Annals of Pharmacology and Pharmaceutics

Review Article
Published: 10 Nov, 2017

Calcium Signaling Proteins in Human Diseases and their Potential as Drug Targets

*Gohain D, Avishek Roy and Ranjan Tamuli**

Department of Biosciences and Bioengineering, Indian Institute of Technology Guwahati, India

Abstract

The calcium (Ca^{2+}) signaling proteins are activated by a transient increase in free resting intracellular free Ca^{2+} concentration and regulate numerous cell process including disease conditions. The neuronal Ca^{2+} sensor-1, calmodulin, Ca^{2+}/calmodulin dependent protein kinases, and calcineurin are some of the important Ca^{2+} signaling proteins known to play an important role various organisms and in human diseases, and have the potential as drug targets.

Introduction

Cell signaling is essential for all living organisms to communicate with both intracellular and extracellular environments. Cell signaling is mediated by several pathways including G-protein coupled receptors (GPCRs), and calcium (Ca^{2+}) signaling pathway that affects almost all cell process ranging from fertilization to death, and therefore, Ca^{2+} is also called as molecule of "life and death"[1].A typical human cell maintains about 2 mM of Ca^{2+} in blood and extracellular fluid, whereas, the resting intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$) is about 100 nM that transiently increases to about 100 M during the Ca^{2+} signaling process [2-3]. In the signaling process, many Ca^{2+} binding proteins binds to the increased $[Ca^{2+}]_i$ to regulated downstream effectors and also act as buffers to maintain the Ca^{2+} homeostasis in the cell [3-5].The Ca^{2+} signaling proteins have emerged as potential biomarkers for several disorders and also as drug targets for the treatment of infectious diseases in human. In this mini-review, cell functions of Ca^{2+}- signaling proteins neuronal calcium sensor-1, calmodulin, Ca^{2+}/calmodulin dependent protein kinases, and calcineurin, their roles in human diseases and potential as drug targets have been discussed.

Neuronal Calcium Sensor-1

One of the Ca^{2+}-binding proteins, neuronal calcium sensor-1 (NCS-1) is highly conserved from fungi to human containing four-EF hand Ca^{2+} binding domains, although, only three of the EF binds to Ca^{2+}[6-9]. NCS-1 has a critical physiological role in various organisms[7-10], such as neuronal growth, secretion, and regulation of Ca^{2+} channels in *Lymnaea stagnalis*, *Xenopus*, *Drosophila*, and mammals [11],memory and learningin *Caenorhabditis elegan*[12] and mice [13], neurotransmitter release in *Drosophila* [14], activity dependent synaptic facilitation of voltage-gated Ca^{2+} channels in rat calyceal nerve terminal [15], and in short-term synaptic plasticity in rat hippocampal neurons[16], long-term depression (LTD) via activation of metabotropic glutamate receptors (mGluRs) in rat cortical neurons[17], exploratory behavior and in the acquisition of spatial memory in mouse [18], and in neurite sprouting and spinal cord regeneration in rat [19]. In human, NCS-1 level was found up regulated in the prefrontal cortex of schizophrenic and bipolar patients [20], but, its level was decreased in leukocytes of schizophrenia and bipolar disorder patients [21], suggesting that NCS-1 may be associated with these abnormalities. In addition, NCS-1 is also a novel binding partner of paclitaxel (taxol), one of the most effective anticancer drugs, and protection of NCS-1 from paclitaxel-induced degradation by inhibiting calpain, a Ca^{2+}-dependent enzyme, might be useful for protection from peripheral neuropathy, a major side effect caused by paclitaxel treatment [22-24].

Calmodulin

The Ca^{2+} binding protein calmodulin (CaM) interacts with various target kinases, and phosphatases including calcineurin [4, 25, 26] The increased CaM level in peripheral blood cells is a distinct feature Alzheimer's disease (AD), although, the changes in CaM level was not correlated with the severity of AD, suggesting that the increased CaM level may be an early manifestation of AD [27]. Moreover, the increased level of CaM level in peripheral blood cells was not detected

OPEN ACCESS

Correspondence:
Ranjan Tamuli, Department of Biosciences and Bioengineering, Indian Institute of Technology Guwahati, India, Tel: +91 361 258 2220, Fax: +91 361 258 2249/269 0762; E-mail: ranjan.tam@gmail.com

Received Date: *01 Aug 2017*
Accepted Date: *20 Oct 2017*
Published Date: *10 Nov 2017*

Citation:
Gohain D, Roy A, Tamuli R. Calcium Signaling Proteins in Human Diseases and their Potential as Drug Targets. Ann Pharmacol Pharm. 2017; 2(11): 1117.

in case of other types of dementia and neurodegenerative disorders such as dementia with Lewy bodies, frontotemporal dementia, amyotrophic lateral sclerosis, Parkinson's disease, and progressive supranuclear palsy [27]. Therefore, CaM is a potential biomarker for early diagnosis of AD and differentiating it with other dementia and neurodegenerative disorders [27]. In addition, the anticancer drug CBP501, which is in clinical trials for patients with non-small cell lung cancer and malignant pleural mesothelioma, inhibits CaM and causes sensitization of cancer cells to cisplatin or bleomycin that might provide the basis for the codrug effect CBP501 [28].

Ca^{2+}/calmodulin dependent protein kinases

Ca^{2+}/calmodulin dependent protein kinases (CaMKs) are Ser/Thr class of kinases such as CaMKK, CaMKI, CaMKII, CaMKIII, and CaMKIV, which are activated by increased $[Ca^{2+}]_i$ and CaM[29-30].The CaMKII inhibition might be effective for the treatment of heart disease [31] Moreover, CaMKIV is essential for mesangial cell proliferation and a treatment target for lupus nephritis [32].

Calcineurin

The Ca^{2+} signaling proteins also play a critical role in infections mediated by viruses, bacteria, and fungi [3, 33-37]. Several Ca^{2+} signaling proteins, including calcineurin has been identified as the major virulence factor in fungal infection of plant and human [38]. Calcineurin comprises of two subunits including a catalytic subunit A, and a regulatory subunit B [39, 40]. The function of the calcineurin is inhibited by the immunosuppressive drugs FK506 and Cyclosporin A (CsA) [41-43]. In recent studies, the calcineurin mediated signaling is found to play a critical role in fungal virulence that might help in understanding the evolution of antifungal resistance and the development of novel antifungal drug [38, 44]. One of the well-known targets of calcineurin is the transcription factor the calcineurin responsive zinc finger-1 (Crz1) in fungi and the nuclear factor of activated T-cells (NFAT) in mammals [45]. The Crz1 modulates various cell functions ranging from homeostasis, stress response, virulence, and hyphal growth in many fungi, including *Aspergillus*, *Candida*, *Cryptococcus*, and *Fusarium* [38]. In mammals, the NFAT transcription factors play critical roles in numerous cell processes, including organogenesis of immune, nervous, respiratory, and vascular systems [46, 47]. Inhibition of calcineurin might have a significant role in survival of a recipient [48, 49]. In addition, inhibition of the calcineurin B homologous protein 1(CHP1), results in suppression of angiogenesis in cancer cells [50]. Moreover, in transgenic mice, expression of the activated forms of calcineurin or its target transcription factor NF-AT3, which is dephosphorylated by calcineurin and activates cardiac zinc finger transcription factor GAT4 in the nucleus, in the heart develops cardiac hypertrophy and heart failure like in the case of human heart disease [51]. Therefore, cardiac specific inhibition of calcineurin might be beneficial in the treatment of cardiac hypertrophy in humans [51, 52].

Conclusion

The Ca^{2+} signaling proteins NCS-1, CaM, CaMKs, and calcineurin play a critical role in human diseases. The NCS-1 has a putative role in schizophrenia and bipolar disorder, and might be useful protection form side effect from the anticancer drug. CaM plays a role in Alzheimer's disease and a potential biomarker for early diagnosis of Alzheimer's disease, and might be a target for anticancer drug therapy. In addition, CaMKs play roles in several diseases, including autoimmune, cancer, and cardiac. Another Ca^{2+} signaling protein calcineurin has been implicated in cardiac hypertrophy, and calcineurin in pathogenic fungi plays a key role in infection. Thus, some of these Ca^{2+} signaling proteins are expected to be developed as biomarkers for several human diseases and potent drug targets for fungal infection in future.

Acknowledgments

DG and AR were supported by research fellowships from the Ministry of Human Resource Development, Government of India.

References

1. Berridge MJ, Bootman MD, Lipp P. Calcium- a life and death signal. Nature. 1998;395(6703):645-8.
2. Clapham DE. Calcium signaling. Cell. 2007;131(6):1047-58.
3. Pu F, Chen N, Xue S. Calcium intake, calcium homeostasis and health. Food Sci Hum Wellness. 2016;5(1):8-16.
4. Chin D, Means AR. Calmodulin: a prototypical calcium sensor. Trends Cell Biol. 2000;10(8):322-8.
5. Barman A, Tamuli R. The pleiotropic vegetative and sexual development phenotypes of *Neurospora crassa* arise from double mutants of the calcium signaling genes *plc-1*, *splA2*, and *cpe-1*. Curr Genet. 2017.
6. Burgoyne RD, Weiss JL. The neuronal calcium sensor family of Ca^{2+}-binding proteins. Biochem J. 2001;353(Pt 1):1-12.
7. Tamuli R, Kumar R, Deka R. Cellular roles of neuronal calcium sensor-1 and calcium/calmodulin-dependent kinases in fungi. J Basic Microbiol. 2011;51(2):120-8.
8. Deka R, Kumar R, Tamuli R. *Neurospora crassa* homologue of Neuronal Calcium Sensor-1 has a role in growth, calcium stress tolerance, and ultraviolet survival. Genetica. 2011;139(7):885-94.
9. Gohain D, Deka R, Tamuli R. Identification of critical amino acid residues and functional conservation of the *Neurospora crassa* and *Rattus norvegicus* orthologues of neuronal calcium sensor-1. Genetica. 2016;144(6):665-674.
10. Burgoyne RD, Haynes LP. Understanding the physiological roles of the neuronal calcium sensor proteins. Mol Brain. 2012;5(1):2.
11. Weiss JL, Hui H, Burgoyne RD. Neuronal calcium sensor-1 regulation of calcium channels, secretion, and neuronal outgrowth. Cell Mol Neurobiol. 2010;30(8):1283-92.
12. Gomez M, De Castro E, Guarin E, Sasakura H, Kuhara A, Mori I, et al. Ca^{2+} signaling via the neuronal calcium sensor-1 regulates associative learning and memory in *C. elegans*. Neuron. 2001;30(1):241-8.
13. Mun HS, Saab BJ, Ng E, McGirr A, Lipina TV, Gondo Y, et al. Self-directed exploration provides a Ncs1-dependent learning bonus. Sci Rep. 2015;5:17697.
14. Pongs O, Lindemeier J, Zhu XR, Theil T, Endelkamp D, Krah-Jentgens I, et al. Frequenin – A novel calcium-binding protein that modulates synaptic efficacy in the drosophila nervous system. Neuron. 1993;11(1):15-28.
15. Tsujimoto T, Jeromin A, Satoh N, Roder JC, Takahashi T. Neuronal calcium sensor 1 and activity-dependent facilitation of P/Q-type calcium channel currents at presynaptic nerve terminals. Science. 2002; 295(5563):2276-9.
16. Sippy T, Cruz-Martin A, Jeromin A, Schweizer FE. Acute changes in short-term plasticity at synapses with elevated levels of neuronal calcium sensor-1. Nature Neurosci. 2003;6(10):1031-8.
17. Jo J, Heon S, Kim MJ, Son GH, Park Y, Henley JM, et al. Metabotropic glutamate receptor-mediated LTD involves two interacting Ca^{2+} sensors, NCS-1 and PICK1. Neuron. 2008;60(6):1095-111.
18. Saab BJ, Georgiou J, Nath A, Lee FJ, Wang M, Michalon A, et al. NCS-1 in the dentate gyrus promotes exploration, synaptic plasticity, and rapid acquisition of spatial memory. Neuron. 2009;63(5):643-56.

19. Yip PK, Wong LF, Sears TA, Yanez-Munoz RJ, McMahon SB. Cortical over expression of neuronal calcium sensor-1 induces functional plasticity in spinal cord following unilateral pyramidal tract injury in rat. PLoS Biol. 2010;8(6): e1000399.

20. Koh PO, Undie AS, Kabbani N, Levenson R, Goldman-Rakic PS, Lidow MS. Up-regulation of neuronal calcium sensor-1 (NCS-1) in the prefrontal cortex of schizophrenic and bipolar patients. Proc Natl Acad Sci U S A. 2003;100(1):313-317.

21. Torres KC, Souza BR, Miranda DM, Sampaio AM, Nicolato R, Neves FS, et al. Expression of neuronal calcium sensor-1 (NCS-1) is decreased in leukocytes of schizophrenia and bipolar disorder patients. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33(2):229-34.

22. Spencer CM, and Diana F. Paclitaxel. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of cancer. Drugs 1994;48(5)794-847.

23. Boehmerle W, Splittgerber U, Lazarus MB, McKenzie KM, Johnston DG, Austin DJ, et al. Paclitaxel induces calcium oscillations via an inositol 1,4,5-trisphosphate receptor and neuronal calcium sensor 1-dependent mechanism.Proc Natl Acad Sci U S A. 2006;103(48):18356-61.

24. Benbow JH, DeGray B, Ehrlich BE. Protection of neuronal calcium sensor 1 protein in cells treated with paclitaxel. J Biol Chem. 2011;286(40):34575-82.

25. Yap KL, Kim J, Truong K, Sherman M, Yuan T, Ikura M. Calmodulin target database. J Struct Funct Genomics. 2000;1(1):8-14.

26. Laxmi V, Tamuli R. The calmodulin gene in *Neurospora crassa* is required for normal vegetative growth, ultraviolet survival, and sexual development. Arch Microbiol. 2017;199(4):531-542.

27. Esteras N, Alquézar C, de la Encarnación A, Villarejo A, Bermejo-Pareja F, Martín-Requero Á. Calmodulin levels in blood cells as a potential biomarker of Alzheimer's disease. Alzheimers Res Ther. 2013;5(6):55.

28. Mine N, Yamamoto S, Saito N, Yamazaki S, Suda C, Ishigaki M, et al. CBP501-Calmodulin Binding Contributes to Sensitizing Tumor Cells to Cisplatin and Bleomycin. Mol Cancer Ther. 2011;10(10):1929-1938.

29. Swulius MT, Waxham MN. Ca^{2+}/calmodulin-dependent protein kinases. Cell Mol Life Sci. 2008;65(17):2637-2657.

30. Kumar R, Tamuli R. Calcium/calmodulin-dependent kinases are involved in growth, thermotolerance, oxidative stress survival, and fertility in *Neurospora crassa*. Arch Microbiol. 2014;196(4):295-305.

31. Schulman H, Anderson ME. Ca^{2+}/Calmodulin-dependent Protein Kinase II in Heart Failure. Drug Discov Today Dis Mech. 2010;7(2):e117-e122.

32. Ichinose K, Rauen T, Juang Y-T, Kis-Toth K, Mizui M, Koga T, et al. Cutting edge: calcium/calmodulin-dependent protein kinase type IV is essential for mesangial cell proliferation and lupus nephritis. J Immunol. 2011;187(11):5500-4.

33. TranVan Nhieu G, Clair C, Grompone G, Sansonetti P. Calcium signalling during cell interactions with bacterial pathogens. Biol Cell. 2004;96(1):93-101.

34. Zhou Y, Xue S, Yang JJ. Calcium and Viruses. In: Encyclopedia of Metalloproteins. Springer. 2013; p: 415-424.

35. Rana A, Ahmed M, Rub A, Akhter Y. A tug-of-war between the host and the pathogen generates strategic hotspots for the development of novel therapeutic interventions against infectious diseases. Virulence. 2015;6(6):566-580.

36. Tisi R, Rigamonti M, Groppi S, Belotti F. Calcium homeostasis and signaling in fungi and their relevance for pathogenicity of yeasts and filamentous fungi. AIMS Mol Sci. 2016; 3(4): 505-549.

37. Tamuli R, Deka R, Borkovich KA. Calcineurin Subunits A and B Interact to Regulate Growth and Asexual and Sexual Development in *Neurospora crassa*. PLoS One. 2016;11(3): e0151867.

38. Liu S, Hou Y, Liu W, Lu C, Wang W, Sun S. Components of the calcium-calcineurin signaling pathway in fungal cells and their potential as antifungal targets. Eukaryot Cell. 2015;14(4):324-334.

39. Klee CB, Crouch TH, Krinks MH. Calcineurin: a calcium-and calmodulin-binding protein of the nervous system. Proc Natl Acad Sci. 1979;76(12):6270-6273.

40. Klee CB, Ren H, Wang X. Regulation of the calmodulin-stimulated protein phosphatase, calcineurin. J Biol Chem. 1998;273(22):13367-13370.

41. Borel JF. Comparative study of in vitro and in vivo drug effects on cell-mediated cytotoxicity. Immunology. 1976;31(4):631-641.

42. Kino T, Hatanaka H, Hashimoto M, Nishiyama M, Goto T, Okuhara M, et al. FK-506, a novel immunosuppressant isolated from a Streptomyces. I. Fermentation, isolation, and physico-chemical and biological characteristics. J Antibiot. 1987;40(9):1249-1255.

43. Sieber M, Baumgrass R. Novel inhibitors of the calcineurin/NFATc hub-alternatives to CsA and FK506?. Cell Commun Signal. 2009; 7:25.

44. Juvvadi PR, Lamoth F, Steinbach WJ. Calcineurin as a multifunctional regulator: unraveling novel functions in fungal stress responses, hyphal growth, drug resistance, and pathogenesis. Fungal Biol Rev. 2014;28(2-3):56-69.

45. Chen Ying-Lien, Kozubowski L, Cardenas ME, Heitman J. On the roles of calcineurin in fungal growth and pathogenesis. Curr Fungal Infect Rep. 2010;4(4):244-255.

46. Rao A, Luo C, Hogan PG. Transcription factors of the NFAT family: regulation and function. Annu Rev Immunol. 1997;15:707-747.

47. Wu W, Misra RS, Russell JQ, Flavell RA, Rincón M, Budd RC. Proteolytic regulation of nuclear factor of activated T (NFAT) c2 cells and NFAT activity by caspase-3. J Biol Chem. 2006;281(16):10682-10690.

48. Isakova T, Xie H, Messinger S, Cortazar F, Scialla JJ, Guerra G, et al. Inhibitors of mTOR and risks of allograft failure and mortality in kidney transplantation. Am J Transplant. 2013;3(1):100-110.

49. Yeh H, Markmann JF. Transplantation: are calcineurin inhibitors safer than mTOR inhibitors?. Nat Rev Nephrol. 2013;9(1):11-13.

50. Kim BS, Lee K, Jung HJ, Bhattarai D, Kwon HJ. HIF-1α suppressing small molecule, LW6, inhibits cancer cell growth by binding to calcineurin b homologous protein 1. Biochem Biophys Res Commun. 2015;458(1):14-20.

51. Molkentin JD, Lu J-R, Antos CL, Markham B, Richardson J, Robbins J, et al. A calcineurin-dependent transcriptional pathway for cardiac hypertrophy. Cell. 1998;93(2):215–228.

52. Molkentin JD. Calcineurin and Beyond. Circ Res. 2000;87(9):731-738.