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Mini Review

Voltage Gated Sodium Channels -

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ABSTRACT

Voltage-Gated (-dependent) Sodium Channels (VGSCs) are heterotrimeric transmembrane proteins that control the initiations of the action potential. Those channels are involved in many diseases, including cardiac arrhythmias, neuropathic pain, and epilepsy. VGSCs are therapeutic targets for the improvement of many Central nervous system drugs. In this minireview, we discuss the VGSCs localization, expression, and the relationship between those channels and miRNAs and pain briefly.

Keywords: VGSCs; miRNAs; Epilepsy

INTRODUCTION

Voltage Gated (-dependent) Sodium Channels (VGSCs) are heterotrimeric transmembrane proteins depending on the electrochemical gradient they form selective passages to transfer sodium ions from and into cells, in other word the sodium channels proteins control the movement of the sodium ion across the cell membrane. VGSCs play an important function in neurons by initiation and generation of the action potential. Those channels consist of one (big) pore-forming α subunit (~260kDa) and associated smaller size one or more non-pore forming β subunits (30-40 kD) [1]. Mammalian genomes contain 9 α VGSC (NaV1.1 to Nav1.9) subunits, and 5 β subunits (β1- β4 and β1B). Ten genes encodes α subunits (SCN1A-SCN10A) and four genes encodes β subunits (SCN1B-SCN4B) [2]. VGSC alpha subunits include all the components and mechanisms required to conduct the ions on the cell surface, expression, gating, inactivation, and voltage sensing. VGSC beta subunits are not only simple associates to alpha subunit. VGSC β subunits are multifunctional. They present unique mechanisms, control cellular excitability, are involved in brain development, not linked to alpha subunits in some functions [1].

Localization and Expression

Voltage-Gated sodium channel genes have been recognized in many animal cells, including leeches, flies, jellyfish, and squid, also in mammalian vertebrates [3]. VGSCs Na1.1, Na1.2, Na1.3, and Na 1.6 are the Central Nervous System's (CNS) Na channels. While Na1.7, Na1.8, and Na 1.9 are the primary Na channels in the Peripheral Nervous system (PNS). In skeletal muscle and heart, the main sodium channels are Na1.4, and Na1.5 respectively [4]. Mammalian VGSCs have different expression profiles and subcellular localization during development, regular with every channel's definite physiological functions in mammals. The chromosome segments containing VGSCs genes are paralogous, and every chromosome contains a group of genes (Hox genes), which encode the transcriptional factors associated with the regulation of developmental patterning. Genes encoding VGSCs Nav1.1, Nav1.2, Nav1.3, and Nav1.7 are found on chromosome two in humans and mice cells. These channels have similarities in their sequence, biological and physiological properties, and they can be blocked via very small concentrations (nanomolar) of the Tetrodotoxin (TTX). The second group of genes encoding human Sodium channels Nav1.5, 1.8, and 1.9 is found on chromosome 3p21-24, while in mouse it's located on chromosome three. The Beta subunits chromosomal locations are identified in humans. VGSCs β 1 gene (SCN1B) located on chromosome 19q13, and β 2(SCN2B) and β 3(SCN3B) are located on chromosome 11q22-23. β3 (SCN3B) shares some similarities with β 1 gene in sequence and some functions [5].

Sodium Channels and miRNAs

MiRNAs are a group of non-coding RNAs (measuring~ 22 nucleotides) that bind to complementary sequences often within the 3 UTR of their target mRNAs [6]. To date, the relationship between miRNAs and VGSCs are not well investigated. Only a few studies reported the involvement of those molecules in pain and some diseases linked to VGSCs. As we know, many miRNAs are highly expressed in the brain, such as miR-210, miR-377, miR-128, and miRNA-30b. Interestingly, many genes encoding sodium channels α and β subunits are expressed in the brain; for example, SCN1B, the gene coding β1 subunit, this gene has been shown to be linked to epilepsy, seizures, and Brugada Syndrome. Various miRNAs have been reported to enhance the improvement of epilepsy and acute seizures [7]. Recently, a study reported that miR-155 could be linked with the seizure risks, and SCN1A could be one of the miR-155 targets. Downregulation of miR-155 may help to prevent postoperative seizure by upregulation of SCN1A expression [8], another study reported that there are multiple miRNAs in Na1.1 are linked to epilepsy [9]. In VGSCs β2, in VGSCs β2, microRNA-7a is involved in pain [10], while microRNA-9 has been shown to play a vital role in acute cerebral ischemia [11]. Interestingly, miR-30b is decreased in the spinal ganglion of a mouse nerve damage model. Local injection of this miRNA agomir in spinal ganglion alleviates pain and reduces increased expression of the VGSCs Nav1.7 [12]. Mutations in SCN9A (gene encodes Nav1.7) have been reported to play a vital role in epilepsy [13], but this role in epilepsy is not well investigated [14,15]. miR-132 plays a critical function in neurodegenerative disorder. A study described the regulation impact of this miRNA on Nav1.1 and Nav1.2 expression, and the study showed that miR- 132 could efficiently promote the memory function in rats; it inhibits the expression of both Nav1.1 and Nav1.2 and relieves neuron pathological injury. Misregulation of this miRNA with elevated Nav1.1/Nav1.2 gives a possible mechanism for improving memory loss [16]. Ion channels that target miRNAs can control the neuron's intrinsic excitability and affect the brain's whole networks. Their role in seizures and epilepsy may involve the disease phenotype. However, studies are required to understand how microRNAs control Na ion channels to regulate neuronal excitability.

VGSCs and Pain

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [17]. VGSCs manage the noxious information transport from the affected cells or tissues to the spinal cord. Stimulation of the channel receptors via surface stimuli changes the membrane depolarization, action potential creation at the peripheral terminal [18]. Nav1.8 has a higher action potential production threshold (-30 to -40mV) than Nav1.9; it is somewhat slowly inactivated and rapidly repressed. Contrary, at a voltage potential near the resting potential (-60 to -70mV), Nav1.9 is slowly triggered, causing a tonic Na ion current and facilitating cell depolarization. The only way to reach the binding sites on the alpha subunit is by bypassing the axon membranes. This feature can be done by using lidocaine derivatives such as monocarboxylic acid amide (QX314) [19].

REFERENCES

1. Bennett DL, Clark AJ, Huang J, Waxman SG, Dib-Hajj SD. The Role of Voltage-Gated Sodium Channels in Pain Signaling. Physiol Rev. 2019 Apr 1;99(2):1079-1151. doi: 10.1152/physrev.00052.2017. PMID: 30672368.
2. Catterall WA, Perez-Reyes E, Snutch TP, Striessnig J. International Union of Pharmacology. XLVIII. Nomenclature and structure-function relationships of voltage-gated calcium channels. Pharmacol Rev. 2005 Dec;57(4):411-25. doi: 10.1124/pr.57.4.5. PMID: 16382099.
3. Goldin AL. Evolution of voltage-gated Na(+) channels. J Exp Biol. 2002 Mar;205(Pt 5):575-84. PMID: 11907047.
4. Catterall WA. Voltage-gated sodium channels at 60: structure, function and pathophysiology. J Physiol. 2012 Jun 1;590(11):2577-89. doi: 10.1113/jphysiol.2011.224204. Epub 2012 Apr 2. PMID: 22473783; PMCID: PMC3424717.
5. Frank HY, Catterall WA. Overview of the voltage-gated sodium channel family. 2003;4(3):1-7. https://tinyurl.com/y8fewvvl
6. Bartel DPC. Metazoan micrornas. 2018;173(1):20-51. https://tinyurl.com/y7xyynk4
7. Tiwari D, Pearlso K, Gross C. MicroRNA-induced silencing in epilepsy: Opportunities and challenges for clinical application. Dev Dyn. 2018 Jan;247(1):94-110. doi: 10.1002/dvdy.24582. Epub 2017 Oct 4. PMID: 28850760; PMCID: PMC5740004.
8. Zhang Z, Wang Z, Zhang B, Liu Y. Downregulation of microRNA-155 by preoperative administration of valproic acid prevents postoperative seizures by upregulating SCN1A. Mol Med Rep. 2018 Jan;17(1):1375-1381. doi: 10.3892/mmr.2017.8004. Epub 2017 Nov 7. PMID: 29115566.
9. Li T, Kuang Y, Li B. The genetic variants in 3' untranslated region of voltage-gated sodium channel alpha 1 subunit gene affect the mRNA-microRNA interactions and associate with epilepsy. BMC Genet. 2016 Jul 29;17(1):111. doi: 10.1186/s12863-016-0417-y. PMID: 27473590; PMCID: PMC4966731.
10. Sakai A, Saitow F, Miyake N, Miyake K, Shimada T, Suzuki H. miR-7a alleviates the maintenance of neuropathic pain through regulation of neuronal excitability. Brain. 2013 Sep;136(Pt 9):2738-50. doi: 10.1093/brain/awt191. Epub 2013 Jul 16. PMID: 23861446.
11. Sun LH. MicroRNA-9 induces defective trafficking of Nav1. 1 and Nav1. 2 by targeting Navβ2 protein coding region in rat with chronic brain hypoperfusion. 2015;10(1):1-15. https://tinyurl.com/yby649m3
12. Shao J, Cao J, Wang J, Ren X, Su S, Li M, Li Z, Zhao Q, Zang W. MicroRNA-30b regulates expression of the sodium channel Nav1.7 in nerve injury-induced neuropathic pain in the rat. Mol Pain. 2016 Oct 19;12:1744806916671523. doi: 10.1177/1744806916671523. PMID: 27765894; PMCID: PMC5081156.
13. Singh NA, Pappas C, Dahle EJ, Claes LR, Pruess TH, De Jonghe P, Thompson J, Dixon M, Gurnett C, Peiffer A, White HS, Filloux F, Leppert MF. A role of SCN9A in human epilepsies, as a cause of febrile seizures and as a potential modifier of Dravet syndrome. PLoS Genet. 2009 Sep;5(9):e1000649. doi: 10.1371/journal.pgen.1000649. Epub 2009 Sep 18. PMID: 19763161; PMCID: PMC2730533.
14. Korotkov A, Mills JD, Gorter JA, van Vliet EA, Aronica E. Systematic review and meta-analysis of differentially expressed miRNAs in experimental and human temporal lobe epilepsy. Sci Rep. 2017 Sep 14;7(1):11592. doi: 10.1038/s41598-017-11510-8. PMID: 28912503; PMCID: PMC5599629.
15. Gross C, Tiwari D. Regulation of Ion Channels by MicroRNAs and the Implication for Epilepsy. Curr Neurol Neurosci Rep. 2018 Jul 25;18(9):60. doi: 10.1007/s11910-018-0870-2. PMID: 30046905; PMCID: PMC6092942.
16. Hu XL, Wang XX, Zhu YM, Xuan LN, Peng LW, Liu YQ, Yang H, Yang C, Jiao L, Hang PZ, Sun LH. MicroRNA-132 regulates total protein of Nav1.1 and Nav1.2 in the hippocampus and cortex of rat with chronic cerebral hypoperfusion. Behav Brain Res. 2019 Jul 2;366:118-125. doi: 10.1016/j.bbr.2019.03.026. Epub 2019 Mar 15. PMID: 30885820.
17. Su S, Shao J, Zhao Q, Ren X, Cai W, Li L, Bai Q, Chen X, Xu B, Wang J, Cao J, Zang W. MiR-30b Attenuates Neuropathic Pain by Regulating Voltage-Gated Sodium Channel Nav1.3 in Rats. Front Mol Neurosci. 2017 May 5;10:126. doi: 10.3389/fnmol.2017.00126. PMID: 28529474; PMCID: PMC5418349.
18. Dib-Hajj SD, Cummins TR, Black JA, Waxman SG. Sodium channels in normal and pathological pain. Annu Rev Neurosci. 2010;33:325-47. doi: 10.1146/annurev-neuro-060909-153234. PMID: 20367448.
19. Binshtok AM, Bean BP, Woolf CJ. Inhibition of nociceptors by TRPV1-mediated entry of impermeant sodium channel blockers. Nature. 2007 Oct 4;449(7162):607-10. doi: 10.1038/nature06191. PMID: 17914397.