Journal of Pain & Relief
ISSN: 2167-0846

Chen, et al., J Pain Relief 2023, 12:S2

Commentary Open Access

Silent Synapses in Cortical Excitation: Chronic Pain and Emotional Disorders

Qi-Yu Chen[1,2] and Min Zhuo[2,3*]

[1]CAS Key Laboratory of Brain Connectome and Manipulation, Interdisciplinary Center for Brain Information, Chinese Academy of Sciences Shenzhen Institute of Advanced Technology, Shenzhen, China

[2]Department of Neurology, Zhuomin International Institute for Brain Research, Qingdao, China

[3]Department of Physiology, University of Toronto, Toronto, Canada

[*]**Corresponding author:** Dr. Min Zhuo, Department of Physiology, University of Toronto, Toronto, Canada, E-mail: min.zhuo@utoronto.ca

Received: 02-01-2024, Manuscript No. JPAR-24-124040; **Editor assigned:** 04-Jan-2024, PreQC No. JPAR-24- 124040 (PQ); **Reviewed:** 18-Jan-2024, QC No. JPAR-24-124040; **Revised:** 25-Jan-2024, Manuscript No. JPAR-24-124040 (R); **Published:** 01-Feb-2024, DOI: 10.4172/2167-0846.13.S3.001

Citation: Chen QY, Zhuo M (2024) Silent Synapses in Cortical Excitation: Chronic Pain and Emotional Disorders. J Pain Relief Open S3: 001.

Abstract

A recent review summarized some recent work of silent synapses in pain-related cortex, and proposed that it may exist as a key synaptic mechanism for cortical circuit LTP and its spreading in chronic pain. We highlighted those key findings of silent synapses and further extended the theories to explaining the mechanism of how cortical-related connections mediated the chronic pain and its related emotional disorders.

Keywords: Chronic pain; Anterior cingulate cortex; Silent synapses; AMPA receptors; NMDA receptors

Description

Filopodia in the adult cortex

A recent study by Vardalaki, et al. demonstrates a substantial amount of filopodia in deep layer V pyramidal cells of the adult visual cortex, are silent synapses [1]. Filopodia are found to lack AMPA-receptor-mediated transmission, but they exhibit NMDA-receptor-mediated synaptic transmission. They could be "unsilenced" by spike-timing protocol which induces Long-Term Potentiation (LTP). These results suggest that silent synapses that are sensitive to LTP recruitment exist in adult cortical neurons, and filopodia can serve as a marker for silent synapses in the adult brain.

Silent synapses and their contribution to LTP

Silent synapses were first discovered in young hippocampal neurons in the hippocampal CA1 region and spinal cord dorsal horn [2-5]. They have been defined as the synapses that lack functional receptors of presynaptic neurotransmitters [2,6,7]. In addition to the hippocampus, studies demonstrated that silent synapses exist in the developing cortices [8,9]. Interestingly, recent studies using MED-64 recording channels found that some silent responses can be detected in the adult Anterior Cingulate Cortex (ACC) after applying the LTP-inducing protocol [10-13]. Such recruitment of silent responses may be due to the recruitment of silent synapses. Future studies are clearly needed to examine such a possibility.

The signaling pathway of the silent synapse is similar to that in chronic pain

Previous studies of the intracellular mechanism of ACC-LTP and chronic pain provide a possible explanation for the basic mechanisms of the recruitment of silent synapses. In addition to the potentiation of existing AMPA receptor-mediated responses, the recruitment of silent synapses also serves as a key mechanism for a postsynaptic form of LTP in the ACC. Genetic and pharmacological findings indicate that calcium calcium-stimulated Adenylyl Cyclase subtype 1 (AC1) or AC1 activity is required for the recruitment of silent responses in the ACC [11-13]. Activation of NMDA receptors increases postsynaptic Ca^{2+}, which increases second messenger cAMP and then leads to activation of PKA, and the phosphorylation of AMPA receptors by PKA plays important roles in the potentiation of AMPA receptor receptor-mediated responses as well as the recruitment of silent responses [10,11]. In addition, PKMζ activity and Fragile X Mental Retardation Protein (FMRP) may also be required [11].

In addition to the NMDA receptor-dependent silent synapse, serotonin can trigger activation of silent synapses between some primary sensory afferents and dorsal horn neurons in the spinal cord by recruiting AMPA receptors. This activation of silent synapses requires protein interactions involving the GluR2/3 C-terminus as well as PKC [5].

Functional implications for adult silent synapses in chronic pain and emotion

Cortical excitation or potentiation has been proposed to contribute to chronic pain and pain-related anxiety [14-19]. Silent synapses add new mechanisms for critical potentiation/excitation in adult animals. Furthermore, the recruitment of silent synapses may lay the basis for spreading the excitation within the cortical circuit and cortical-related connections. For example, the reciprocal connection between the ACC and Basolateral Amygdala (BLA) may lay the foundation of chronic pain-related emotional disorders. It is important to understand possible different mechanisms or molecules that may be involved, and this new information may help us to find better treatment for patients with chronic pain and its related emotional disorders.

References

1. Vardalaki D, Chung K, Harnett MT (2022) Filopodia are a structural substrate for silent synapses in adult neocortex. Nature 612: 323-327.
2. Kerchner GA, Nicoll RA (2008) Silent synapses and the emergence of a postsynaptic mechanism for LTP. Nat Rev Neurosci 9: 813-825.
3. Malinow R. Mainen ZF and Hayashi Y (2000) LTP mechanisms: from silence to four-lane traffic. Curr Opin Neurobiol 10: 352-357.
4. Li P, Zhuo M (6686) Silent glutamatergic synapses and nociception in mammalian spinal cord. Nature 393: 695-698.
5. Li P, Kerchner GA, Sala C, Wei F, Huettner JE, et al. (1999) AMPA receptor-PDZ interactions in facilitation of spinal sensory synapses. Nat Neurosci 2: 972-977.
6. Isaac JTR, Crair MC, Nicoll RA, Malenka RC (1997) Silent synapses during development of thalamocortical inputs. Neuron 18: 269-280.
7. Liao D, Hessler NA, Malinow R. (1995) Activation of postsynaptically silent synapses during pairing-induced LTP in CA1 region of hippocampal slice. Nature 375: 400-404.
8. Feldman DE, Nicoll RA, Malenka RC (1999) Synaptic plasticity at thalamocortical synapses in developing rat somatosensory cortex: LTP, LTD, and silent synapses. J Neurobiol 41: 92-101.
9. Wang YQ, Wang J, Xia SH, Gutstein HB,Huang YH,et al. (2021) Neuropathic pain generates silent synapses in thalamic projection to anterior cingulate cortex. Pain 162: 1322-1333.
10. Song Q, Zheng HW, Li XH, Huganir RL, Kuner T, et al.(2017) Selective phosphorylation of AMPA receptor contributes to the network of long-term potentiation in the anterior cingulate cortex. J Neurosci 37: 8534-8548.
11. Chen T, Lu JS, Song JS, Liu MG, Koga K, et al. (2014) Pharmacological rescue of cortical synaptic and network potentiation in a mouse model for fragile X syndrome. Neuropsychopharmacology 39: 1955-1967.
12. Li XH, Matsuura T, Liu RH, Xue M, Zhuo M, et al. (2019) Calcitonin gene-related peptide potentiated the excitatory transmission and network propagation in the anterior cingulate cortex of adult mice. Mol Pain 15: 1744-8069.
13. Zhou SB, Xue M, Liu W, Chen YX, Chen QY, et al.(2023) Age-related attenuation of cortical synaptic tagging in the ACC is rescued by BDNF or a TrkB receptor agonist in both sex of mice. Mol Brain 16: 4-8.
14. Liauw J, Wu LJ, Zhuo M (2005) Calcium-stimulated adenylyl cyclases required for long-term potentiation in the anterior cingulate cortex. J Neurophysiol 94: 878-882.
15. Liu MG, Kang SJ, Shi TY, Koga K, Zhang MM, et al. (2013) Long-term potentiation of synaptic transmission in the adult mouse insular cortex: multielectrode array recordings. J Neurophysiol 110: 505-521.
16. Koga K, Descalzi G, Chen T, Ko HG, Lu J, et al. (2015) Coexistence of two forms of LTP in ACC provides a synaptic mechanism for the interactions between anxiety and chronic pain. Neuron 85: 377-389.
17. Bliss TVP, Collingridge GL, Kaang BK, Zhuo M, et al. (2016) Synaptic plasticity in the anterior cingulate cortex in acute and chronic pain. Nat Rev Neurosci 17: 485-96.
18. Yamanaka M, Matsuura T, Pan H, Zhuo M (2017) Calcium-stimulated adenylyl cyclase subtype 1 (AC1) contributes to LTP in the insular cortex of adult mice. Heliyon 3: 330-338.
19. Zhuo M (2016) Neural mechanisms underlying anxiety-chronic pain interactions. Trends Neurosci 39: 136-145.