REVIEW ARTICLE

INTERNATIONAL JOURNAL OF ANATOMY PHYSIOLOGY AND BIOCHEMISTRY

http://www.eternalpublication.com

IJAPB: Volume: 3; Issue: 12; December 2016 *ISSN(Online):2394-3440*

Calcium Signalling In Neurons

Published online on 05th December 2016©www.eternalpublication.com

DR. ABHAY KUMAR PANDEY [1]

1 Department of Physiology, GMC, Banda

Corresponding Author:

Dr. Abhay Kumar Pandey
Department of Physiology
Government Medical College
Banda-211001 (Uttar Pradesh, India)
+917607980255
abhay.aslp@gmail.com

Received: 10th Nov 2016; Accepted: 26th Nov 2016

How to cite this article: Pandey AK. Calcium dignalling in neurons. International Journal of Anatomy Physiology and Biochemistry 2016; 3(12):1-8.

Abstract:

Specialization of cell systems in organism is accompanied with increased role of intracellular signal systems which direct and co-ordinate organized multicellular responses to realize a particular physiological function. Higher organisms possess multiple specialized signalling systems that recognize environmental signals and transform them into intracellular signals. The information meets transduction to appropriate functional elements, perhaps programmed genetically to respond, adapt or suffer derangement. Most of such signalling systems use calcium as second messenger. Calcium mediated signal transduction has acquired complexity through evolution, timing to improve signalling pathways and to establish new communications. Signalling drives excitability and propagation of nervous action potential, and its disruption is responsible for several diseases, including toxic impacts. The significance of Ca^{2+} signalling in living systems is testified by evolved Ca^{2+} channel toxins in various animal venoms. Calcium influx from the exterior and calcium release intra-cellularly forms distinct facets for investigation in effects of chemicals and drugs. Most calcium channels contain multiple binding sites for agonists and antagonists. Transduction function of calcium channels accords them high biological, particularly neuro-physiological, significance across space and time of understanding and applications. This article attempts to cover facets of neuronal calcium signalling.

Keywords: calcium signal, calcium channel, neuronal calcium signaling

Sketch of the system:

Resting intracellular concentration of free calcium ions is generally 20000 times lower than extracellular concentration in most excitable tissues. Ca^{2+} is the commonest of signal transduction elements, essential to life while prolonged high intracellular Ca^{2+} levels may cause cell death. Tight regulation of intracellular Ca^{2+} levels must be done as it cannot be metabolized. Phosphates constituting intracellular energy currency would suffer precipitation with calcium. Numerous binding proteins and specialized extruding mechanisms for calcium have therefore evolved, which dramatically regulate cell calcium.

Depolarization from resting membrane potential (-70 mV), initiates conformational changes in calcium ion selective channels via special voltage sensing regions in the protein molecule. Ca^{2+} flood is thus catalysed across the membrane. Calcium ion is important modulator of phospholipases and calmodulin kinases. Co-ordinated opening of clusters of intracellular inositol triphosphate receptor (IP_3), ryanodine reseptor linked channels provide mechanisms for Ca^{2+} induced calcium

release from endoplasmic reticulum. Ryanodine receptor mechanisms that activate Ca^{2+} sensitive K^{+} channels trigger membrane hyperpolarization and control the excitability of neuron. After signalling function is accomplished, Ca^{2+} is rapidly removed from cytoplasm by various pumps and exchangers.[1] Mitochondria close to internal calcium channels, rapidly take up Ca^{2+}, which stimulates their ATP synthesis. Mitochondria are also important sequestrates of Ca^{2+}, rapidly during the development of signal. They then release Ca^{2+} break slowly in recovery process. This is important in determining the amplitude and time-span of calcium signal.[2]

Calcium Channels:

An α_1 subunit is the pore forming unit of high voltage activated calcium channels in neurons and determines the dependency on voltage or membrane potential. Calcium channel blocking drugs and naturally occurring toxicants bind to this subunit cause Ca^{2+} channel blockade. High voltage calcium channel is multimeric protein constituted of many subunits. The α subunit is co-expressed with different β subunits, which determines differences in rates of channel inactivation. One of the subtypes of high voltage activated Ca^{2+} channels Ca^{2+} 2.2, the β subunit displays role in properties of voltage dependence, prepulse facilitation and modulation by G proteins.[3]

Infringements of any kind in the channel subunits have potential to cause channel dysfunction and channel hypoactivity is demonstrated as associated with mutation in the β subunit.[4] Voltage operated calcium channels are multimeric transmembrane proteins, crucially involved in control of calcium homeostasis. Multiple types of voltage operated calcium channels are described in nervous system and peripheral tissues. Different channels can be classified according to their biophysical and pharmacological properties, localization and functional role.[5] Most neurons have low as well as high voltage activated calcium currents. Low voltage activated T type calcium channels are maximally activated with small depolarization. They are fast inactivating and slow deactivating. The high voltage activated L type (long lasting) and N type (Neither L or T kind) channels are activated with large depolarization. L type channels express throughout nervous system as well as in other tissues. N type channels are largely restricted to neurons. Based on differences in agents that block or fail to block, further P, Q, R subtypes of neuronal high voltage activated channels are described. Heterogeneity is also within class of L type channels located in different tissues and exhibiting differences in degrees of blockade by blocking agents and electrophysiological properties.

Localization of different voltage gated Ca^{2+} channels in nervous system helps to elucidate their contribution to specific physiological processes. L-type Ca^{2+} channels are concentrated in neuronal cell bodies and at bases of major dendrites. N-type channels are clustered presynaptically at active sites of neurotransmitter release.[5]

Presumed pre and post-synaptic localization of the N and L type channels indicates different roles. Low threshold or activation and transient kinetics of low voltage gated T calcium channels indicates their role in controlling cell excitability and pacemaker activity. Ca^{2+} influx through T type channels is the predominant calcium source in several neuronal cell types and carries out specific signalling roles. Often T channels signalling occur in select subcellular compartments. It is mediated through strategically co-localized targets and used for unique physiological functions.[7] The high threshold activation and long lasting kinetics of high voltage gated L calcium channels suggests their role in large increases in intracellular Ca^{2+} concentration necessary to serve as second messenger.

Heterogeneity and biophysical differences of L and N type channels may suit their involvement in allowing Ca^{2+} influx for different purposes. The N type channels in pre-synaptic zones control calcium influx triggering neurotransmitter release. Localization of L type channels on neuron cell

bodies and bases of dendrites is suited to regulate Ca^{2+} influx to trigger different somatic activities eg. enzyme regulation, cytoskeletal organization, gene expression etc. Relative roles of L type versus N type channels differ for control of neurotransmitter release depending on mechanism causing depolarization i.e. due to high potassium or due to stimulus by electric field.[8]

Signalling and regulations:

G proteins directly interact with the channel and can cause a voltage dependent channel inhibition.[9] In addition, phosphorylation by kinases like protein Kinase C and tyrosine kinases are shown to inhibit the Ca^{2+} channels.[10,11]

Phosphorylation is common mechanism for modulation of Ca^{2+} channels. Different protein kinase C isoenzymes appear to be targeting different subtypes of Ca^{2+} channels and may exist in complex with the channels.[12,13]

The receptor- tyrosine kinases are receptors on membrane surface with integrated catalytic domains. There are non-receptor tyrosine kinases which associate receptors but bear no intrinsic kinase activity. G protein coupled receptor actions via tyrosine kinases are understood. Their receptor mechanisms, intracellular transduction pathways and the effectors that mediate neuronal responses are characterised.[14]

G protein coupled receptors (GPCRs) directly do not interact with ion channels in membrane and second messenger producing enzymes. Linking of the GPCRs with their targets occurs through transduction systems when surface receptor is bound by a ligand, its conformation changes. The receptor in changed conformation is able to bind the G protein inside and activate it. Activated G proteins then modulate activity of variety of target proteins.

Phospholipase C_β is activated by induction of G protein class Gq and then activates protein kinase C (PKC) to cause Ca^{2+} release from IP_3 sensitive calcium stores. The tyrosine phosphorylation of delayed rectifier type $K^+_{v1.2}$ potassium channel results in suppression of K^+ current.[15]

PKC activation also causes upregulation of function of NMDA receptors, through intermediary tyrosine kinase and Src. The metabotropic glutamate receptors coupled to phosphorylase C can activate PKC, followed by activation of tyrosine kinase. A long term depression of synaptic transmission then occurs. Inhibition of calcium activated potassium current following stimulation of metabotropic glutamate receptors can be reduced by inhibition of tyrosine kinase.[16]

Protein tyrosine kinases tonically upregulate some voltage gated Ca^{2+} channel subtypes and in neurons inhibitor of protein tyrosine kinase like genistine decrease calcium influx through high voltage gated neuronal Ca^{2+} channels.[17]

Calcium channel modulation may result from binding of lipid PIP_2 which is involved in functioning of G protein for regulation of inward rectifier K^+ channels.[18]

G protein mediated modulations of channel activity involves disruption of interaction between channels subunits by phosphorylation. Similar disruption occurs in calmodulin mediated calcium dependent inactivation of voltage gated Ca^{2+} channels.[19]

Multiple G-protein mediated pathways converge in modulating calcium channels. Complex timing of events is controlled by interactions between components of several signalling pathways and a dynamic network of cytoskeletal and scaffolding structures. These serve as ground for interaction with channel.

Modulation of Ca^{2+} channels by GPCR is transient process. Prolonged exposure to stimuli eg. neurotransmitters, causes decline of neuronal sensitivity. $GABA_B$ receptor mediated inhibition of calcium currents gets desensitized in just 100 seconds. Change in cellular environment per se can cause changes in channel activity. The specificity of Ca^{2+} effects on neuronal physiology is partly determined by magnitude, kinetics and spatial location of the Ca^{2+} signal.[20]

The neuronal calcium sensing proteins are implicated in many functional roles ranging from regulation of ion channels, membrane traffic, neuronal growth and survival learning etc.[21] Timing impacts how information is relayed from external stimuli via Ca^{2+} signals in to specific physiological effects. The broad community of calcium handling proteins, which increase, decrease and buffer cytoplasmic calcium, provide diverse kinetics of assembly of signalling molecules appropriate for cellular functions. These proteins regulate the duration and periodicity of calcium signal. Setting up spatial gradients of activity or disrupting those rapidly within cells.[22]

Distributed heterogeneity of Ca^{2+} regulated proteins along with their spatial distribution, mediating Ca^{2+} homeostasis, provides for large number of physiological responses to be directed by calcium signal transduction pathway.[23]

Intracellularly Ca^{2+} comes to bind a versatile protein calmodulin in several isoforms. Calmodulin with bound Ca^{2+}, associates with different affinity with various proteins and changes their biological functions and activities.[24]

Calmodulin dependent protein kinase II (CamPKII) is the major postsynaptic density protein. Ca^{2+} currents mediated by L type calcium channels, as well as through channels activated by NMDA receptors prevalent in postsynaptic dendrites, target CamPKII. This kinase plays role in inducing long term potentiation and memory.[25]

Presynaptically CamPK II phosphorylates synapsin. Affinity of synapsin to the vesicles containing neurotransmitters, gets reduced. This is mechanism of neurotransmitter release by depolarisation.[26]

Calcineurin is major calmodulin binding protein implicated in modulating calcium signalling affecting diverse neuronal functions. It dephosphorylates the inhibitor of low specific phosphatise I. It co-localizes with protein kinase C and has potential to reverse PKC action.[27]

Of the several isoforms of adenyl cyclise in neuron, some are activated and some inhibited by calmodulin binding with impact on cAMP signalling function.[28] Such interactions influence a co-ordinated control of neuronal physiology.

Cyclic nucleotide phosphodiesterase catalyse degradation of major second messengers, cAMP and cGMP. These enzymes are targets of calmodulin binding and modulations.[29]

These enzymes are co-expressed in neuron with the calmodulin-dependent nitric oxide synthase, and terminate action of nitric oxide by hydrolysing cGMP. Thus calmodulin dependent cGMP phosphodiesterase enables nitric oxide function as retrograde signal molecule.[30]

Calcium pump from plasma membrane extrudes out calcium. The complex of Ca^{2+}/calmodulin affects function of calcium pump and has complex regulatory effects on brain physiology.[31]

The ryanodine receptors are Ca^{2+} and caffein sensitive intracellular calcium channels. These contribute to calcium current after depolarization or stimulation of neuron by NMDA. The ryanodine receptor activation by ADP-ribose is mediated by calmodulin.[32]

In addition, an isoform of IP_3 receptor (the Ca^{2+} channel in endoplasmic reticulum) binds calmodulin.[33]

The calcium binding proteins exhibit enzymatic and ion channel function. They bind, buffer and transport intracellular Ca^{2+} as well as regulate activities of calcium dependent enzyme systems.[34] They can also modulate neuronal activity.[35]

Physiological role of intracellular calcium store:

The luminal calcium concentration in endoplasmic reticulum has regulatory bearing on neuronal function. The state of filling of calcium stores impacts calcium entry and cell signalling.[36] Depletion of intracellular stores can affect the cytoplasmic signal transduction pathways or may trigger and regulate biological processes.

Intracellular calcium store has influence on:

a) entry of calcium through unidentified calcium channels.[37]
b) transcription of genes.

c) cell growth and progression through cell cycle
d) activation of nitric oxide synthase.[38]
e) inhibition of protein synthesis.

Calcium and mitochondria:

Mitochondria are source for physiological reactive oxygen species (ROS). Calcium ions in mitochondria stimulate tricarboxylic acid cycle and oxidative phosphorylation. More oxygen is consequently consumed to produce ATP. The process also increase leak of electrons making more free radicals with oxygen. In contrast inhibition of mitochondrial complexes serving electron transfer reaction (as results in hypoxic state) causes premature leak of electrons increasing ROS generation. Ca^{2+} also stimulates extra-mitochondrial ROS generation by activating NADPH oxidases. Ca^{2+} is also activator of antioxidant enzyme systems. Net Ca^{2+} effects on ROS generation and removal are context dependant. The ROS oxidize sulfhydryl groups of voltage activated calcium channel L and inhibit calcium influx. In contrast, intracellularly ROS activate ryanodine recptors and increase sensitivity to IP_3 signal causing enhanced release of Ca^{2+} from endoplasmic reticulum. Plasma membrane Ca^{2+} ATPase (PMCA) and sarcoplasmic reticulum Ca^{2+} ATPase (SERCA) are both sensitive to Ca^{2+}. The Na^{+}/ Ca^{2+} exchange (NCX) is also Ca^{2+} sensitive. ROS effect on Ca^{2+} signalling can thus vary from stimulation to suppression, depending on the type of oxidants; their concentration and duration of exposure.[39] Neurons have high mitochondrial reserve and tolerance to oxidative stress.

Nitric oxide and calcium signal:

In the nervous tissue, nitric oxide is synthesised by neuronal nitric oxide synthase, which is coupled to activation of the NMDA receptors. The voltage dependant calcium entry in neurons occurs through multimeric channels. Nitric oxide interacts with these channels by more than one mechanism resulting in increasing Ca^{2+} signal.[40] Nitric oxide directly activates intracellular ryanodine receptors increasing Ca^{2+} release from intracellular stores in neuron. The Ca^{2+} signal is therefore prolonged. Such effect mediates neuronal plasticity and also neuronal death in state of ischaemia.[41]

Endogenous nitric oxide impacts chemical signalling, including glutamate release in surrounding synapse terminals. Nitric oxide also modulates NMDA-evoked calcium flux and particularly causes Ca^{2+} release from mitochondria.[42]

Glutamate and calcium signal:

Glutamate is major excitatory neurotransmitter in central nervous system and is involved in various physiological and pathological phenomena. Glutamate induces increase in cytoplasmic calcium concentration directly by activating AMPA and NMDA receptors channels and by direct activation of voltage gated Ca^{2+} channels.[43] Desensitization is the crucial mechanism for regulation of glutamate receptors. Ca^{2+} is closely linked to physiology of NMDA receptors and modulates different kinds of desensitization. Ca^{2+} is crucial player in the synaptic and toxic consequences mediated by NMDA receptors. Calcium is involved in slower desensitization which in the turn regulates Ca^{2+} influx into neurons. The regulatory effect of Ca^{2+} can occur both intracellularly and at ion channel sites. The mechanism appears to involve conformational change of channel protein.[44]

Epilogue:

Specialization of cell systems in organism is accompanied with increased role of intracellular signal systems which direct and co-ordinate organized multicellular responses to realize a particular physiological function. Higher organisms possess multiple specialized signalling systems that recognize environmental signals and transform them in to intracellular signals. The information meets transduction to appropriate functional elements, perhaps programmed genetically to respond, adapt or suffer derangement. Most of such signalling systems use calcium as second

messenger. Calcium mediated signal transduction has acquired complexity through evolution, timing to improve signalling pathways and to establish new communications.

Calcium influx supported by its electrochemical gradient and the opening of selective conductance pathways is a crucial means by which transient and localized increase in concentration of intracellular calcium is generated in most cells. The IP_3- Ca^{2+} messenger system as well as formation of diacylglycerol and phosphorylation of cellular proteins by calcium dependent protein kinases, constitute calcium mechanisms for influencing physiological functions. The structures of this system include receptors of the plasma membrane, enzymes coupled to the receptor and kinases transducing a signal on to cytoplasmic targets in to genome.

Conflict of interest statement:

There is no conflict of interest among the authors.

References:

1. Pozzan T, Ruzzuto R, Volpe P, Meldolesi J. Molecular and cellular physiology of intracellular calcium stores. Physiol Rev 1994;74:595-636.
2. Csordas G, Thomas AP, Hajnoczky G. Quasi synaptic calcium signal transmission between endoplasmic reticulum and mitochondria. EMBO J 1999;18:96-108.
3. Hanlon MR, Berrow NS, Dulphin AC, Wallace BA. Modelling of a voltage dependent Ca^{2+} channel β subunit as a basis for understanding its functional properties. FEBS Lett. 1999;455:366-70.
4. Burgess DL, James JM, Maisler MH, Noebels JL. Mutation of the Ca^{2+} channel β subunit gene is associated with ataxia and seizares in the lethargic mouse. Ann NY Acad Sci 1997;868:144-59.
5. Sher E, Biancardi E, Passafaro M, Clementi P. Physiopathology of neuronal voltage operated calcium channels. FASEB J 1991;5:2677-83.
6. Smith SJ, Augustine GJ. Calcium ions, active zones and synaptic transmitter release. Trends Neuroscience 1988;11:458-64.
7. Cueni L, Canepari M, Adelman JP, Luthi A. Ca^{2+} signalling by T type Ca^{2+} channels in neurons. Pflugers Arch 2009;457:1161-72.
8. Herdon H, Nahorski SR. Investigations of the role of dihydropyridine and omega-conotoxin sensitive calcium channels in mediating depolarizations evoked endogenous dopamine release from striatal slices. Naunym Schmidtbergs Archieves Pharmacol 1989;340:36-40.
9. Mille B. Modulation of ion channel function by G protein coupled receptors. Adv Second Messenger Phosphorylation Res 1994;33:131-42.
10. Rane SG, Dunlap K. Kinase C activator oleoyl acetate glycerol attenuates voltage-dependent calcium current in sensory neurons. PNAS 1986;83:184-88.
11. Diverse-Pierluissi M, Remmers AE, Neubig RR, Dunlap K. Novel form of crosstalk between G protein and tyrosine kinase pathways. PNAS 1997;94:5417-21.
12. Maeno-Hikichi Y, Chang S, Matsumura K, Lai M, Lin H, Nakagawa N et al. A PKC epsilon-ENH channel complex specifically modulates N type calcium channels. Nat Neurosci 2003;6:468-75.
13. Yu XM, Satter MW. Src, a molecular switch governing gain control of synaptic transmission mediated by NMDA receptors. PNAS 1999;96:7697-704.
14. Merinissen MJ, Gurkind JS. G protein coupled receptors and signalling networks: emerging paradigms. Trends Pharmacol Sci 2001;22:368-76.
15. Huang XY, Morielli AD, Peralta EG. Tyrosine kinase-dependent suppression of potassium channel by G protein coupled M.1-muscarinic acetyl choline receptor. Cell 1993;75:1145-56.
16. Abdulghani MA, Valiante TA, Carlen PL, Pennefather PS. Tyrosine kinase inhibitors

enhance a calcium activated K+ current (I_{AHP}) and reduce I_{AHP} suppression by metabotropic glutamate receptor agonist in rat dentate granule neurons. J Physiol 1996;496:139-44.
17. Potier B, Rovira. Protein tyrosine kinase inhibitors reduce high voltage activating calcium currents in CAI pyramidal neurons from rat hippocampal slices. Brain Res 1999;816:587-97.
18. Lai Q, Jones MB, Talley EM, Garrison JC, Bayliss DA. Molecular mechanisms mediating inhibition of G protein coupled inward rectifying K+ channels. Mol Cells 2003;15:1-9.
19. Spafford JD, Zumponi CW. Functional interactions between pre-synaptic Ca2+ channels and the neurotransmitter release machinery. Curr Opin Neurobiol 2003;13:308-14.
20. Berridge MJ, Lipp P, Boatman MD. The versatility and universality of calcium signalling. Nat Rev Mol Cell Biol 2000;1:11-21.
21. Burgoyne RD. Neuronal calcium sensor proteins: generating diversity in neuronal calcium signalling. Nat Rev Neurosci 2007;8:182-93.
22. Boulware MJ, Marchant JS. Timing in cellular calcium signalling. Curr Biol 2008;18:769-76.
23. Miller RJ. Neuronal calcium: getting it up and keeping it up. Trends Neurosci 1992;15:317-9.
24. Kasai H. Cytosolic calcium gradients, calcium binding proteins and synaptic plasticity. Neurosci Res 1993;16:1-7.
25. Fukunaga K, Muller D, Miyamoto E. CamKinase II in long term potentiation. Neurochem Int 1996;28:343-58.
26. Burgoyne RD, Morgan A. Ca2+ and secretory vesicle dynamics. Trends Neurosci 1995;18:191-6.
27. Seki K, Chen H, Huang KP. Dephophorylation of protein kinase C substrate neurogranin, neuromodulin and MARCKs by calcineurine and protein phosphatise I. Arch Biochem Biophys 1985;316:71-6.
28. Cooper D, Mons N, Kurpen JW. Adenylcyclase and the interaction between calcium and cAMP signalling. Nature 1975;374:421-4.
29. Kakiuchi S, Yamazaki K. Calcium dependent phosphodiesterase activity and its activation factor. Biochem Biophys Res Commun 1970;41:1104-10.
30. Mayer B, Koesling D, Bohme E. Characterisation of nitric oxide synthase, soluble guanyl cyclise and Ca2+/calmodulin stimulated cGMP phosphodiesterase as components of neuronal signal transduction. In Advances in Second messenger and Phosphorylation Research. Vol 28. Eds. B.L. Brown & PRM Dobson. Raven Press. New York. 1993:111-9.
31. Lehotski S. Plasma membrane calcium pump functional specialization in brain: complex of isoforms expression and regulation by effectors. Mol Chem Neuropathol 1995;25:175-87.
32. Simpson PB, Challis R, Nahorski SR. Involvement of intracellular stores in the calcium response to NMDA and depolarization in cerebellar granule cells. J Neurochem. 1993;61:760-1.
33. Yamada M, Miyawaki A, Saito K, Nakajima T, Yamamotohimo M. The calmodulin binding domain in the mouse type IP_3 receptor. Biochem J 1995;308:83-8.
34. Naher E, Augustine GJ. Calcium gradients and buffers in bovine chromaffin cells. J Physiol 1999;450:273-301.
35. Bainbridge KG, Cello MR, Rogers JH. Calcium binding proteins in the nervous system. Trends Neurosci 1992;15:303-8.
36. Berridge MJ. Capacitative calcium entry. Biochem J 1995;312:1-11.
37. Fasolato C, Innocenti B, Pozzan T. Receptor activated calcium influx: how many mechanisms for how many channels? Trends Pharmacol Sci 1994;15:77-83.
38. Xu X, Star RA, Totforici G, Muallem S. Depletion of intracellular calcium stores activates nitric oxide synthase to generate

cGMP and regulate Ca2+ influx. J Biol Chem 1994;269:12645-53.
39. Yan Y, Wei CH, Zhang W, Cheng H, Liu J. Cross talk between calcium and reactive oxygen species signalling. Acta Pharmacologica Sinica 2006;27:822-6.
40. Tozer AJB, Forsythe ID, Steinert JR. Nitric oxide signalling augments neuronal voltage gated L type (Cav.1) and P/Q type (Ca v.2.1) channels in the mouse medial nucleus of trapezoid body. PLoS One 2012;7:e32256.
41. Kakizawe S, Yonazawa T, Chen Y, Ito A, Muramaya T. Nitric oxide induced calcium release via ryanodine receptors regulates neuronal function. EMBO J 2012;31:417-28.
42. Horn T, Wolf G, Dufy S, Weiss S, Kelshoff G, MaVica R. Nitric oxide promotes intracellular calcium release from mitochondria in striatal neurons. FASEB J 2002;16:1611-22.
43. Mattson MP. Calcium and neurodegeneration. Aging Cell 2007;6:337-50.
44. Zorumski CF, Thio LL. Properties of vertebrate glutamate receptors: calcium mobilization and desensitization. Progress in Neurobiology 1992;39:295-336.