Cellular mechanisms of hippocampal gamma frequency oscillations

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Abstract

Gamma oscillations are known as cognitive rhythms due to their occurrence during the cognitive functions such as working memory, episodic memory, memory encoding and retrieval, sensory binding and attention. Gamma oscillations can be easily transferred into epileptic activity. Altered gamma rhythms are seen during the brain disorders such as schizophrenia, dementia and autism. Hence, studying the mechanisms of gamma rhythms is of great importance. Recent discoveries revealed new details of gamma oscillations. The classical view about the parvalbumin containing perisomatic basket cells that drives the gamma oscillation is valid for CA3 region of hippocampus but it may not be so for CA1 region. However, medial ganglionic eminence (MGE) derived axo-axonic cells action potential discharge follows the gamma rhythm in CA1 together with caudal ganglionic eminence (CGE) derived trilaminar and back-projecting interneurons. Oriense-Lacunosum-Moleculare (O-LM) cells appear to have dual origine and can be modulated by gamma frequency. Using the modern technologies and relying on the current knowledge and new insights about neuronal elements in gamma frequency oscillation will help the scientists to study the mechanisms of cognitive rhythms in more details.

Keywords

Gamma oscillations, Interneurons, hippocampus, perisomatic, O-LM

Introduction

In his phenomenal book "Rhythms of the brain" Gregor Buzsaki describes the chronology of discovery of different rhythms named according to Greek alphabet corresponding to the order of encountering and registering the neuronal potential fluctuations. The term "gamma oscillations" were first applied by Jasper and Andrews in 1938. Other terms describing the same rhythm are "40 Hz" and "cognitive rhythm" (Buzsaki, 2006).

In 1974 Professionals at the International Federation of Society for Electroencephalography and Clinical Neurophysiology decided to refresh the classification of rhythms and finding the exact boundary between different oscillations. Up to now gamma rhythm has a broad boundaries and it is even questioned whether the wide range of frequencies known as gamma rhythm depend on the same neuronal mechanism or not. Thus, the boundaries of gamma rhythms are still differently described by different scientists, e.g. gamma rhythm is described as 30-80 Hz activity in some literature (Buzsaki, 2006). The others write that 30-60 Hz is a low gamma frequency and 60-120 Hz is high gamma frequency, other sources show that 60-200 Hz is a high gamma frequency and above this is a very short-lasting rhythmic activity (100-200 Hz) known as "ripple", the latter is considered as a type of gamma as well (Uhlhaas et al, 2011).

Gamma rhythms are registered in most behavioural and cognitive states including slow-wave sleep (Whittington et al., 2011). These oscillations are correlated with working memory and storage of memory (Lisman and Idiart, 1995), sensory binding (Singer, 1993), consciousness (Llinas et al., 1998), long-term episodic memory (Nyhus and Curran, 2010), neuronal communications and long-term potentiation (Fell, Axmacher, 2011), attention (Engel et al., 2001). Gamma oscillation are reduced in age (Vreugdenhil & Toesco, 2005). This rhythm can easily be transferred into epileptic seizures due to the imbalance between inhibition and excitation. Altered gamma oscillations are seen in brain disorders such as schizophrenia, dementia and autism (Ulhaas & Singer, 2006). Therefore, learning the cellular mechanisms of this rhythm will enable scientists and medical researchers to develop proper treatment for above mentioned disorders.

Thus, studying neuronal activity at gamma frequency is very important, since the rhythm is associated with cognitive functions (Buzsaki, 2006). Gamma oscillations recorded from different regions of the brain of various species has similar kinetics. This enable to speculate the composition of the mechanisms of this rhythm. Gamma frequency oscillations are

described in different parts of new cortex, entorhynal cortex, hippocampus, amygdala, thalamus, striatum, olfactory bulbs etc. (Buzsaki & Wang, 2012).

Ways of generating gamma oscillations

In vitro gamma oscillations can be induced by different methods in vitro or in vivo in different settings (in interface and submerged chambers). The following methods are used to induce gamma oscillations in vitro: high frequency electrical stimulation of afferent fibers of hippocampus in vitro (Whittington et al., 1995), kainite application under the pressure (Hajos et al., 2000), increasing extracellular potassium concentration (LeBeau et al., 2002), applying carbachol - the muscarinic acetylcholine receptor agonist (Buhl et al., 1998; Hajos et al., 2004) and activation of metabotrobic glutamatergic receptors (mGluR) (Whittington et al., 1995).

Characteristics of gamma oscillations in vitro in interface and submerged chambers

In vivo gamma rhythm is transient and lasts for several seconds. Inducing gamma oscillations in vitro in submerged chamber by pressure ejection of kainite causes short-lasting, transient activity, similar to the one taking place in vivo. In recent investigation it was shown that abrupt kainite application under the pressure caused 7.55 ± 3.77 ms long neuronal activity in gamma frequency (49.89 ± 10.59 Hz). At the end of field potential oscillations the frequency dropped to 44.92 ± 9.33 Hz. Power of gamma frequency remarkably decreased throughout the neuronal activity. Mean amplitude of local field potential was 0.23 mV (Kipiani, 2018)

Kainate bath application induced gamma oscillation amplitudes recorded in area CA3 in interface chamber are always 5-8 times larger than in area CA1 (Fano et al., 2007). The average frequency of the oscillatory activity was 32.1 ± 4.6 Hz in area CA3 and 30 ± 6.2 Hz in area CA1. Other scientists showed the similar activity using kainate bath application: induced gamma oscillations in interface chambers had larger amplitude - from 0.8 to 2 mV in area CA3 (Mean value 1.1 ± 0.15) and from 0.15 to 0.3 mV in area CA1 (mean value 0.15 ± 0.03) (Wojtowicz et al., 2009).

The amplitude of carbachol-induced gamma oscillations had range of 0.4 to 1 mV in area CA3 (mean value 0.7 ± 0.09) and 0.2 to 0.4 mV in area CA1 (mean value 0.24 ± 0.03). Peak frequency of these oscillations were lower than the peak frequency of kainite induced gamma oscillations in both area (Wojtowicz et al., 2009)

Models of oscillations

Theoretically there are described three principal ways in which gamma oscillations can be generated (Mann & Paulsen, 2007). One possibility is the existence of external pacemaker that drives the network with gamma frequency. Alternatively, the rhythmic firing of a subset of neuronal populations can entrain the network intrinsically (Whittington et al., 1995), or network oscillations could emerge from synaptic recurrent feedback loops (Freeman, 1968).

Currently two accepted hypothesis exist about the oscillations: ING (interneurons network gamma) and PING (Pyramidal cells - interneurons network gamma) models (Whittington et al., 2011). Gamma rhythms can be seen in interneuronal networks alone. When Interneurons are connected by gap junctions and they create Golgian syncytium and when principal cells do not send phasic excitatory input to inhibitory interneurons due to the pharmacological isolation and the interneurons are depolarized tonicly they readily produce a local circuit gamma rhythm (Whittington et al., 1995).

PING model oscillations is weak while Interneuron-pyramidal cell oscillations amplitude is higher. GABAergic perisomatic interneurons are connected by both chemical and electrical synapses (gap junctions). Pyramidal cells have branched dendritic tree and are suitable for temporal integration, interneurons on the contrary, have rapid integration time constant (Mann and Paulsen, 2007). Reciprocal interaction between the pyramidal cells and interneurons is very important during gamma oscillations. Pressure ejection of chemical substances, e.g. glutamate depolarizes both interneurons and pyramidal cells resulting in spike rates around gamma frequency. Similarly, intense tetanic excitation and transient elevation of extracellular potassium also generate PING rhythm which may persist for several seconds following stimulus termination (Whittington et al., 2011). Experimentally it is hard to separate these two modes of rhythm generation.

Inhibitory interneurons as a part of a gamma mechanisms

In 1995 it was shown that gamma oscillations are driven by the network of interneurons (Whittington et al., 1995). They say, that a major conceptual advance was the realization that synaptic inhibition plays a fundamental role in rhythmogenesis, either in an interneuronal network or in reciprocal excitatory-inhibitory loop (Wang, 2010). The same time other scientist investigated and published the data about the importance of perisomatic inhibitory interneurons in hippocampal neuronal synchronization (Bragin et al., 1995).

Brain rhythms are synchronized activity of large numbers of neurons because synchronouse currents sum together to generate large amplitude local field potential (LFP) fluctuations (Colgin, 2016). Improved technologies enabled neuroscientists to study the cellular mechanisms of oscillations. Knowing the electrophysiological properties of single neurons became possible after inventing parch-clamp technique by Bert Sakman and Ernst Nehr. Identifying morphology of single cells was done by applying immunohistochemical staining methods. Depending on morphology there are many types of interneurons in the hippocampus. The best known and studied ones in network oscillations are perisomatic basket and axo-axonic cells, bistratified, trilaminar, oriense-lacunosum-moleculare (O-LM) cells and some others. These interneurons, that are just 5 % of all cells, innervate different parts of the pyramidal cells and thus, control various dendritic domains.

For identification of the inhibitory neurons the most appropriate method appeared finding special molecular markers. These markers are somatostatin, parvalbumin (PV), neuropeptide Y (NYP), vasoactive intestinal protein (VIP), carletinin, releen, cholecystokinin etc. The prompter of the specific marker was connected with the enhanced green fluorescent protein (GFP) that enabled the cells the express the fluorescent protein under the special light. In this way scientist could see the desired cells in vitro under the fluorescent light. However, it appeared that the classical marker for the perisomatic interneurons – parvalbumin may not be considered as an ideal one, since O-LM interneurons were reported as slightly immunopositive to PV as well (Klausberger et al., 2003; Kipiani, 2009; Leão et al., 2012). PV is a low molecular weight soluble protein that binds calcium ions with high affinity and is strongly implicated in intracellular calcium regulation and trafficking. "Classical interneuron markers like somatostatin (or parvalbumin to some extent) should be used with caution when striving to separate functionally distinct interneuron populations. Alternative genetic markers are now available that may serve as better tools for investigation of interneuron function." (Mikulovic et al., 2015).

Regardless the same morphology and the same molecular markers the neurons of the same group may have different electrophysiology. This led the scientists to start investigating the reasons of this difference. It appeared that in certain cases different physiology of the same morphological type of interneurons resulted from the distinct embryonic origin of the same group cells either from medial ganglionic eminence (MGE) or caudal ganglionic eminence (CGE) (Chittajallu et al., 2013).

Interneurons involving in gamma oscillations of CA3 and CA1 - perisomatic interneurons (basket and axo-axonic cells), O-LM, trilaminar, bistratified, back-projecting interneurons

Recent discoveries show that the inhibitory interneurons that were described during the gamma oscillations in CA3 region of the hippocampus may discharge action potentials in a different manner in CA1 in relation to their embryonic origin.

O-LM cells were observed already by Ramon y Cajal. These interneurons were hypothesized to coordinate cell assemblies in hippocampus with theta (3-8 Hz) frequency (Gloveli et al., 2005; Klausberger & Somogyi, 2008). O-LM cells are very vulnerable interneuron population in models of epilepsy (Dinocourt et al., 2003). However, there are compelling evidence about their involvement in generating gamma (40-80 Hz) frequency oscillations in hippocampus (Tort et al., 2007, Kipiani, 2009).

Somatostatin has been frequently used as a molecular marker for identifying O-LM cells (Ferro et al., 2015). Previously it had been shown that O-LM interneurons are weakly immunopositive for parvalbumin (Klausberger et al., 2003). Parvalbumine positive O-LM interneurons were recorded from CA1 hippocampus that fired action potentials with gamma frequency during kainite induced gamma oscillations in submerged conditions and was suggested the possibility of existence of two different groups of O-LM interneurons (Kipiani, 2009). It was also shown by modelling of neuronal networks that O-LM cells can discharge with gamma frequency during the epilepsy (Tort et al., 2007). It is shown that O-LM interneurons are also interconnected with gap junctions and they create a syncytium.

However, hippocampal O-LM cells were considered as homogenous class of interneurons with the molecular marker SOM until recently when new investigations proved that these cells are heterogenous. More precise molecular marker for CA1 O-LM cells is suggested to be cholinergic receptor, nicotinic, alpha polypeptide 2 (Chrna2) (Leão et al., 2012). These cells were tested on the embryonic origin and appeared that they have dual embryonic origin (Chittajallu et al., 2013).

SOM containing CA1 O-LM interneurons express two different types of molecules: 5-Ht_{3A}R (hydroxytryptamin, serotonin receptors) and Nkx2-1(transcription factor). Those interneurons that derive from caudal ganglionic eminence (CGE) express 5-Ht_{3A}R and the other cohort, derived from medial ganglionic eminence (MGE) express Nkx2-1 (Chittajallu et al., 2013). Due to this distinction, the authors speculated and showed, that serotonergic tone from raphe nuclei preferentially recruited CGE-derived O-LM interneurons over their MGE-

derived counterparts during hippocampal circuit oscillations via activation of 5-Ht_{3A}R. Thus, the dual embryonic origin confers that both cohorts of O-LM cells have unique circuit role and neuromodulatory properties.

In kainate induced gamma oscillations two groups of O-LM interneurons showed different modulations and phase preferences. Mean firing probability for CGE vs MGE-derived O-LM cells was 0.027 ± 0.011 vs 0.061 ± 0.010. The phase preference of these two cohorts was significantly different such that MGE- and CGE-derived O-LM cells had a preference near the peak and the descending phase of the field gamma oscillation respectively, proving that both cohorts of cells provided unique functional contributions to network dynamics.

Thus MGE-derived O-LM cells were far more active during the kainite induced gamma oscillations than the CGE-derived ones. Craig and McBain investigated whether the interneurons derived from MGE play more important role in shaping gamma oscillations (Craig and McBain 2015). PV containing perisomatic targeting interneurons are thought to drive gamma oscillations. The investigation showed that firing probability for MGE-derived PV containing perisomatic interneurons was 0.34 in CA3 region and 0.12 in CA1 area, Also, there was no significant phase locking noticed. However, the other interneurons derived from CGE and significantly phase locked with gamma oscillations were putative trilaminar cells (firing probability 0.31) and back-projecting interneurons (firing probability 0.13). From MGE derived interneurons during CA1 gamma oscillations axo-axonic cells had a mean firing probability 0.35 and biphasic phase preference. They fired more than once during a single gamma cycle, contrasting with fast spiking basket cells, which had a lower firing probability with no phase preference. The other group derived from MGE and phase locked with field gamma oscillation was bistratified cells (Craig & McBain 2015).

Summing up, current results show that interneurons involved in oscillations should be learned by considering the embryonic origin of these cells. Not only one type of interneurons contribute to loal field oscillations but several groups of them. Molecular markers should be chosen with more precision to simplify the finding the targets during the network oscillations.

All these above mentioned investigations create valuable knowledge about the parts of mechanisms of gamma oscillation. Functional differences among the inhibitory interneurons that control the oscillations are likely to contribute differently to generation, maintenance and termination of gamma oscillations. Future studies are necessary to address the underlying mechanisms and answer the following questions: Do the broad range of gamma rhythms have different mechanisms led by different groups of interneurons? Can one and the same interneuronal network lead different rhythms of the brain according to various brain-state?

Do Gamma rhythms need the simultaneous involvement of different types of interneurons like perisomatic, trilaminar, bistratified, axo-axonic or O-LM in CA1 and CA3 area of hippocampus?

Conflict of interests

none

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