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Jianhua Zhao

Department of Neurology, First Affiliated Hospital of Xinxiang Medical University, Weihui 453100, Henan, China; Henan Joint International Research Laboratory of Neurorestoratology for Senile Dementia / Henan Key Laboratory of Neurorestoratology, Weihui 453100, Henan, China;

Ailin Du

Henan International Joint Laboratory for Non-invasive Brain Modulation / Key Laboratory for Brain Research of Henan Province, Xinxiang Medical University, Xinxiang 453003, Henan, China; Department of Physiology and Neurophysiology, Xinxiang Medical University, Xinxiang 453003, Henan, China

Chengbiao Lu

Henan Joint International Research Laboratory of Neurorestoratology for Senile Dementia / Henan Key Laboratory of Neurorestoratology, Weihui 453100, Henan, China; Henan International Joint Laboratory for Non-invasive Brain Modulation / Key Laboratory for Brain Research of Henan Province, Xinxiang Medical University, Xinxiang 453003, Henan, China; Department of Physiology and Neurophysiology, Xinxiang Medical University, Xinxiang 453003, Henan, China

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REVIEW ARTICLE

Brain gamma rhythm and potential treatment of neurodegenerative disease

Jianhua Zhao^{1,2}, Ailin Du^{3,4}, Chengbiao Lu^{2,3,4} (✉)

¹ Department of Neurology, First Affiliated Hospital of Xinxiang Medical University, Weihui 453100, Henan, China

² Henan Joint International Research Laboratory of Neurorestoratology for Senile Dementia / Henan Key Laboratory of Neurorestoratology, Weihui 453100, Henan, China

³ Henan International Joint Laboratory for Non-invasive Brain Modulation / Key Laboratory for Brain Research of Henan Province, Xinxiang Medical University, Xinxiang 453003, Henan, China

⁴ Department of Physiology and Neurophysiology, Xinxiang Medical University, Xinxiang 453003, Henan, China

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ABSTRACT

In this mini-review, we illustrate the brain network oscillations in different brain areas, including the medial septal diagonal band complex (MSDB) and hippocampus, especially at gamma frequency bands (γ , 30–80 Hz) and theta frequency bands (θ , 4–12 Hz), and their induction and modulation by physical stimulation, such as light and sound, and pharmacological stimulation with agents such as agonists of the kainite subunit ionotropic glutamate receptor, metabotropic glutamate receptor, metabotropic cholinergic receptor, and nicotinic cholinergic receptor. Recent findings demonstrate that boosting gamma oscillations in specific brain areas appears to be able to restore cognitive function and reduce relative pathology in neurodegenerative diseases, such as Alzheimer's disease. Thus, exploration of strategies to enhance or restore impaired gamma oscillations may be a new and effective method to improve the conditions in these devastating diseases.

1 Introduction

The synchronized activity of neural network oscillations at a gamma frequency band (γ , 30–80 Hz) is generated by activated, mutually connected neurons, including principle cells and interneurons [1]. Gamma oscillations dynamically modulate intercommunication between neurons by providing a time marker of millisecond scale precision for neuronal firing and, thus, play an important role in sensory binding, learning, and

memory [2–4]. Present in many brain areas, including the hippocampus, gamma oscillations are not surprisingly associated with spatial learning and memory [5, 6]. Fast-spiking, parvalbumin-positive inhibitory interneurons (basket cells) are critical for gamma generation [7, 8]. Accumulating evidence indicates that gamma oscillations are impaired in neurodegenerative diseases, such as Alzheimer's disease (AD) [9, 10], and psychiatric disorders, such as schizophrenia, which suggests that gamma oscillations may serve as an early,

Corresponding author: Chengbiao Lu, E-mail: johnlu9000@hotmail.com

sensitive biomarker for these diseases [11–13].

2 Physical stimulation-induced gamma oscillations

Recent studies have demonstrated that boosting gamma oscillations in specific brain areas effectively reduce A β -associated pathologies in an animal model of AD, a disease which is well known for the lack of effective therapies. Interestingly, physical stimulation, such as 40-Hz LED light stimulation, enhances gamma oscillatory power in the visual cortex, and reduces A β 1-40 and A β 1-42 load and AD pathology via effects on microglia activity [14]. Recently, studies have further demonstrated that these stimulations also improved the learning and memory of mice with

AD [15] [Fig. 1(A)]. The cellular and molecular mechanisms for the improvement in behavior and A β pathology of the AD animal model after 40-Hz stimulation remain largely unknown and need to be investigated. However, boosting gamma oscillations in specific brain areas may be an effective way to treat brain disorders.

3 Pharmacological induction of gamma oscillations

Gamma oscillations can be recorded *in vivo* or *in vitro*. The *in vitro* slice recordings of gamma oscillations are usually induced by pharmacological agents, such as kainate (KA), an agonist of the KA subunit glutamate receptor, or carbachol, a metabotropic cholinergic agonist.

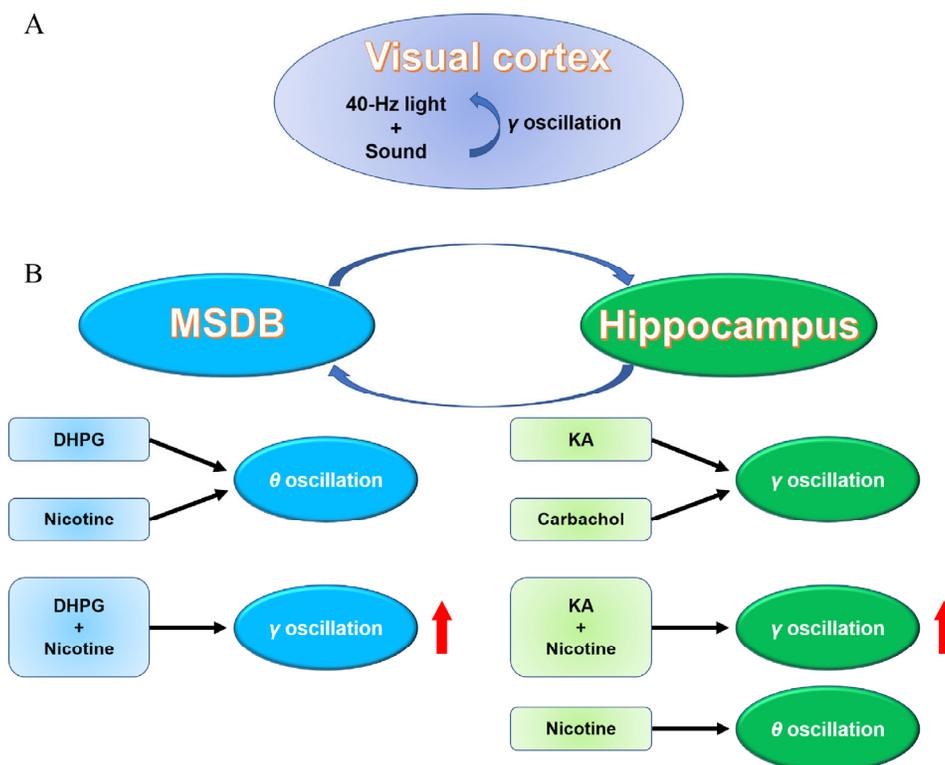


Fig. 1 Neural network oscillations induced by physical and pharmacological stimulation. (A) A 40-Hz light and sound stimuli evoked gamma oscillations in the visual cortex. (B) A metabotropic glutamate receptor (mGluR) agonist [e.g. dihydroxyphenylglycine (DHPG) or nicotine] induced theta oscillations in medial septal diagonal band complex (MSDB) slices. The combination of DHPG and nicotine induced gamma oscillations in MSDB slices. Administration of either the ionotropic glutamate receptor agonist kainate (KA) or metabotropic cholinergic agonist carbachol induced gamma oscillations in the CA3 area of hippocampal slices. Nicotine alone only induced theta oscillations in hippocampal slices but combined administration of KA and nicotine induced gamma oscillations in hippocampal slices.

Within a high micromolar dose range, KA induces seizure activity in the hippocampus. However, at nanomolar concentrations (100–200 nM), KA induces persistent, rhythmic gamma oscillation activity in the hippocampus [16] and entorhinal cortex [17]. Similarly, carbachol (5–20 μ M) induces oscillations at a gamma frequency band [1] [Fig. 1(B)]. Pharmacologically induced gamma oscillations are long-lasting, relatively easy to record, and highly similar to gamma oscillations recorded *in vivo* [18]; thus, they have become a popular model in recent studies. Theoretically, the concentration of KA used to induce gamma oscillations is well below the dose used to induce epileptic activity. This low concentration of KA should improve learning and memory deficits in AD. However, this hypothesis remains to be further investigated.

4 Nicotinic acetylcholine receptor modulation of hippocampal network activity

Nicotinic acetylcholine receptors (nAChRs) are highly expressed in the hippocampus. Nicotine, an nAChR agonist, was found to induce theta rhythms in hippocampal slices [19] and modulate the existing gamma oscillations induced by KA in hippocampal slices. Different concentrations of nicotine have opposing effects on gamma oscillations. A low dose of nicotine (0.1–10 μ M) enhances hippocampal gamma oscillations via activation of both the α 4 β 2-nAChR and α 7-nAChR. Studies indicate that low-dose nicotine or a selective nAChR agonist may improve AD cognitive function [20] [Fig. 1(B)]. It was also demonstrated that at a high dose of 100 μ M, nicotine rapidly inhibited gamma oscillations via N-methyl-D-aspartate receptor (NMDAR) over-activation [20]. Given that the abnormal gamma oscillations in schizophrenia and the popularity of smoking among patients with schizophrenia,

we assume that a high dose of nicotine or selective nicotinic agonist may be effective in treating patients with schizophrenia.

Through further analysis of the cellular mechanisms of nicotine-induced enhancement of hippocampal gamma power, it was found that the protein kinase A (PKA)-NMDAR-phosphatidylinositol 3-kinase (PI3K) pathway modifies cellular properties required for the nicotinic enhancement of gamma oscillations, which are also dependent on protein kinase C and extracellular signal-regulated kinase activities. These signaling pathways provide evidence for restoring gamma oscillations in pathological conditions affecting cognition. The suppression of gamma oscillations with 100 μ M nicotine was dependent on PKA-NMDAR activation and may be due to remarkably high intracellular calcium levels [21].

5 Network oscillations recorded from medial septal diagonal band complex slices

Although KA and carbachol can induce gamma oscillations in the hippocampus, neither of them can elicit gamma oscillations in the somatosensory cortex alone; only the combination of KA and carbachol can elicit gamma oscillations in the somatosensory cortex [22]. The medial septal diagonal band complex (MSDB), a brain area with cholinergic and GABAergic neurons projecting to the hippocampus and forming the septohippocampal pathway, is thought to be critical for the generation and/or maintenance of hippocampal theta rhythms *in vivo* [23]. AD involves a serious deficit in cholinergic septohippocampal innervation and altered patterns of synchronous activity [24]. In the *in vitro* slices of MSDB, KA can only induce theta activity, which indicates that MSDB is capable of generating and maintaining its own rhythmic firing activity,

a mechanism by which it could impose theta frequency oscillatory activity on the hippocampus [25], which is critical for phenomena including attention and acquisition of sensory information [26]. These observations indicate that KA-induced network activity differs in oscillatory frequency among the different brain areas.

6 Nicotinic acetylcholine receptor and metabotropic glutamate receptor modulation of medial septal diagonal band complex network activity

The perfusion of MSDB slices with nicotine induced theta oscillations [27]. Similarly, the perfusion of MSDB slices with the group I metabotropic glutamate receptor (mGluR) agonist (RS)-3,5-dihydroxyphenylglycine (DHPG) induce oscillatory activity at theta bands [28]. DHPG-induced theta oscillations persist for hours after a washout of DHPG and are dependent on the α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/KA receptor, which suggests that a form of synaptic plasticity similar to long-term potentiation exists for these oscillatory activities [29]. Interestingly, co-administration of nicotine and DHPG induce gamma oscillations in MSDB [27] [Fig. 1(B)]. The impact of gamma oscillations induced by activation of two different receptor agonists on hippocampal rhythms and/or function remains to be studied. However, such a regimen of induction of gamma oscillations in MSDB indicates new strategies that may be useful to modulate the septohippocampal pathway and correct the deficits in cholinergic septohippocampal innervation in patients with AD.

Considering deficient or abnormal gamma oscillations in neuropsychological disorders, boosting gamma oscillations by either physical stimulation (i.e., light or sound) or pharmacological stimulation via activation of specific receptors,

such as the nAChR, mGluR1, or a combination of these receptors, may provide a powerful tool to modulate brain gamma oscillations in specific areas and may serve as an effective therapy for neuropsychological disorders.

Conflict of interests

The authors declare no conflict of interests in this work.

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Jianhua Zhao, M.D., received his Ph.D. degree from the First Affiliated Hospital of Zhengzhou University, China (2017), and then received his postdoctoral training in Harvard Medical School. He is an associate professor and associate chief physician of neurology in the First Affiliated Hospital of Xinxiang Medical University, Henan Key Laboratory of Neurorestoratology, Henan Joint International Research Laboratory of Neurorestoratology for Senile Dementia. He has published many high-quality papers in international journals (e.g., *iScience*, *Aging Cell*, *Medicine*, *Cytokine*). His current research interests include the neural mechanism of learning and memory and molecular basis of cerebral small vascular disease (CSVD). E-mail: 051092@xxmu.edu.cn, zjh0913@163.com



Ailin Du received his M.D. degree from the First Affiliated Hospital of Zhengzhou University, China (2018). He is an associate professor at Henan Key Laboratory of Brain Research, Xinxiang Medical University. His current research interests focus on the neural mechanism of learning and memory. E-mail: 051007@xxmu.edu.cn, duailin@126.com



Chengbiao Lu received his Ph.D. degree from Birmingham University, UK (2007), and received his postdoctoral training in Leeds University and Durham University. He is currently a Taihang-Scholar professor of physiology and neurophysiology, Henan Joint International Research Laboratory of Non-invasive Neural Modulation, Xinxiang Medical University, Henan, China. He has published many high-quality papers in journals such as *PNAS*, *Aging Cell*, *Frontiers in Cellular Neuroscience*, and *Circulation*. His current research interests include the cellular and molecular mechanisms of neural network oscillations, aging and aging related diseases, and the non-invasive neural modulation of neuropsychological disorders. E-mail: johnlu9000@hotmail.com