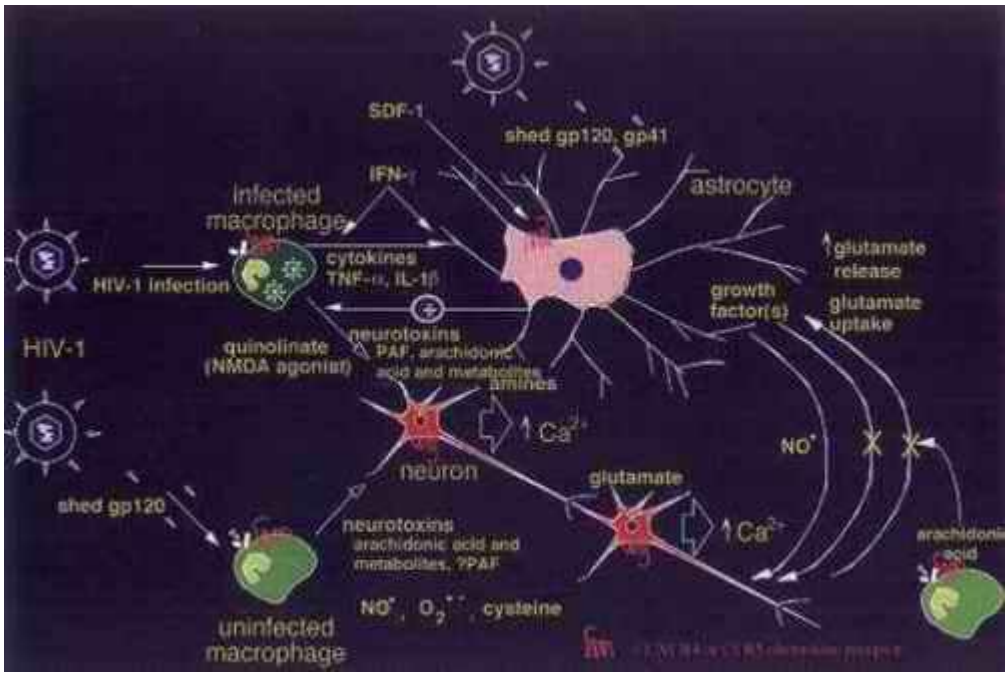
Just as plastic moulds easily to different shapes, neuronal circuits can change their patterns of behavior too (based on prior experiences). Plainly and simply put, this is synaptic plasticity. Chapter 8 entitled "Addiction and Glutamate-dependent plasticity" defines neuroplasticity as "the ability of the nervous system to modify its response to a stimulus based on prior experience" (page 127). Synaptic plasticity forms the basis of the theory of learning as propounded by Donald Olding Hebb (1904 - 1985), an influential psychologist at McGill University in Canada.

Hebbian theory describes a basic mechanism for synaptic plasticity wherein an increase in synaptic efficacy arises from the presynaptic cell's repeated and persistent stimulation of the postsynaptic cell. In 1949 he theorized that when an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.

This theory is often summarized as "*cells that fire together, wire together*", though this is certainly an oversimplification of the nervous system and should not be taken literally. In general synaptic plasticity underlies much of what we call "brain function" and understanding how it happens has been a holy grail for neurobiologists for decades.

Synaptic plasticity (or "brain function" as we may like to call it in simpler terms) does not involve any single phenomenon obviously. Many phenomena contribute to it. One major phenomenon which has been associated with synaptic plasticity (and hence with learning) is Long-term potentiation (LTP). Glutamate and NMDA receptors play a central part in LTP.

Color plate 5: Current model of HIV-associated neuronal injury. Immune activated and HIV-infected brain macrophages/microglia release potentially neurotoxic substances (Color plate 5 from this book)



LTP is the term used to describe a long-lasting (hours in vitro, days or weeks in vivo) enhancement of synaptic transmission that occurs at various CNS synapses following a short (conditioning) burst of presynaptic stimulation, typically at about 100 Hz for 1 second. Its counterpart is long-term depression (LTD) which is produced by a longer train of stimuli at lower frequency. These phenomena have been studied in great detail in the hippocampal region.

The association between LTP and learning and memory appears quite obvious. NMDA-receptor antagonists applied to the hippocampus impair learning in rats. Furthermore LTP like changes have been detected after learning has taken place. Thus scientists hope that drugs capable of enhancing LTP may improve memory and learning.

Excitotoxicity

Excitotoxicity refers to the toxic action of glutamate on neurons (despite its ubiquitous role as a neurotransmitter). This appears paradoxical since glutamate has such an important role in neurotransmission. Under certain conditions such as during times of trauma, ischemia, hypoglycemia and status epilepticus, excessive amounts of glutamate are released and this can trigger neuronal damage and death. For this reason glutaminergic transmission has been a subject of intense research. Many environmental toxins acting as agonists on glutamate receptors such as Domoic acid have been identified as the cause of epidemics of severe mental and neurological deterioration. One such epidemic occurred in a group of Newfoundlanders in 1987. Domoic acid is produced by mussels. The Canadian government now marks the location and time of harvesting of mussels and mussels are tested for the presence of domoic acid. Similarly on the island of Guam, there exists a plant whose seeds contain an excitotoxic amino acid "beta-methylaminoalanine". This too acts as an agonist on glutamate receptors. Consumption of seeds of this plant results in a syndrome featuring dementia, paralysis and Parkinson's disease.

Glutamate obviously is a very complex, albeit fascinating subject. When the book came to us, our primary job was to find two leading experts on glutamate receptors. These were Ramesh Kaul of USA and V.V.Pillay of India. The book was sent to them and both experts were requested to evaluate the book independently.

The reviewers were not only requested to send us detailed reviews, but were asked to rate this book on a scale of ten. The following rating scale was provided to the reviewers.

0: Waste of time
1: Of minimal interest
2: Of little interest
3: Of some interest
4: Slightly below average
5: Average
6: Slightly above average
7: Good
8: Very Good
9: Excellent
10: Truly Outstanding

Here are both the reviews - with ratings.

Review 1 by Ramesh Kaul, USA

Review 2 by V.V.Pillay, India

Further Reading

1. Glutamate Receptors - Structures and Functions (http://www.bris.ac.uk/Depts/Synaptic/info/glutamate.html)

2. Glutamate and Aspartate receptors (http://www.neuro.wustl.edu/neuromuscular/lab/glutamat.htm)

3. Glycine receptors (http://www.neuro.wustl.edu/neuromuscular/lab/glycine.htm)

4. Rang HP, Dale MM, Ritter JM, Moore PK (2003). Pharmacology, 5th edition. Churchill Livingstone (An imprint of Elsevier Science), UK

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