Review Article

Access this article online

Quick Response Code:

Website: http://www.braincirculation.org

DOI: 10.4103/bc.bc_14_21

The unsolved mystery of hippocampal cholinergic neurostimulating peptide: A potent cholinergic regulator

Justin Y. Cho, Noriyuki Matsukawa[1]

Abstract:

Cholinergic efferent networks located from the medial septal nucleus to the hippocampus play a pivotal role in learning and memory outcomes by generating regular theta rhythms that enhance information retention. Hippocampal cholinergic neurostimulating peptide (HCNP), derived from the N-terminus of HCNP precursor protein (HCNP-pp), promotes the synthesis of acetylcholine in the medial septal nuclei. HCNP-pp deletion significantly reduced theta power in CA1 possibly due to lower levels of choline acetyltransferase-positive axons in CA1 stratum oriens, suggesting cholinergic disruptions in the septo-hippocampal system. This review also explores HCNP as a potent cholinergic regulator in the septo-hippocampal network while also examining the limitations of our understanding of the neurostimulating peptide.

Keywords:

Cholinergic projection, hippocampal cholinergic neurostimulating peptide, hippocampal cholinergic neurostimulating peptide precursor protein, septo-hippocampal network, theta power

Introduction

Theta rhythm, a significant rhythmic type within the hippocampal local field potential, possesses a vital role in memory processing.[1] This theta oscillation is generated by cholinergic projections, which stems from the medial septal nucleus to the CA1-CA stratum oriens of hippocampal functional areas and is crucial for maintaining normal theta rhythmic patterns.[2-5] With the internal pacemaker, information is better retained and encoded in episodic memory.[6,7]

Molecular changes within the medial septal nuclei may affect cholinergic projections, affecting normal theta rhythms and functional memory processes. One notable molecule is the hippocampal cholinergic neurostimulating peptide (HCNP), which is cleaved from a 186 amino acid, 21 kD, long precursor protein (HCNP-pp) along the N-terminus.[8] HCNP was seen to promote acetylcholine production by increasing choline acetyltransferase (ChAT) expression level within the medial septal nuclei,[9] which may affect the cholinergic septo-hippocampal system, correlating to healthy episodic memory retention.

Hippocampal Cholinergic Neurostimulating Peptide-pp Genetic Models

HCNP-pp, also referred to as Raf kinase inhibitory protein or phosphatidylethanolamine-binding protein 1, is an ATP-binding, multifunctional protein with inhibitory abilities on Erk signaling pathways.[10,11] HCNP may be synthesized from HCNP-pp cleavage by the thiol protease group.[8] Studies have demonstrated that HCNP-pp transgenic mice exhibit behavioral

Department of Neurosurgery and Brain Repair, University of South Florida Morsani College of Medicine, Tampa, Florida, USA, [1]Department of Neurology, Nagoya City University, Nagoya, Japan

Address for correspondence:
Dr. Noriyuki Matsukawa, Department of Neurology, Nagoya City University, 1 Kawasumi, Mizuho-Cho, Mizuho-Ku, Nagoya, Aichi 467-8601, Japan.
E-mail: norim@med.nagoya-cu.ac.jp

Submission: 03-11-2020
Revised: 10-12-2020
Accepted: 15-12-2020
Published: 30-03-2021

How to cite this article: Cho JY, Matsukawa N. The unsolved mystery of hippocampal cholinergic neurostimulating peptide: A potent cholinergic regulator. Brain Circ 2021;7:29-32.

depressive-like phenotype[12] and electrophysiological higher amplitude of hippocampal field excitatory postsynaptic potentials that is regulated through M1 receptor activation.[3] In addition, these mice may inhibit the regulation of Aß oligomer-induced glutamatergic neuronal activity in the hippocampus through the muscarinic M1 receptor.[4] On the other hand, conditional HCNP-pp knockout mice using Cre-ERT/loxP system by CaMKII-Cre transgenic mice revealed reduced power of theta rhythms in CA1 regions, whereas those mice showed no significant behavioral abnormality in locomotor, anxiety, or cognitive function.[13] In this model, downregulation of HCNP-pp expressions was possibly limited in cells controlled by CaMKII promoter, a hippocampal excitatory neuronal expression regulator, while HCNP-pp expressions are known to exist in inhibitory neurons, oligodendroglia, and hippocampal pyramidal neurons.[14,15] Further investigations are needed to provide a plausible explanation for HCNP function, including HCNP-pp downregulation in other kinds of cells by using Cre-transgenic mice driven other promotors.

Hippocampal Cholinergic Neurostimulating Peptide

HCNP in 14-day-old postnatal hippocampi[9] was initially isolated and later exhibited nerve- and fibroblast-like abilities, which enhanced cell growth.[16,17] Cholinergic axon terminals also decreased in stratum oriens of mice with inadequate HCNP-pp levels,[13] suggesting ChAT regulatory abilities of HCNP in septal cholinergic neuronal cells. Furthermore, HCNP in the hippocampus was found to be correlated to theta activity. Specifically, theta rhythms were observed at reduced power in CA1 regions of mice with inadequate HCNP-pp expressions. These same mice also exhibited lowered hippocampal cholinergic projection,[1,18] proposing a correlation between HCNP-pp/HCNP with cholinergic projection and theta rhythm. On the other hand, overexpressing HCNP was seen to increase ChAT and promote cholinergic effects, enhancing hippocampal activity under unsaturated conditions of the glutamatergic pathway.[4] However, the same effect was not present in saturated conditions.

Due to its likely involvement in synaptic density maintenance,[3,8,19-21] HCNP is a potent cholinergic modulator in the septo-hippocampal system that may improve learning and memory outcomes. HCNP may also support neuronal growth and survival, acting as a neurotrophic-like factor.[8] However, we have not yet caught any evidence that HCNP functions in behavioral cognitive phenotype.

Cholinergic Activity

Hippocampal cholinergic systems play a crucial role in the formation of memory. Recent studies have proposed an additional link between cholinergic effects and anxiety and depression.[12,22,23] Upregulation and overexpression of HCNP-pp caused by CMKII promoter resulted in depressive symptoms,[12] demonstrating potential adverse effects of HCNP-pp alterations. However, inhibiting or removing HCNP-pp alone does not express significant cognitive dysfunctions or depression. In addition, knockout model mice of acetylcholine receptors, such as M1 receptor or alpha 7 nicotinic receptor, do not hinder memory or learning functions,[24,25] suggesting a combination of cholinergic dysfunctions may arise to produce cognitive and behavioral deficits. In other words, reducing acetylcholine alone would not induce dysfunctions in the hippocampus, and removal of HCNP should be followed up with additional cholinergic-correlated dysfunctions to exhibit hippocampal deficits.

Studies have also suggested that sufficient ChAT activity may result in normal behaviors due to other present cholinergic regulators,[26-31] masking HCNP cognitive behavioral deficits in behavioral tests. However, discrepancies arose when observing tropomyosin receptor kinase A (TrkA), a major cholinergic regulator receptor, in relation to cognitive deficits. Specifically, some studies demonstrated no significant changes in behavior when removing TrkA in specific areas with low levels of cholinergic terminals while similar studies exhibited significant cognitive abnormalities;[32,33] this discrepancy was likely due to the difference in gene deletion and animal usage within the studies.[32-34]

A recent study on HCNP-pp KO mice failed to evaluate behaviors dependent on septo-hippocampal systems in behavioral tests on locomotion, anxiety, memory, and depression.[13] However, electrophysiological evaluation demonstrated lower hippocampal cholinergic activity in HCNP-pp KO mice, indicative of hippocampal dysfunction through HCNP reduction. There is a potential that suitable tests were needed to specifically assess septo-hippocampal cholinergic functions even though cholinergic dysfunctions were revealed. As another potential, incomplete suppression of glutamatergic activity in the hippocampus may be necessary to investigate HCNP or HCNP-pp on hippocampal cognitive behavior.[4] Because other hippocampal molecules, such as vinpocetine, recover behavioral and memory outcomes through enhanced cholinergic neurotransmission, HCNP may also improve cognitive functions by targeting cholinergic activity,[35] which are also exhibited by stem cell administrations.[36] Further investigations are necessary to examine the functions of

HCNP due to acetylcholine releases. Alzheimer's disease could be used to examine behavioral phenotypes under glutamatergic neuronal conditions.[4]

Conclusion

HCNP and cholinergic projections are potent targets for recovering learning and memory deficits. There is a likely relationship between cholinergic activity and HCNP-pp; removing HCNP-pp in mice models resulted in decreased choline acetyltransferase-positive axons in the CA1 stratum oriens, which lowered theta oscillations. Lowered hippocampal cholinergic activity in HCNP-pp KO mice models provide evidence of cholinergic functional enhancement abilities of HCNP and demonstrate HCNP-dependent alterations to hippocampal networks, suggesting HCNP to be a cholinergic regulator in the septo-hippocampal system. Although the effects of HCNP on theta rhythms and behavioral outcomes are evident, the function of HCNP is yet to be determined; it is unclear whether the HCNP is dependent on acetylcholine release acceleration or direct trophic effects. Furthermore, observable behavioral changes through hippocampal dysfunction were undetected in cognitive and depressive tests. Future investigations should experiment direct reduction of acetylcholine activity in the hippocampus or number of cholinergic neuronal cells in the medial septal nucleus in addition to testing phenotypic hippocampal dysfunction through suitable behavioral tests possibly under glutamatergic neuronal conditions, such as Alzheimer's disease.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Colgin LL. Rhythms of the hippocampal network. Nat Rev Nuerosci 2016;17:239-49.
2. Mesulam MM, Mufson EJ, Wainer BH, Levey AI. Central cholinergic pathways in the rat: An overview based on an alternative nomenclature (Ch1-Ch6). Neuroscience 1983;10:1185-201.
3. Ohi Y, Kato D, Mizuno M, Sato T, Ueki Y, Borlongan CV, *et al*. Enhancement of long-term potentiation via muscarinic modulation in the hippocampus of HCNP precursor transgenic mice. Neurosci Lett 2015;597:1-6.
4. Sato T, Ohi Y, Kato D, Mizuno M, Takase H, Kanamori T, *et al*. Hippocampal Cholinergic Neurostimulating Peptide as a Possible Modulating Factor against Glutamatergic Neuronal Disability by Amyloid Oligomers. Cell Transplant 2017;26:1542-50.
5. Green JD, Arduini AA. Hippocampal electrical activity in arousal. J Neurophysiol 1954;17:533-57.
6. Dupret D, O'Neill J, Csicsvari J. Dynamic reconfiguration of hippocampal interneuron circuits during spatial learning. Neuron 2013;78:166-80.
7. Jezek K, Henriksen EJ, Treves A, Moser EI, Moser MB. Theta-paced flickering between place-cell maps in the hippocampus. Nature 2011;478:246-9.
8. Ojika K, Mitake S, Tohdoh N, Appel SH, Otsuka Y, Katada E, *et al*. Hippocampal cholinergic neurostimulating peptides (HCNP). Prog Neurobiol 2000;60:37-83.
9. Ojika K, Kojima S, Ueki Y, Fukushima N, Hayashi K, Yamamoto M. Purification and structural analysis of hippocampal cholinergic neurostimulating peptide. Brain Res 1992;572:164-71.
10. Hengst U, Albrecht H, Hess D, Monard D. The phosphatidylethanolamine-binding protein is the prototype of a novel family of serine protease inhibitors. J Biol Chem 2001;276:535-40.
11. Yeung K, Seitz T, Li S, Janosch P, McFerran B, Kaiser C, *et al*. Suppression of Raf-1 kinase activity and MAP kinase signalling by RKIP. Nature 1999;401:173-7.
12. Matsukawa N, Furuya Y, Ogura H, Ojika K. HCNP precursor protein transgenic mice display a depressive-like phenotype in old age. Brain Res 2010;1349:153-61.
13. Madokoro Y, Yoshino Y, Kato D, Sato T, Mizuno M, Kanamori T, *et al*. Reduced Cholinergic Activity in the Hippocampus of Hippocampal Cholinergic Neurostimulating Peptide Precursor Protein Knockout Mice. Int J Mol Sci 2019;20:5367.
14. Yuasa H, Ojika K, Mitake S, Katada E, Matsukawa N, Otsuka Y, *et al*. Age-dependent changes in HCNP-related antigen expression in the human hippocampus. Brain Res Dev Brain Res 2001;127:1-7.
15. Mitake S, Ojika K, Katada E, Otsuka Y, Matsukawa N, Fujimori O. Distribution of hippocampal cholinergic neurostimulating peptide (HCNP) immunoreactivity in the central nervous system of the rat. Brain Res 1996;706:57-70.
16. Sagisaka T, Matsukawa N, Toyoda T, Uematsu N, Kanamori T, Wake H, *et al*. Directed neural lineage differentiation of adult hippocampal progenitor cells via modulation of hippocampal cholinergic neurostimulating peptide precursor expression. Brain Res 2010;1327:107-17.
17. Toyoda T, Matsukawa N, Sagisaka T, *et al*. Suppression of astrocyte lineage in adult hippocampal progenitor cells expressing hippocampal cholinergic neurostimulating peptide precursor in an *in vivo* ischemic mode. Cell Transplant 2012;21:2159-69.
18. Lee MG, Chrobak JJ, Sik A, Wiley RG, Buzsáki G. Hippocampal theta activity following selective lesion of the septal cholinergic system. Neuroscience 1994;62:1033-47.
19. Imai H, Matsukawa M, Okado N. Lamina-selective changes in the density of synapses following perturbation of monoamines and acetylcholine in the rat medial prefrontal cortex. Brain Res 2004;1012:138-45.
20. Uematsu N, Matsukawa N, Kanamori T, Arai Y, Sagisaka T, Toyoda T, *et al*. Overexpression of hippocampal cholinergic neurostimulating peptide in heterozygous transgenic mice increases the amount of ChAT in the medial septal nucleus. Brain Res 2009;1305:150-7.
21. Mele T, Jurič DM. Metrifonate, like acetylcholine, up-regulates neurotrophic activity of cultured rat astrocytes. Pharmacol Rep 2014;66:618-23.
22. Ishisaka M, Kakefuda K, Yamauchi M, Tsuruma K, Shimazawa M, Tsuruta A, *et al*. Luteolin shows an antidepressant-like effect via suppressing endoplasmic reticulum stress. Biol Pharm Bull 2011;34:1481-6.
23. Al-Kuraishy HM, Abdulhadi MH, Hussien NR, Al-Niemi MS, Rasheed HA, Al-Gareeb AI. Involvement of orexinergic system in psychiatric and neurodegenerative disorders: A scoping review. Brain Circ 2020;6:70-80.
24. Wess J, Duttaroy A, Zhang W, Gomeza J, Cui Y, Miyakawa T, *et al*. M1-M5 muscarinic receptor knockout mice as novel tools to study the physiological roles of the muscarinic cholinergic system. Recept Channels 2003;9:279-90.
25. Leaderbrand K, Chen HJ, Corcoran KA, Guedea AL, Jovasevic V,

Wess J, *et al*. Muscarinic acetylcholine receptors act in synergy to facilitate learning and memory. Learn Mem 2016;23:631-8.
26. Burke RM, Norman TA, Haydar TF, *et al*. BMP9 ameliorates amyloidosis and the cholinergic defect in a mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A 2013;110:19567-72.
27. Crutcher KA, Collins F. *In vitro* Evidence for two distinct hippocampal growth factors: Basis of neuronal plasticity? Science 1982;217:67-8.
28. Korsching S, Auburger G, Heumann R, Scott J, Thoenen H. Levels of nerve growth factor and its mRNA in the central nervous system of the rat correlate with cholinergic innervation. EMBO J 1985;4:1389-93.
29. Holtzman DM, Li Y, Parada LF, Kinsman S, Chen CK, Valletta JS, *et al*. p140trk mRNA marks NGF-responsive forebrain neurons: Evidence that trk gene expression is induced by NGF. Neuron 1992;9:465-78.
30. Koh S, Higgins GA. Differential regulation of the low-affinity nerve growth factor receptor during postnatal development of the rat brain. J Comp Neurol 1991;313:494-508.
31. Pioro EP, Cuello AC. Distribution of nerve growth factor receptor-like immunoreactivity in the adult rat central nervous system. Effect of colchicine and correlation with the cholinergic system--I. Forebrain. Neuroscience 1990;34:57-87.
32. Müller M, Triaca V, Besusso D, Costanzi M, Horn JM, Koudelka J, *et al*. Loss of NGF-TrkA signaling from the CNS is not sufficient to induce cognitive impairments in young adult or intermediate-aged mice. J Neurosci 2012;32:14885-98.
33. Sanchez-Ortiz E, Yui D, Song D, Li Y, Rubenstein JL, Reichardt LF, *et al*. TrkA gene ablation in basal forebrain results in dysfunction of the cholinergic circuitry. J Neurosci 2012;32:4065-79.
34. Madisen L, Zwingman TA, Sunkin SM, Oh SW, Zariwala HA, Gu H, *et al*. A robust and high-throughput Cre reporting and characterization system for the whole mouse brain. Nat Neurosci 2010;13:133-40.
35. Al-Kuraishy HM, Al-Gareeb AI, Naji MT, Al-Mamorry F. Role of vinpocetine in ischemic stroke and poststroke outcomes: A critical review. Brain Circ 2020;6:1-0.
36. Carvajal HG, Suárez-Meade P, Borlongan CV. Amnion-derived stem cell tranplantation: A novel treatment for neurological disorders. Brain Circ 2016;2:1-7.